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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

JAZZ PHARMACEUTICALS, INC. and JAZZ PHARMACEUTICALS IRELAND LIMITED, **Plaintiffs,** **v.** **MALLINCKRODT PLC, MALLINCKRODT INC., and MALLINCKRODT LLC,** **Defendants.**	**Civil Action No. _____** **COMPLAINT FOR PATENT INFRINGEMENT** **(Filed Electronically)**

Plaintiffs Jazz Pharmaceuticals, Inc. and Jazz Pharmaceuticals Ireland Limited (collectively, "Jazz Pharmaceuticals" or "Plaintiffs"), by their undersigned attorneys, for their Complaint against Defendants Mallinckrodt plc, Mallinckrodt Inc., and Mallinckrodt LLC (collectively "Mallinckrodt" or "Defendants"), allege as follows:

Nature of the Action

1. This is an action for patent infringement under the patent laws of the United States, 35 U.S.C. §100, *et seq.*, arising from Mallinckrodt's filing of an Abbreviated New Drug Application ("ANDA") with the United States Food and Drug Administration ("FDA") seeking approval to commercially market a generic version of Jazz Pharmaceuticals' XYREM® drug

product prior to the expiration of United States Patent Nos. 7,668,730 (the "'730 patent"), 7,765,106 (the "'106 patent"), 7,765,107 (the "'107 patent"), 7,895,059 (the "'059 patent"), 8,457,988 (the "'988 patent"), 8,589,182 (the "'182 patent"), 8,731,963 (the "'963 patent"), 8,772,306 (the "'306 patent"), 9,050,302 (the "'302 patent"), and 9,486,426 (the "'426 patent") owned by Jazz Pharmaceuticals (collectively, "the patents-in-suit").

The Parties

2. Plaintiff Jazz Pharmaceuticals, Inc. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 3170 Porter Drive, Palo Alto, California 94304.

3. Plaintiff Jazz Pharmaceuticals Ireland Limited is a corporation organized and existing under the laws of Ireland, having a principal place of business at Waterloo Exchange, Waterloo Road, Dublin, Ireland 4.

4. On information and belief, Defendant Mallinckrodt plc is a limited liability company organized and existing under the laws of Ireland, having a principal place of business at 675 McDonnell Boulevard, Hazelwood, Missouri 63042. On information and belief, Mallinckrodt plc is in the business of, *inter alia*, developing, manufacturing, distributing, and selling pharmaceutical products throughout the United States, including within this District, either on its own or through its affiliates, including Mallinckrodt Inc. and Mallinckrodt LLC.

5. On information and belief, Defendant Mallinckrodt Inc. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 675 McDonnell Boulevard, Hazelwood, Missouri 63042. On information and belief, Mallinckrodt Inc. is in the business of, *inter alia*, developing, manufacturing, distributing, and selling pharmaceutical products throughout the United States, including within this District, either on its own or through its affiliates, including Mallinckrodt LLC.

6. On information and belief, Defendant Mallinckrodt LLC is a limited liability company organized and existing under the laws of the State of Delaware, having a principal place of business at 675 McDonnell Boulevard, Hazelwood, Missouri 63042. On information and belief, Mallinckrodt LLC is in the business of, *inter alia*, manufacturing, distributing, and selling pharmaceutical products throughout the United States, including within this District, either on its own or through its affiliates, including Mallinckrodt Inc.

7. On information and belief, Mallinckrodt Inc. and Mallinckrodt LLC are wholly-owned subsidiaries of Mallinckrodt plc.

8. On information and belief, following any FDA approval of ANDA No. 210936, Defendants Mallinckrodt plc, Mallinckrodt Inc., and Mallinckrodt LLC will work in concert with one another to make, use, offer to sell, and/or sell the generic products that are the subject of ANDA No. 210936 throughout the United States, and/or import such generic products into the United States.

Jurisdiction and Venue

9. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

10. On information and belief, Mallinckrodt plc is subject to personal jurisdiction in New Jersey because Mallinckrodt plc has purposely availed itself of the benefits and protections of New Jersey's laws such that it should reasonably anticipate being haled into court in New Jersey. On information and belief, Mallinckrodt plc manufactures, markets, and/or sells generic drugs throughout the United States and within the State of New Jersey and, therefore, transacts business within the State of New Jersey related to Plaintiffs' claims, and/or has engaged in systematic and continuous business contacts within the State of New Jersey.

11. On information and belief, Mallinckrodt Inc. is subject to personal jurisdiction in New Jersey because, among other things, Mallinckrodt Inc. has purposely availed itself of the benefits and protections of New Jersey's laws such that it should reasonably anticipate being haled into court in New Jersey. On information and belief, Mallinckrodt Inc. manufactures, markets, and/or sells generic drugs throughout the United States and within the State of New Jersey and, therefore, transacts business within the State of New Jersey related to Plaintiffs' claims, and/or has engaged in systematic and continuous business contacts within the State of New Jersey.

12. On information and belief, Mallinckrodt LLC is subject to personal jurisdiction in New Jersey because Mallinckrodt LLC has purposely availed itself of the benefits and protections of New Jersey's laws such that it should reasonably anticipate being haled into court in New Jersey. On information and belief, Mallinckrodt LLC manufactures, markets, and/or sells generic drugs throughout the United States and within the State of New Jersey and, therefore, transacts business within the State of New Jersey related to Plaintiffs' claims, and/or has engaged in systematic and continuous business contacts within the State of New Jersey.

13. On information and belief, Mallinckrodt Inc. is registered to do business in New Jersey (business identification number 0100412015) and has appointed Corporation Trust Company, located at 820 Bear Tavern Road West, Trenton, NJ 08628, as its registered agent for the receipt of service of process.

14. On information and belief, Mallinckrodt LLC is registered to do business in New Jersey (business identification number 0600393793) and has appointed Corporation Trust Company, located at 820 Bear Tavern Road, West Trenton, NJ 08628, as its registered agent for the receipt of service of process.

15. On information and belief, Mallinckrodt Inc. and Mallinckrodt LLC have availed themselves of the jurisdiction of this cCourt by initiating litigation in this District. *See, e.g., Mallinckrodt Inc. and Mallinckrodt LLC v. Watson Laboratories, Inc. – Florida*, Civ. Action No. 12-6744 (NLH)(JS) (D.N.J.), *Mallinckrodt LLC, et al. v. Zydus Pharmaceuticals (USA) Inc.*, Civ. Action No. 14-4901 (NLH)(AMD) (D.N.J.), *Mallinckrodt Inc. v. Watson Laboratories, Inc.-Florida, et al.*, Civ. Action No. 10-6424 (FSH)(PS) (D.N.J.), *Mallinckrodt LLC, et al. v. Metrics, Inc.*, Civ. Action No. 14-2219 (SDW)(MCA) (D.N.J.), *Mallinckrodt LLC, et al. v. Watson Laboratories, Inc. – Florida*, Civ. Action No. 15-3800 (KSH)(CLW) (D.N.J.), and *Mallinckrodt LLC, et al. v. Par Pharmaceutical Inc.*, Civ. Action No. 15-7694 (KSH)(CLW) (D.N.J.).

16. On information and belief, Mallinckrodt plc, Mallinckrodt Inc., and Mallinckrodt LLC are alter egos and work in concert with respect to the regulatory approval, manufacturing, marketing, sale, and distribution of generic pharmaceutical products throughout the United States, including in this Judicial District.

17. On information and belief, the acts of Mallinckrodt Inc. complained of herein were done at the direction of, with the authorization of, and with the cooperation, participation, and assistance of Mallinckrodt plc and Mallinckrodt LLC.

18. On information and belief, by virtue of, *inter alia*, Defendants' continuous and systematic contacts with New Jersey, including, but not limited to, the above-described contacts, and the actions on behalf of Defendants in connection with ANDA No. 210936, this Court has personal jurisdiction over Defendants. These activities satisfy due process and confer personal jurisdiction over Defendants consistent with New Jersey law.

19. On information and belief, Mallinckrodt plc, Mallinckrodt Inc., and Mallinckrodt LLC share corporate officers, use the same Mallinckrodt Pharmaceuticals' logo, and have a

regular and established place of business in this Judicial District at 1425 US-206, Bedminster Township, NJ 07921.

20. Venue is proper in this District pursuant to 28 U.S.C. §§ 1391 and 1400(b).

The Patents-In-Suit

21. On February 23, 2010, the USPTO duly and lawfully issued the ’730 patent, entitled “Sensitive Drug Distribution System and Method.” A copy of the ’730 patent is attached hereto as Exhibit A.

22. On July 27, 2010, the USPTO duly and lawfully issued the ’106 patent entitled, “Sensitive Drug Distribution System and Method.” A copy of the ’106 patent is attached hereto as Exhibit B.

23. On July 27, 2010, the USPTO duly and lawfully issued the ’107 patent entitled, “Sensitive Drug Distribution System and Method.” A copy of the ’107 patent is attached hereto as Exhibit C.

24. On February 22, 2011, the USPTO duly and lawfully issued the ’059 patent entitled, “Sensitive Drug Distribution System and Method.” A copy of the ’059 patent is attached hereto as Exhibit D.

25. On June 4, 2013, the USPTO duly and lawfully issued the ’988 patent entitled, “Sensitive Drug Distribution System and Method.” A copy of the ’988 patent is attached hereto as Exhibit E.

26. On November 19, 2013, the USPTO duly and lawfully issued the ’182 patent entitled, “Sensitive Drug Distribution System and Method.” A copy of the ’182 patent is attached hereto as Exhibit F.

27. On May 20, 2014, the USPTO duly and lawfully issued the '963 patent entitled, "Sensitive Drug Distribution System and Method." A copy of the '963 patent is attached hereto as Exhibit G.

28. On July 8, 2014, the USPTO duly and lawfully issued the '306 patent entitled, "Method of Administration of Gamma Hydroxybutyrate with Monocarboxylate Transporters." A copy of the '306 patent is attached hereto as Exhibit H.

29. On June 9, 2015, the USPTO duly and lawfully issued the '302 patent entitled, "Method of Administration of Gamma Hydroxybutyrate with Monocarboxylate Transporters." A copy of the '302 patent is attached hereto as Exhibit I.

30. On November 8, 2016, the USPTO duly and lawfully issued the '426 patent entitled, "Method of Administration of Gamma Hydroxybutyrate with Monocarboxylate Transporters." A copy of the '426 patent is attached hereto as Exhibit J.

The XYREM® Drug Product

31. Jazz Pharmaceuticals holds an approved New Drug Application ("NDA") under Section 505(a) of the Federal Food Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. § 355(a), for sodium oxybate oral solution (NDA No. 21-196), which it sells under the trade name XYREM®. The claims of the patents-in-suit cover, *inter alia*, methods of use and administration of sodium oxybate or pharmaceutical compositions containing sodium oxybate. Jazz Pharmaceuticals owns the patents-in-suit.

32. Pursuant to 21 U.S.C. § 355(b)(1) and attendant FDA regulations, the patents-in-suit are listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to XYREM®.

33. The labeling for XYREM® instructs and encourages physicians, other healthcare workers, and patients to administer XYREM® according to the methods claimed in several of the patents-in-suit.

Acts Giving Rise to This Suit

34. Pursuant to Section 505 of the FFDCA, Mallinckrodt filed ANDA No. 210936 ("Mallinckrodt's ANDA") seeking approval to engage in the commercial manufacture, use, sale, offer for sale, or importation of 500 mg/mL sodium oxybate oral solution ("Mallinckrodt's Proposed Product"), before the patents-in-suit expire.

35. On information and belief, in connection with the filing of its ANDA as described in the preceding paragraph, Mallinckrodt has provided a written certification to the FDA, as called for by Section 505 of the FFDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Mallinckrodt's Paragraph IV Certification"), alleging that the claims of the patents-in-suit are invalid, unenforceable, and/or will not be infringed by the activities described in Mallinckrodt's ANDA.

36. No earlier than November 21, 2017, Jazz Pharmaceuticals received written notice of Mallinckrodt's Paragraph IV Certification ("Mallinckrodt's Notice Letter") pursuant to 21 U.S.C. § 355(j)(2)(B). Mallinckrodt's Notice Letter alleged that the claims of the patents-in-suit are invalid, unenforceable, and/or will not be infringed by the activities described in Mallinckrodt's ANDA. Mallinckrodt's Notice Letter also informed Jazz Pharmaceuticals that Mallinckrodt seeks approval to market Mallinckrodt's Proposed Product before the patents-in-suit expire.

37. On information and belief, Mallinckrodt has not submitted a statement to the FDA pursuant to 21 U.S.C. § 355(j)(2)(A)(viii) that Mallinckrodt seeks to market its Proposed Product for a use other than the uses claimed in the patents-in-suit.

38. Under applicable laws and regulations, the FDA will not approve Mallinckrodt's Proposed Product with labeling that does not include information regarding dose modification in patients receiving concomitant administration of sodium oxybate and valproate that is necessary for the safe and effective use of sodium oxybate.

Count I: Infringement of the '730 Patent

39. Plaintiffs repeat and reallege the allegations of paragraphs 1-38 as though fully set forth herein.

40. Mallinckrodt's submission of its ANDA to obtain approval to engage in the commercial manufacture, use, sale, offer for sale, or importation of sodium oxybate oral solution, prior to the expiration of the '730 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

41. There is a justiciable controversy between the parties hereto as to the infringement of the '730 patent.

42. Unless enjoined by this Court, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will infringe the '730 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Mallinckrodt's Proposed Product in the United States.

43. Unless enjoined by this Court, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will induce infringement of the '730 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Mallinckrodt's Proposed Product in the United States. On information and belief, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will intentionally encourage acts of direct infringement with knowledge of the '730 patent and knowledge that its acts are encouraging infringement.

44. Unless enjoined by this Court, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will contributorily infringe the '730 patent under 35 U.S.C. § 271(c) by making,

using, offering to sell, importing, and/or selling Mallinckrodt's Proposed Product in the United States. On information and belief, Mallinckrodt has had and continues to have knowledge that Mallinckrodt's Proposed Product is especially adapted for a use that infringes the '730 patent and that there is no substantial non-infringing use for Mallinckrodt's Proposed Product.

45. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Mallinckrodt's infringement of the '730 patent is not enjoined.

46. Jazz Pharmaceuticals does not have an adequate remedy at law.

47. This case is an exceptional one, and Jazz Pharmaceuticals is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count II: Infringement of the '106 Patent

48. Plaintiffs repeat and reallege the allegations of paragraphs 1-47 as though fully set forth herein.

49. Mallinckrodt's submission of its ANDA to obtain approval to engage in the commercial manufacture, use, sale, offer for sale, or importation of sodium oxybate oral solution, prior to the expiration of the '106 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

50. There is a justiciable controversy between the parties hereto as to the infringement of the '106 patent.

51. Unless enjoined by this Court, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will infringe the '106 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Mallinckrodt's Proposed Product in the United States.

52. Unless enjoined by this Court, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will induce infringement of the '106 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Mallinckrodt's Proposed Product in the United

States. On information and belief, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will intentionally encourage acts of direct infringement with knowledge of the '106 patent and knowledge that its acts are encouraging infringement.

53. Unless enjoined by this Court, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will contributorily infringe the '106 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Mallinckrodt's Proposed Product in the United States. On information and belief, Mallinckrodt has had and continues to have knowledge that Mallinckrodt's Proposed Product is especially adapted for a use that infringes the '106 patent and that there is no substantial non-infringing use for Mallinckrodt's Proposed Product.

54. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Mallinckrodt's infringement of the '106 patent is not enjoined.

55. Jazz Pharmaceuticals does not have an adequate remedy at law.

56. This case is an exceptional one, and Jazz Pharmaceuticals is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count III: Infringement of the '107 Patent

57. Plaintiffs repeat and reallege the allegations of paragraphs 1-56 as though fully set forth herein.

58. Mallinckrodt's submission of its ANDA to obtain approval to engage in the commercial manufacture, use, sale, offer for sale, or importation of sodium oxybate oral solution, prior to the expiration of the '107 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

59. There is a justiciable controversy between the parties hereto as to the infringement of the '107 patent.

60. Unless enjoined by this Court, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will infringe the '107 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Mallinckrodt's Proposed Product in the United States.

61. Unless enjoined by this Court, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will induce infringement of the '107 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Mallinckrodt's Proposed Product in the United States. On information and belief, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will intentionally encourage acts of direct infringement with knowledge of the '107 patent and knowledge that its acts are encouraging infringement.

62. Unless enjoined by this Court, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will contributorily infringe the '107 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Mallinckrodt's Proposed Product in the United States. On information and belief, Mallinckrodt has had and continues to have knowledge that Mallinckrodt's Proposed Product is especially adapted for a use that infringes the '107 patent and that there is no substantial non-infringing use for Mallinckrodt's Proposed Product.

63. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Mallinckrodt's infringement of the '107 patent is not enjoined.

64. Jazz Pharmaceuticals does not have an adequate remedy at law.

65. This case is an exceptional one, and Jazz Pharmaceuticals is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count IV: Infringement of the '059 Patent

66. Plaintiffs repeat and reallege the allegations of paragraphs 1-65 as though fully set forth herein.

67. Mallinckrodt's submission of its ANDA to obtain approval to engage in the commercial manufacture, use, sale, offer for sale, or importation of sodium oxybate oral solution, prior to the expiration of the '059 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

68. There is a justiciable controversy between the parties hereto as to the infringement of the '059 patent.

69. Unless enjoined by this Court, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will infringe the '059 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Mallinckrodt's Proposed Product in the United States.

70. Unless enjoined by this Court, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will induce infringement of the '059 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Mallinckrodt's Proposed Product in the United States. On information and belief, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will intentionally encourage acts of direct infringement with knowledge of the '059 patent and knowledge that its acts are encouraging infringement.

71. Unless enjoined by this Court, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will contributorily infringe the '059 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Mallinckrodt's Proposed Product in the United States. On information and belief, Mallinckrodt has had and continues to have knowledge that Mallinckrodt's Proposed Product is especially adapted for a use that infringes the '059 patent and that there is no substantial non-infringing use for Mallinckrodt's Proposed Product.

72. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Mallinckrodt's infringement of the '059 patent is not enjoined.

73. Jazz Pharmaceuticals does not have an adequate remedy at law.

74. This case is an exceptional one, and Jazz Pharmaceuticals is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count V: Infringement of the '988 Patent

75. Plaintiffs repeat and reallege the allegations of paragraphs 1-74 as though fully set forth herein.

76. Mallinckrodt's submission of its ANDA to obtain approval to engage in the commercial manufacture, use, sale, offer for sale, or importation of sodium oxybate oral solution, prior to the expiration of the '988 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

77. There is a justiciable controversy between the parties hereto as to the infringement of the '988 patent.

78. Unless enjoined by this Court, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will infringe the '988 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Mallinckrodt's Proposed Product in the United States.

79. Unless enjoined by this Court, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will induce infringement of the '988 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Mallinckrodt's Proposed Product in the United States. On information and belief, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will intentionally encourage acts of direct infringement with knowledge of the '988 patent and knowledge that its acts are encouraging infringement.

80. Unless enjoined by this Court, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will contributorily infringe the '988 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Mallinckrodt's Proposed Product in the United

States. On information and belief, Mallinckrodt has had and continues to have knowledge that Mallinckrodt's Proposed Product is especially adapted for a use that infringes the '988 patent and that there is no substantial non-infringing use for Mallinckrodt's Proposed Product.

81. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Mallinckrodt's infringement of the '988 patent is not enjoined.

82. Jazz Pharmaceuticals does not have an adequate remedy at law.

83. This case is an exceptional one, and Jazz Pharmaceuticals is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count VI: Infringement of the '182 Patent

84. Plaintiffs repeat and reallege the allegations of paragraphs 1-83 as though fully set forth herein.

85. Mallinckrodt's submission of its ANDA to obtain approval to engage in the commercial manufacture, use, sale, offer for sale, or importation of sodium oxybate oral solution, prior to the expiration of the '182 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

86. There is a justiciable controversy between the parties hereto as to the infringement of the '182 patent.

87. Unless enjoined by this Court, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will infringe the '182 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Mallinckrodt's Proposed Product in the United States.

88. Unless enjoined by this Court, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will induce infringement of the '182 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Mallinckrodt's Proposed Product in the United States. On information and belief, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt

will intentionally encourage acts of direct infringement with knowledge of the '182 patent and knowledge that its acts are encouraging infringement.

89. Unless enjoined by this Court, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will contributorily infringe the '182 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Mallinckrodt's Proposed Product in the United States. On information and belief, Mallinckrodt has had and continues to have knowledge that Mallinckrodt's Proposed Product is especially adapted for a use that infringes the '182 patent and that there is no substantial non-infringing use for Mallinckrodt's Proposed Product.

90. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Mallinckrodt's infringement of the '182 patent is not enjoined.

91. Jazz Pharmaceuticals does not have an adequate remedy at law.

92. This case is an exceptional one, and Jazz Pharmaceuticals is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count VII: Infringement of the '963 Patent

93. Plaintiffs repeat and reallege the allegations of paragraphs 1-92 as though fully set forth herein.

94. Mallinckrodt's submission of its ANDA to obtain approval to engage in the commercial manufacture, use, sale, offer for sale, or importation of sodium oxybate oral solution, prior to the expiration of the '963 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

95. There is a justiciable controversy between the parties hereto as to the infringement of the '963 patent.

96. Unless enjoined by this Court, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will infringe the '963 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Mallinckrodt's Proposed Product in the United States.

97. Unless enjoined by this Court, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will induce infringement of the '963 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Mallinckrodt's Proposed Product in the United States. On information and belief, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will intentionally encourage acts of direct infringement with knowledge of the '963 patent and knowledge that its acts are encouraging infringement.

98. Unless enjoined by this Court, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will contributorily infringe the '963 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Mallinckrodt's Proposed Product in the United States. On information and belief, Mallinckrodt has had and continues to have knowledge that Mallinckrodt's Proposed Product is especially adapted for a use that infringes the '963 patent and that there is no substantial non-infringing use for Mallinckrodt's Proposed Product.

99. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Mallinckrodt's infringement of the '963 patent is not enjoined.

100. Jazz Pharmaceuticals does not have an adequate remedy at law.

101. This case is an exceptional one, and Jazz Pharmaceuticals is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count VIII: Infringement of the '306 Patent

102. Plaintiffs repeat and reallege the allegations of paragraphs 1-101 as though fully set forth herein.

103. Mallinckrodt's submission of its ANDA to obtain approval to engage in the commercial manufacture, use, sale, offer for sale, or importation of sodium oxybate oral solution, prior to the expiration of the '306 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

104. There is a justiciable controversy between the parties hereto as to the infringement of the '306 patent.

105. Unless enjoined by this Court, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will infringe the '306 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Mallinckrodt's Proposed Product in the United States.

106. Unless enjoined by this Court, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will induce infringement of the '306 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Mallinckrodt's Proposed Product in the United States. On information and belief, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will intentionally encourage acts of direct infringement with knowledge of the '306 patent and knowledge that its acts are encouraging infringement.

107. Unless enjoined by this Court, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will contributorily infringe the '306 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Mallinckrodt's Proposed Product in the United States. On information and belief, Mallinckrodt has had and continues to have knowledge that Mallinckrodt's Proposed Product is especially adapted for a use that infringes the '306 patent and that there is no substantial non-infringing use for Mallinckrodt's Proposed Product.

108. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Mallinckrodt's infringement of the '306 patent is not enjoined.

109. Jazz Pharmaceuticals does not have an adequate remedy at law.

110. This case is an exceptional one, and Jazz Pharmaceuticals is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count IX: Infringement of the '302 Patent

111. Plaintiffs repeat and reallege the allegations of paragraphs 1-110 as though fully set forth herein.

112. Mallinckrodt's submission of its ANDA to obtain approval to engage in the commercial manufacture, use, sale, offer for sale, or importation of sodium oxybate oral solution, prior to the expiration of the '302 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

113. There is a justiciable controversy between the parties hereto as to the infringement of the '302 patent.

114. Unless enjoined by this Court, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will infringe the '302 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Mallinckrodt's Proposed Product in the United States.

115. Unless enjoined by this Court, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will induce infringement of the '302 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Mallinckrodt's Proposed Product in the United States. On information and belief, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will intentionally encourage acts of direct infringement with knowledge of the '302 patent and knowledge that its acts are encouraging infringement.

116. Unless enjoined by this Court, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will contributorily infringe the '302 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Mallinckrodt's Proposed Product in the United

States. On information and belief, Mallinckrodt has had and continues to have knowledge that Mallinckrodt's Proposed Product is especially adapted for a use that infringes the '302 patent and that there is no substantial non-infringing use for Mallinckrodt's Proposed Product.

117. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Mallinckrodt's infringement of the '302 patent is not enjoined.

118. Jazz Pharmaceuticals does not have an adequate remedy at law.

119. This case is an exceptional one, and Jazz Pharmaceuticals is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count X: Infringement of the '426 Patent

120. Plaintiffs repeat and reallege the allegations of paragraphs 1-119 as though fully set forth herein.

121. Mallinckrodt's submission of its ANDA to obtain approval to engage in the commercial manufacture, use, sale, offer for sale, or importation of sodium oxybate oral solution, prior to the expiration of the '426 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

122. There is a justiciable controversy between the parties hereto as to the infringement of the '426 patent.

123. Unless enjoined by this Court, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will infringe the '426 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, importing, and/or selling Mallinckrodt's Proposed Product in the United States.

124. Unless enjoined by this Court, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will induce infringement of the '426 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, importing, and/or selling Mallinckrodt's Proposed Product in the United States. On information and belief, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt

will intentionally encourage acts of direct infringement with knowledge of the '426 patent and knowledge that its acts are encouraging infringement.

125. Unless enjoined by this Court, upon FDA approval of Mallinckrodt's ANDA, Mallinckrodt will contributorily infringe the '426 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, importing, and/or selling Mallinckrodt's Proposed Product in the United States. On information and belief, Mallinckrodt has had and continues to have knowledge that Mallinckrodt's Proposed Product is especially adapted for a use that infringes the '426 patent and that there is no substantial non-infringing use for Mallinckrodt's Proposed Product.

126. Jazz Pharmaceuticals will be substantially and irreparably damaged and harmed if Mallinckrodt's infringement of the '426 patent is not enjoined.

127. Jazz Pharmaceuticals does not have an adequate remedy at law.

128. This case is an exceptional one, and Jazz Pharmaceuticals is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request the following relief:

(A) A Judgment be entered that Mallinckrodt has infringed the patents-in-suit by submitting ANDA No. 210936;

(B) A Judgment be entered that Mallinckrodt has infringed, and that Mallinckrodt's making, using, selling, offering to sell, or importing Mallinckrodt's Proposed Product will infringe one or more claims of the patents-in-suit;

(C) An Order that the effective date of FDA approval of ANDA No. 210936 be a date which is not earlier than the later of the expiration of the patents-in-suit, or any later expiration of exclusivity to which Plaintiffs are or become entitled;

(D) Preliminary and permanent injunctions enjoining Mallinckrodt and its officers, agents, attorneys and employees, and those acting in privity or concert with them, from making, using, selling, offering to sell, or importing Mallinckrodt's Proposed Product until after the expiration of the patents-in-suit, or any later expiration of exclusivity to which Plaintiffs are or become entitled;

(E) A permanent injunction be issued, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Mallinckrodt, its officers, agents, attorneys and employees, and those acting in privity or concert with them, from practicing any methods as claimed in the patents-in-suit, or from actively inducing or contributing to the infringement of any claim of the patents-in-suit, until after the expiration of the patents-in-suit, or any later expiration of exclusivity to which Plaintiffs are or become entitled;

(F) A Declaration that the commercial manufacture, use, sale, or offer for sale, or importation into the United States of Mallinckrodt's Proposed Product will directly infringe, induce and/or contribute to infringement of the patents-in-suit;

(G) To the extent that Mallinckrodt has committed any acts with respect to the methods claimed in the patents-in-suit, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), that Plaintiffs be awarded damages for such acts;

(H) If Mallinckrodt engages in the commercial manufacture, use, sale, or offer for sale, or importation into the United States of Mallinckrodt's Proposed Product prior to the expiration of the patents-in-suit, a Judgment awarding damages to Plaintiffs resulting from such infringement, together with interest;

(I) Attorneys' fees in this action as an exceptional case pursuant to 35 U.S.C. § 285;

(J) Costs and expenses in this action; and

(K) Such further and other relief as this Court may deem just and proper.

Dated: January 2, 2018

By: s/ Charles M. Lizza

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CERTIFICATION PURSUANT TO L. CIV. R. 11.2

I hereby certify that the matters captioned *Jazz Pharmaceuticals, Inc., et al. v. Amneal Pharmaceuticals, LLC, et al.*, Civil Action No. 13-391 (ES)(JAD), and *Jazz Pharmaceuticals, Inc., et al. v. Amneal Pharmaceuticals, LLC*, Civil Action No. 17-1440 (ES)(JAD) are related to the matter in controversy because the matter in controversy involves defendants who filed Abbreviated New Drug Applications seeking to market generic versions of the same drug product.

I further certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court or of any pending arbitration or administrative proceeding.

Dated: January 2, 2018

By: s/ Charles M. Lizza

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EXHIBIT A

US007668730B2

(12) **United States Patent**
Reardan et al.

(10) **Patent No.: US 7,668,730 B2**
(45) **Date of Patent: *Feb. 23, 2010**

(54) **SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD**

(75) Inventors: **Dayton T. Reardan**, Excelsior, MN (US); **Patti Engle**, Eagan, MN (US); **Bob Gagne**, St. Paul, MN (US)

(73) Assignee: **JPI Commercial, LLC.**, Palo Alto, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 446 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/322,348**

(22) Filed: **Dec. 17, 2002**

(65) **Prior Publication Data**

US 2004/0117205 A1 Jun. 17, 2004

(51) **Int. Cl.**
G06Q 10/00 (2006.01)

(52) **U.S. Cl.** **705/2**; 705/3; 600/300

(58) **Field of Classification Search** 705/2, 705/3; 600/300

See application file for complete search history.

(56) **References Cited**

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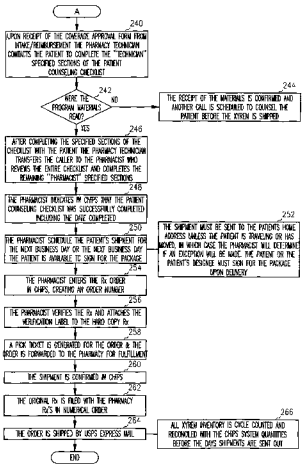
Primary Examiner—Gerald J. O'Connor
Assistant Examiner—Lena Najarian
(74) *Attorney, Agent, or Firm*—Schwegman, Lundberg & Woessner, P.A.

(57) **ABSTRACT**

A drug distribution system and method utilizes a central pharmacy and database to track all prescriptions for a sensitive drug. Information is kept in the database regarding all physicians allowed to prescribe the sensitive drug, and all patients receiving the drug. Abuses are identified by monitoring data in the database for prescription patterns by physicians and prescriptions obtained by patients. Further verification is made that the physician is eligible to prescribe the drug by consulting a separate database, and optionally whether any actions are taken against the physician. Multiple controls beyond those for normal drugs are imposed on the distribution depending on the sensitivity of the drug.

11 Claims, 16 Drawing Sheets



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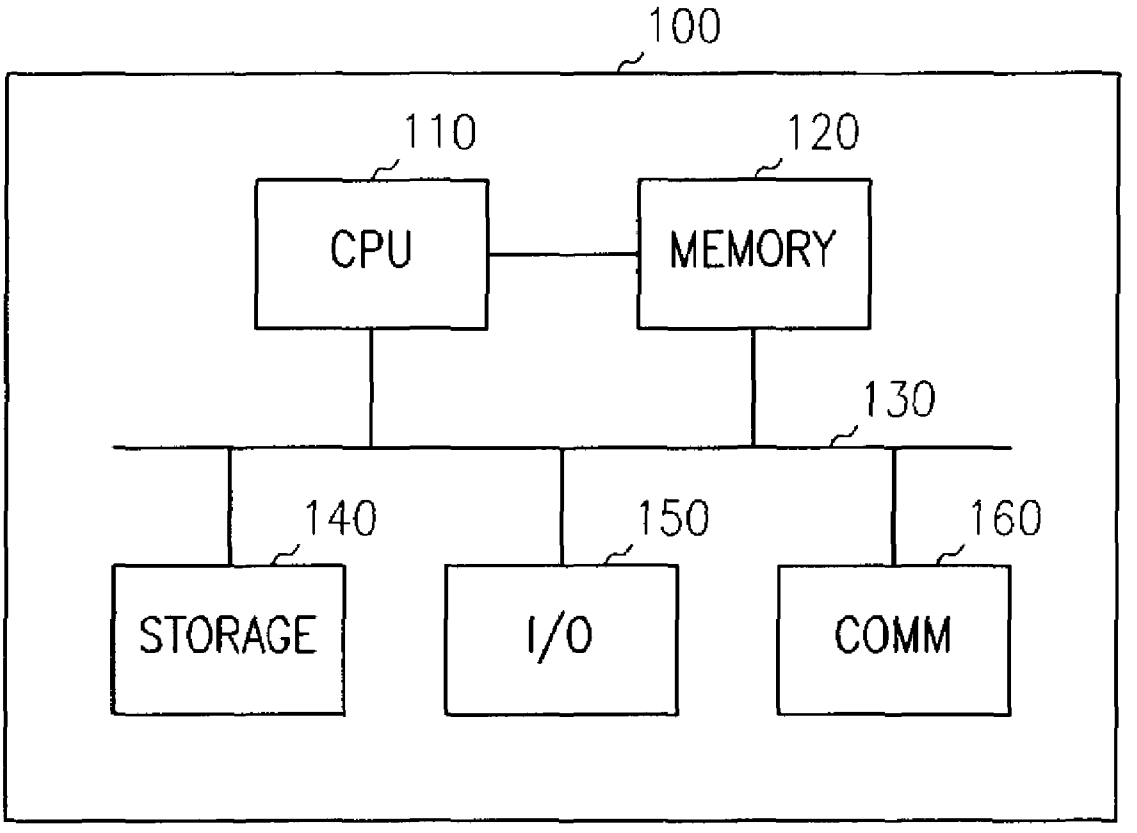

FIG. 1

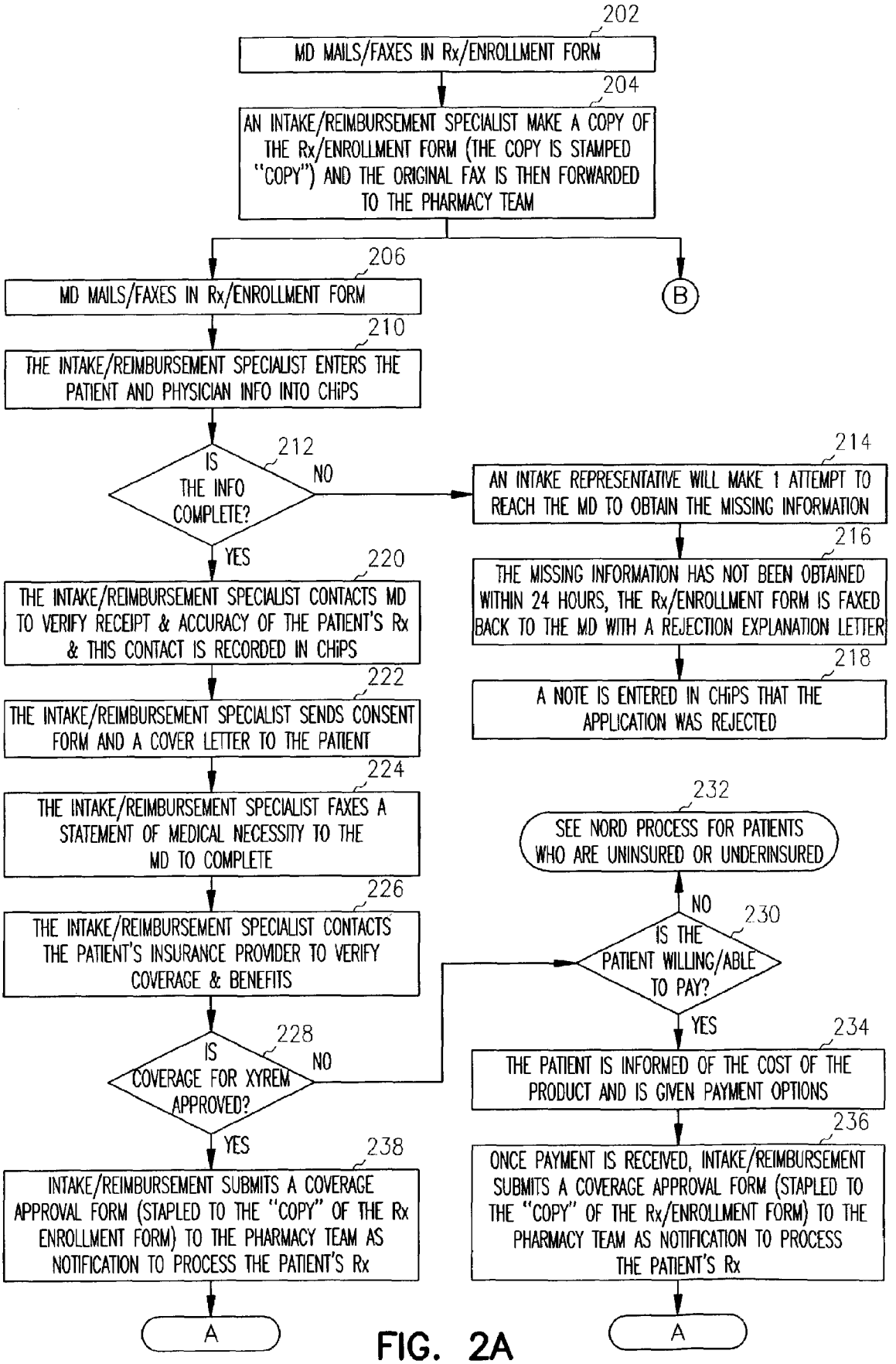
202
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
204
AN INTAKE/REIMBURSEMENT SPECIALIST MAKE A COPY OF THE Rx/ENROLLMENT FORM (THE COPY IS STAMPED "COPY") AND THE ORIGINAL FAX IS THEN FORWARDED TO THE PHARMACY TEAM
206
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
B
210
THE INTAKE/REIMBURSEMENT SPECIALIST ENTERS THE PATIENT AND PHYSICIAN INFO INTO CHiPS
212
IS THE INFO COMPLETE?
NO
214
AN INTAKE REPRESENTATIVE WILL MAKE 1 ATTEMPT TO REACH THE MD TO OBTAIN THE MISSING INFORMATION
216
THE MISSING INFORMATION HAS NOT BEEN OBTAINED WITHIN 24 HOURS, THE Rx/ENROLLMENT FORM IS FAXED BACK TO THE MD WITH A REJECTION EXPLANATION LETTER
218
A NOTE IS ENTERED IN CHiPS THAT THE APPLICATION WAS REJECTED
YES
220
THE INTAKE/REIMBURSEMENT SPECIALIST CONTACTS MD TO VERIFY RECEIPT & ACCURACY OF THE PATIENT'S Rx & THIS CONTACT IS RECORDED IN CHiPS
222
THE INTAKE/REIMBURSEMENT SPECIALIST SENDS CONSENT FORM AND A COVER LETTER TO THE PATIENT
224
THE INTAKE/REIMBURSEMENT SPECIALIST FAXES A STATEMENT OF MEDICAL NECESSITY TO THE MD TO COMPLETE
226
THE INTAKE/REIMBURSEMENT SPECIALIST CONTACTS THE PATIENT'S INSURANCE PROVIDER TO VERIFY COVERAGE & BENEFITS
228
IS COVERAGE FOR XYREM APPROVED?
NO
232
SEE NORD PROCESS FOR PATIENTS WHO ARE UNINSURED OR UNDERINSURED
NO
230
IS THE PATIENT WILLING/ABLE TO PAY?
YES
234
THE PATIENT IS INFORMED OF THE COST OF THE PRODUCT AND IS GIVEN PAYMENT OPTIONS
236
ONCE PAYMENT IS RECEIVED, INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM (STAPLED TO THE "COPY" OF THE Rx/ENROLLMENT FORM) TO THE PHARMACY TEAM AS NOTIFICATION TO PROCESS THE PATIENT'S Rx
YES
238
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM (STAPLED TO THE "COPY" OF THE Rx ENROLLMENT FORM) TO THE PHARMACY TEAM AS NOTIFICATION TO PROCESS THE PATIENT'S Rx
A
A

FIG. 2A

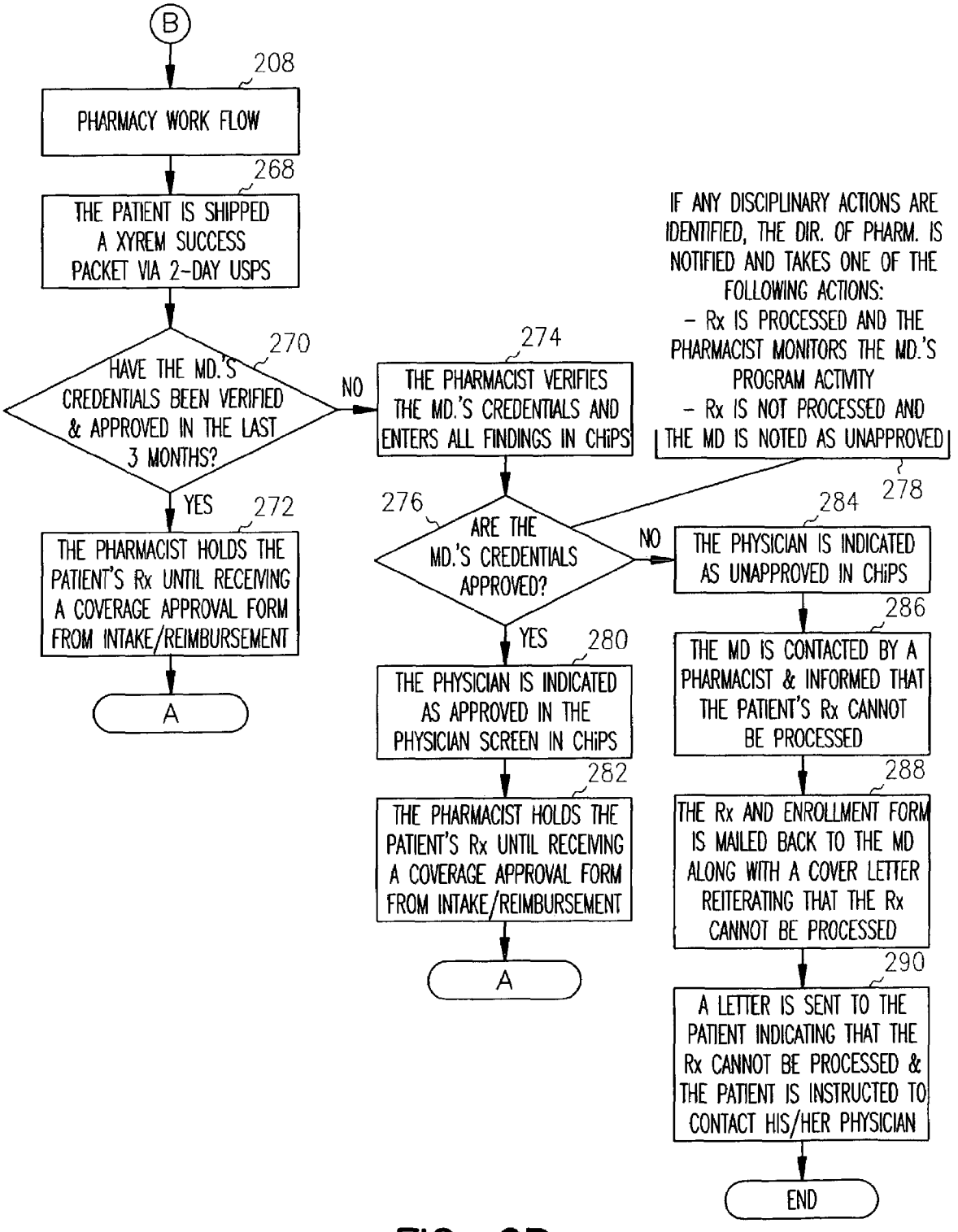
B
208
PHARMACY WORK FLOW
268
THE PATIENT IS SHIPPED A XYREM SUCCESS PACKET VIA 2-DAY USPS
270
HAVE THE MD.'S CREDENTIALS BEEN VERIFIED & APPROVED IN THE LAST 3 MONTHS?
NO
YES
272
THE PHARMACIST HOLDS THE PATIENT'S Rx UNTIL RECEIVING A COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT
A
274
THE PHARMACIST VERIFIES THE MD.'S CREDENTIALS AND ENTERS ALL FINDINGS IN CHiPS
276
ARE THE MD.'S CREDENTIALS APPROVED?
NO
YES
280
THE PHYSICIAN IS INDICATED AS APPROVED IN THE PHYSICIAN SCREEN IN CHiPS
282
THE PHARMACIST HOLDS THE PATIENT'S Rx UNTIL RECEIVING A COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT
A
IF ANY DISCIPLINARY ACTIONS ARE IDENTIFIED, THE DIR. OF PHARM. IS NOTIFIED AND TAKES ONE OF THE FOLLOWING ACTIONS:
- Rx IS PROCESSED AND THE PHARMACIST MONITORS THE MD.'S PROGRAM ACTIVITY
- Rx IS NOT PROCESSED AND THE MD IS NOTED AS UNAPPROVED
278
284
THE PHYSICIAN IS INDICATED AS UNAPPROVED IN CHiPS
286
THE MD IS CONTACTED BY A PHARMACIST & INFORMED THAT THE PATIENT'S Rx CANNOT BE PROCESSED
288
THE Rx AND ENROLLMENT FORM IS MAILED BACK TO THE MD ALONG WITH A COVER LETTER REITERATING THAT THE Rx CANNOT BE PROCESSED
290
A LETTER IS SENT TO THE PATIENT INDICATING THAT THE Rx CANNOT BE PROCESSED & THE PATIENT IS INSTRUCTED TO CONTACT HIS/HER PHYSICIAN
END

FIG. 2B

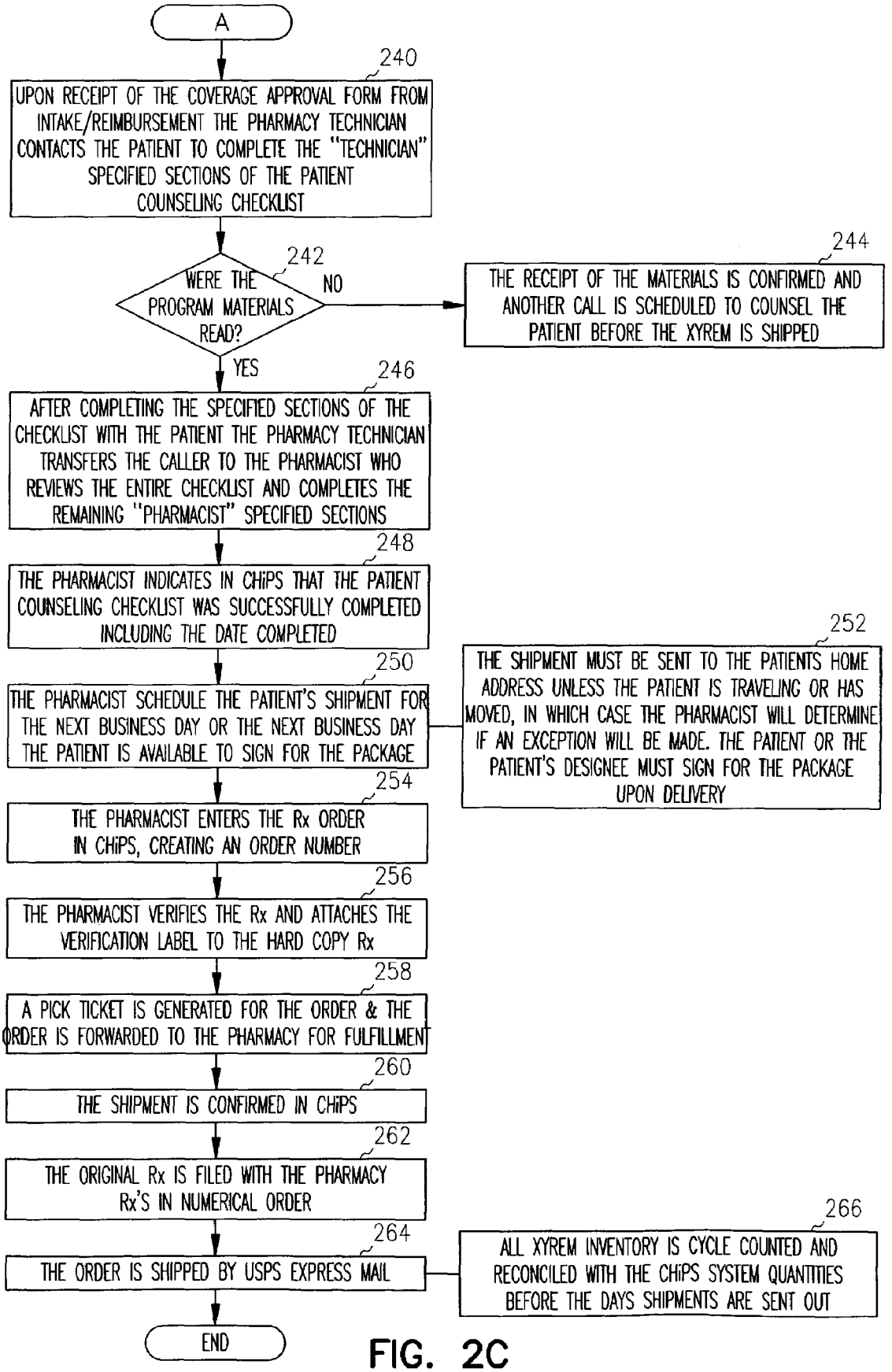
A
240
UPON RECEIPT OF THE COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE THE "TECHNICIAN" SPECIFIED SECTIONS OF THE PATIENT COUNSELING CHECKLIST
242
WERE THE PROGRAM MATERIALS READ?
NO
244
THE RECEIPT OF THE MATERIALS IS CONFIRMED AND ANOTHER CALL IS SCHEDULED TO COUNSEL THE PATIENT BEFORE THE XYREM IS SHIPPED
YES
246
AFTER COMPLETING THE SPECIFIED SECTIONS OF THE CHECKLIST WITH THE PATIENT THE PHARMACY TECHNICIAN TRANSFERS THE CALLER TO THE PHARMACIST WHO REVIEWS THE ENTIRE CHECKLIST AND COMPLETES THE REMAINING "PHARMACIST" SPECIFIED SECTIONS
248
THE PHARMACIST INDICATES IN CHIPS THAT THE PATIENT COUNSELING CHECKLIST WAS SUCCESSFULLY COMPLETED INCLUDING THE DATE COMPLETED
252
THE SHIPMENT MUST BE SENT TO THE PATIENTS HOME ADDRESS UNLESS THE PATIENT IS TRAVELING OR HAS MOVED, IN WHICH CASE THE PHARMACIST WILL DETERMINE IF AN EXCEPTION WILL BE MADE. THE PATIENT OR THE PATIENT'S DESIGNEE MUST SIGN FOR THE PACKAGE UPON DELIVERY
250
THE PHARMACIST SCHEDULE THE PATIENT'S SHIPMENT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
254
THE PHARMACIST ENTERS THE Rx ORDER IN CHIPS, CREATING AN ORDER NUMBER
256
THE PHARMACIST VERIFIES THE Rx AND ATTACHES THE VERIFICATION LABEL TO THE HARD COPY Rx
258
A PICK TICKET IS GENERATED FOR THE ORDER & THE ORDER IS FORWARDED TO THE PHARMACY FOR FULFILLMENT
260
THE SHIPMENT IS CONFIRMED IN CHIPS
262
THE ORIGINAL Rx IS FILED WITH THE PHARMACY Rx'S IN NUMERICAL ORDER
266
ALL XYREM INVENTORY IS CYCLE COUNTED AND RECONCILED WITH THE CHIPS SYSTEM QUANTITIES BEFORE THE DAYS SHIPMENTS ARE SENT OUT
264
THE ORDER IS SHIPPED BY USPS EXPRESS MAIL
END

FIG. 2C

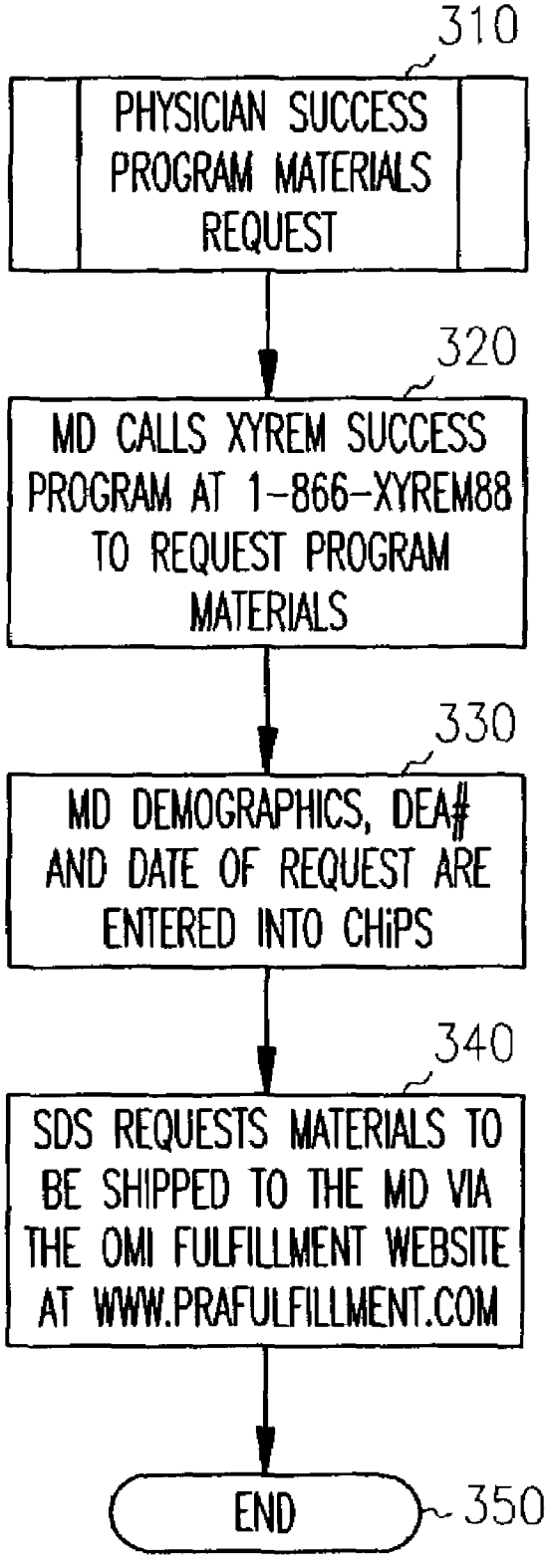
310
PHYSICIAN SUCCESS PROGRAM MATERIALS REQUEST
320
MD CALLS XYREM SUCCESS PROGRAM AT 1-866-XYREM88 TO REQUEST PROGRAM MATERIALS
330
MD DEMOGRAPHICS, DEA# AND DATE OF REQUEST ARE ENTERED INTO CHiPS
340
SDS REQUESTS MATERIALS TO BE SHIPPED TO THE MD VIA THE OMI FULFILLMENT WEBSITE AT WWW.PRAFULFILLMENT.COM
END
350

FIG. 3

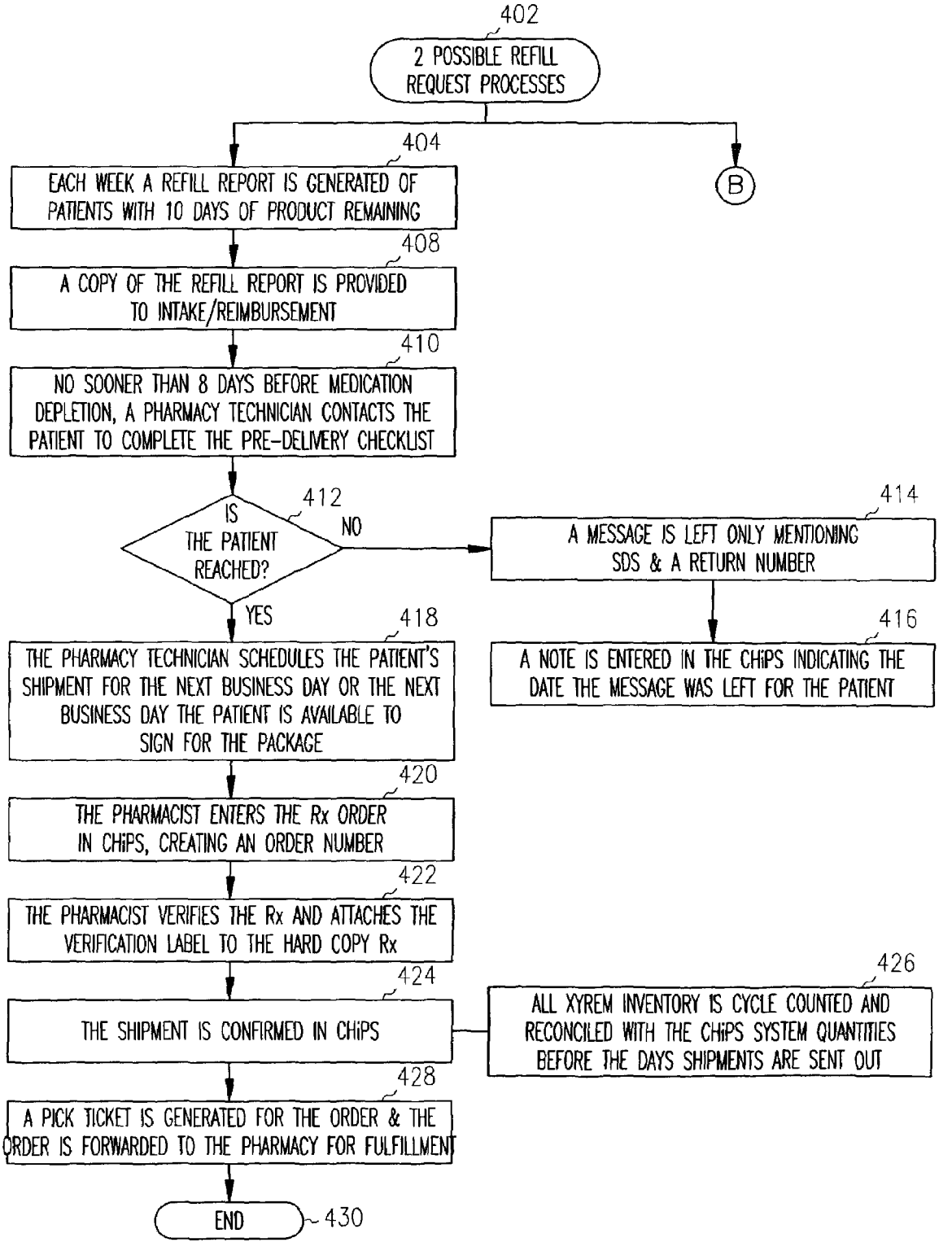
402
2 POSSIBLE REFILL REQUEST PROCESSES
404
EACH WEEK A REFILL REPORT IS GENERATED OF PATIENTS WITH 10 DAYS OF PRODUCT REMAINING
B
408
A COPY OF THE REFILL REPORT IS PROVIDED TO INTAKE/REIMBURSEMENT
410
NO SOONER THAN 8 DAYS BEFORE MEDICATION DEPLETION, A PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE THE PRE-DELIVERY CHECKLIST
412
IS THE PATIENT REACHED?
NO
414
A MESSAGE IS LEFT ONLY MENTIONING SDS & A RETURN NUMBER
YES
418
THE PHARMACY TECHNICIAN SCHEDULES THE PATIENT'S SHIPMENT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
416
A NOTE IS ENTERED IN THE CHIPS INDICATING THE DATE THE MESSAGE WAS LEFT FOR THE PATIENT
420
THE PHARMACIST ENTERS THE Rx ORDER IN CHIPS, CREATING AN ORDER NUMBER
422
THE PHARMACIST VERIFIES THE Rx AND ATTACHES THE VERIFICATION LABEL TO THE HARD COPY Rx
424
THE SHIPMENT IS CONFIRMED IN CHIPS
426
ALL XYREM INVENTORY IS CYCLE COUNTED AND RECONCILED WITH THE CHIPS SYSTEM QUANTITIES BEFORE THE DAYS SHIPMENTS ARE SENT OUT
428
A PICK TICKET IS GENERATED FOR THE ORDER & THE ORDER IS FORWARDED TO THE PHARMACY FOR FULFILLMENT
END
430

FIG. 4A

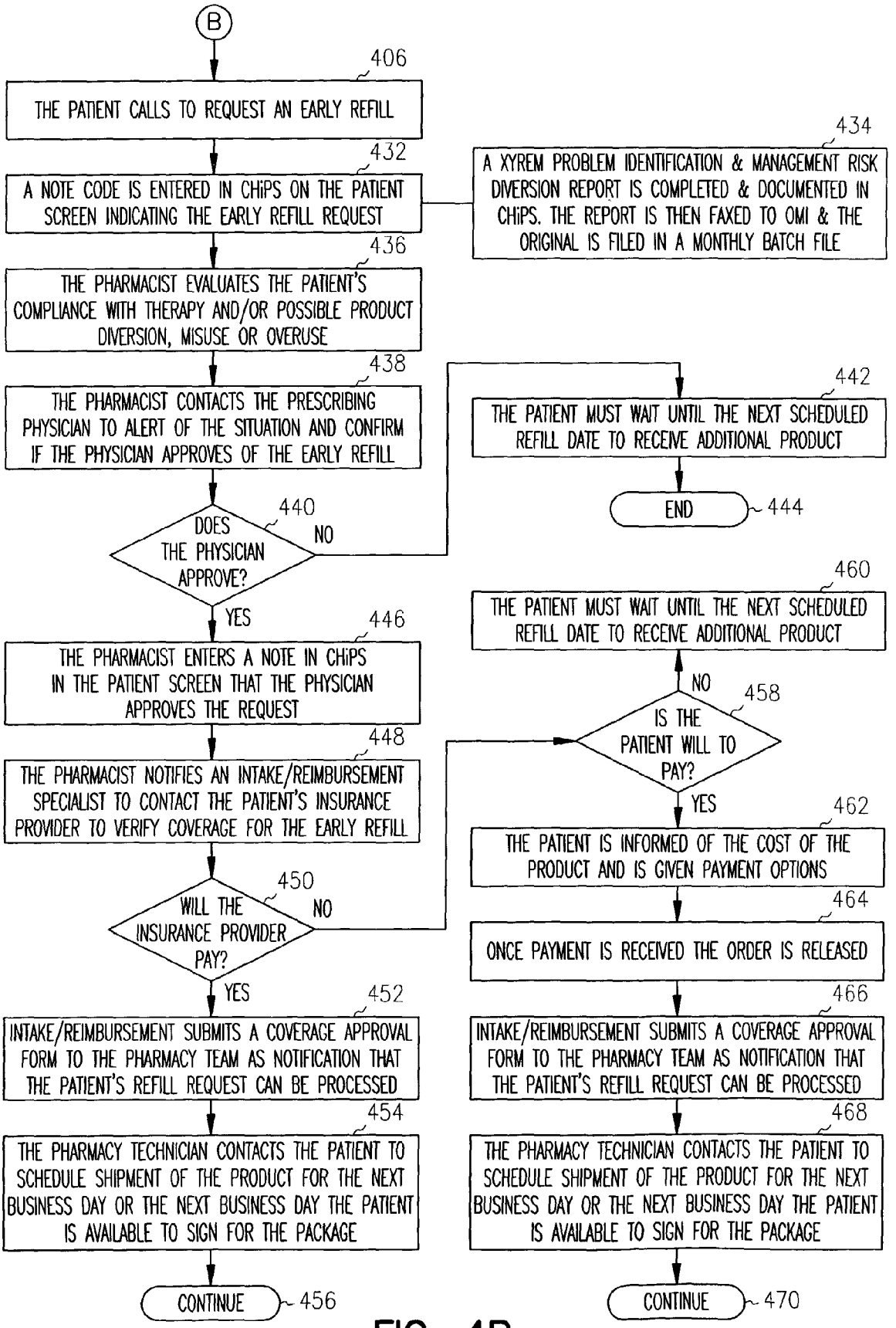
B
406
THE PATIENT CALLS TO REQUEST AN EARLY REFILL
432
A NOTE CODE IS ENTERED IN CHiPS ON THE PATIENT SCREEN INDICATING THE EARLY REFILL REQUEST
434
A XYREM PROBLEM IDENTIFICATION & MANAGEMENT RISK DIVERSION REPORT IS COMPLETED & DOCUMENTED IN CHiPS. THE REPORT IS THEN FAXED TO OMI & THE ORIGINAL IS FILED IN A MONTHLY BATCH FILE
436
THE PHARMACIST EVALUATES THE PATIENT'S COMPLIANCE WITH THERAPY AND/OR POSSIBLE PRODUCT DIVERSION, MISUSE OR OVERUSE
438
THE PHARMACIST CONTACTS THE PRESCRIBING PHYSICIAN TO ALERT OF THE SITUATION AND CONFIRM IF THE PHYSICIAN APPROVES OF THE EARLY REFILL
440
DOES THE PHYSICIAN APPROVE?
NO
442
THE PATIENT MUST WAIT UNTIL THE NEXT SCHEDULED REFILL DATE TO RECEIVE ADDITIONAL PRODUCT
END
444
YES
446
THE PHARMACIST ENTERS A NOTE IN CHiPS IN THE PATIENT SCREEN THAT THE PHYSICIAN APPROVES THE REQUEST
448
THE PHARMACIST NOTIFIES AN INTAKE/REIMBURSEMENT SPECIALIST TO CONTACT THE PATIENT'S INSURANCE PROVIDER TO VERIFY COVERAGE FOR THE EARLY REFILL
450
WILL THE INSURANCE PROVIDER PAY?
NO
460
THE PATIENT MUST WAIT UNTIL THE NEXT SCHEDULED REFILL DATE TO RECEIVE ADDITIONAL PRODUCT
458
IS THE PATIENT WILL TO PAY?
NO
YES
462
THE PATIENT IS INFORMED OF THE COST OF THE PRODUCT AND IS GIVEN PAYMENT OPTIONS
464
ONCE PAYMENT IS RECEIVED THE ORDER IS RELEASED
YES
452
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT'S REFILL REQUEST CAN BE PROCESSED
466
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT'S REFILL REQUEST CAN BE PROCESSED
454
THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO SCHEDULE SHIPMENT OF THE PRODUCT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
468
THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO SCHEDULE SHIPMENT OF THE PRODUCT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
CONTINUE
456
CONTINUE
470

FIG. 4B

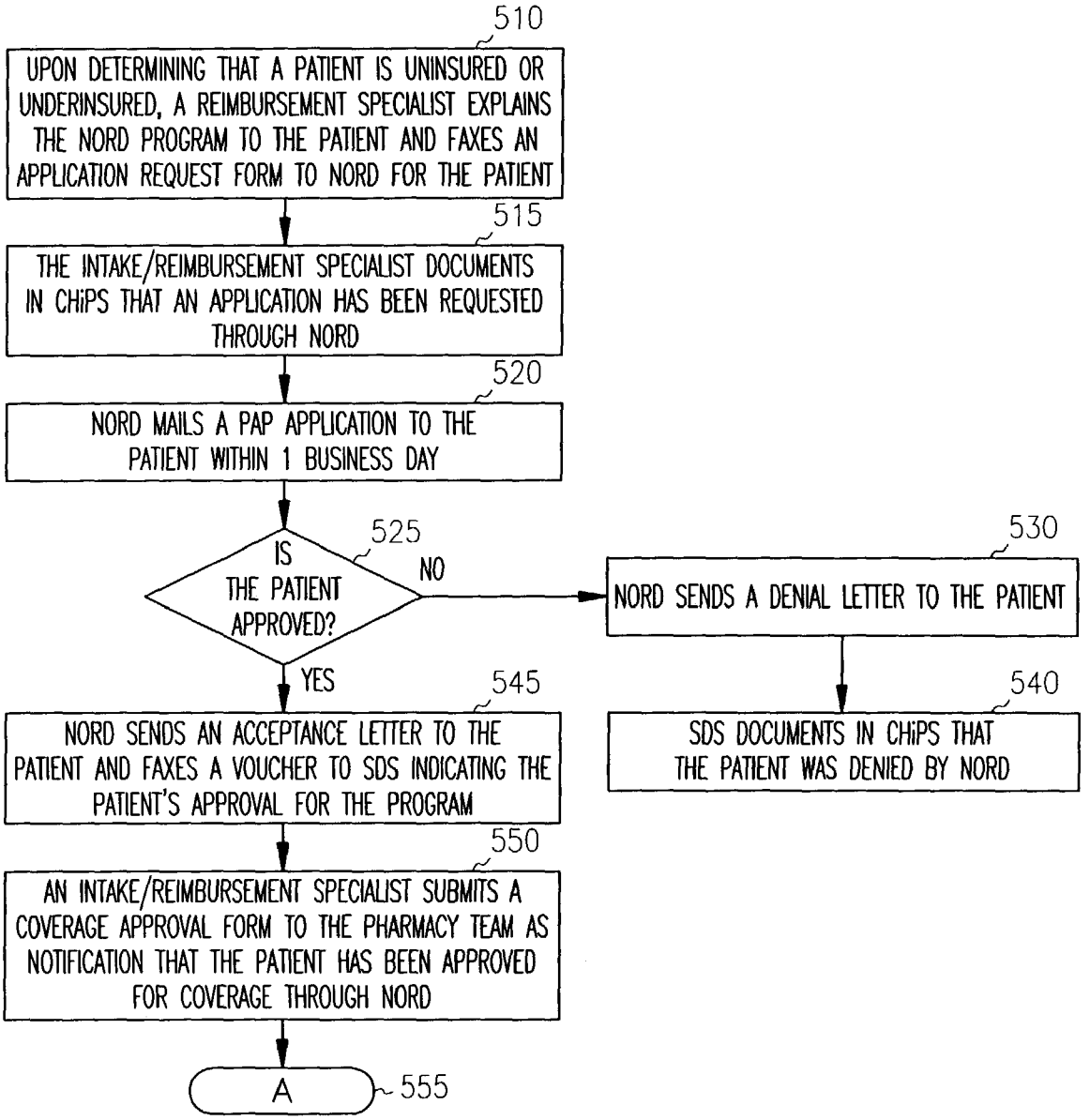
510
UPON DETERMINING THAT A PATIENT IS UNINSURED OR UNDERINSURED, A REIMBURSEMENT SPECIALIST EXPLAINS THE NORD PROGRAM TO THE PATIENT AND FAXES AN APPLICATION REQUEST FORM TO NORD FOR THE PATIENT
515
THE INTAKE/REIMBURSEMENT SPECIALIST DOCUMENTS IN CHiPS THAT AN APPLICATION HAS BEEN REQUESTED THROUGH NORD
520
NORD MAILS A PAP APPLICATION TO THE PATIENT WITHIN 1 BUSINESS DAY
525
IS THE PATIENT APPROVED?
NO
530
NORD SENDS A DENIAL LETTER TO THE PATIENT
YES
545
NORD SENDS AN ACCEPTANCE LETTER TO THE PATIENT AND FAXES A VOUCHER TO SDS INDICATING THE PATIENT'S APPROVAL FOR THE PROGRAM
540
SDS DOCUMENTS IN CHiPS THAT THE PATIENT WAS DENIED BY NORD
550
AN INTAKE/REIMBURSEMENT SPECIALIST SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT HAS BEEN APPROVED FOR COVERAGE THROUGH NORD
A
555

FIG. 5

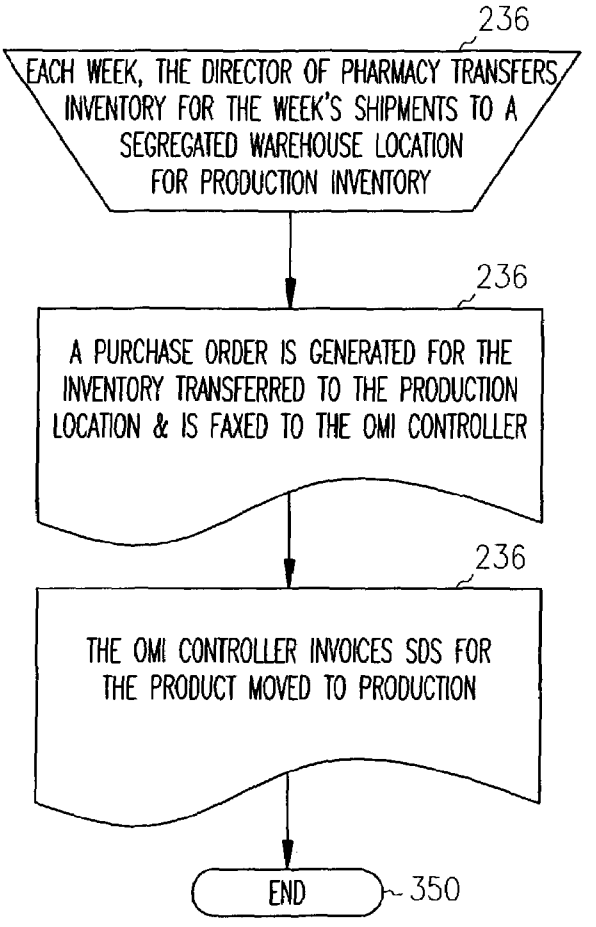

FIG. 6

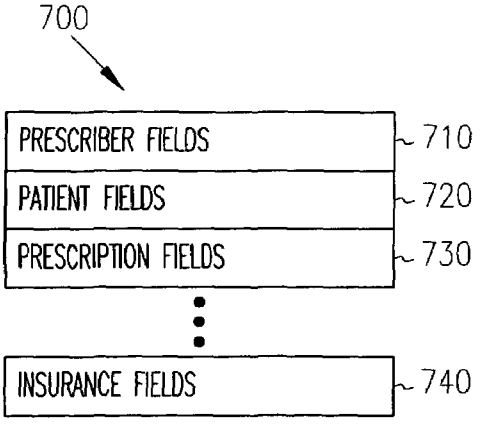

FIG. 7

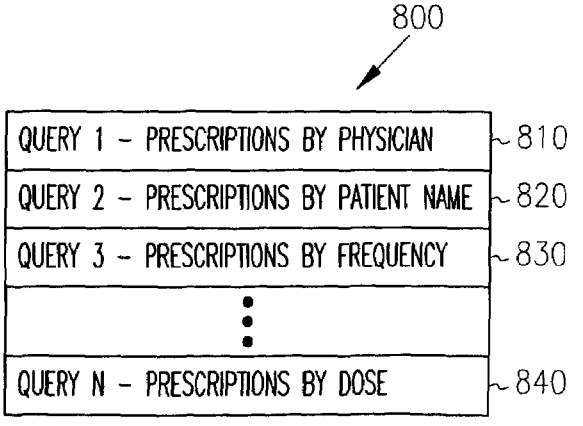

FIG. 8

900

PRESCRIPTION AND ENROLLMENT FORM

PRESCRIBER INFORMATION

PRESCRIBER'S NAME: _____ OFFICE CONTACT: _____
STREET ADDRESS: _____
CITY: _____ STATE: _____ ZIP: _____
PHONE: _____ FAX: _____
LICENSE NUMBER: _____ DEA NUMBER: _____
MD SPECIALTY: _____

PRESCRIPTION FORM

PATIENT NAME: _____ SS#: _____ DOB: _____ SEX M / F
ADDRESS: _____
CITY: _____ STATE: _____ ZIP: _____
Rx: XYREM ORAL SOLUTION (500 mg/mL) 180 ML BOTTLE QUANTITY: _____ MONTHS SUPPLY
SIG: TAKE _____ GMS P.O. DILUTED IN 60 mL WATER AT H.S. AND THEN AGAIN 2 1/2 TO 4 HOURS LATER
REFILLS (CIRCLE ONE): 0 1 2 (MAXIMUM OF 3 MONTH SUPPLY)
_____ DATE: ____/____/____
PRESCRIBER'S SIGNATURE

PHYSICIAN DECLARATION–PLEASE CHECK EACH BOX | TO BE COMPLETED AT INITIAL PRESCRIPTION ONLY

☐ I HAVE READ THE MATERIALS IN THE XYREM PHYSICIAN SUCCESS PROGRAM
☐ I VERIFY THAT THE PATIENT HAS BEEN EDUCATED WITH RESPECT TO XYREM PREPARATION, DOSING AND SCHEDULING.
☐ I UNDERSTAND THAT XYREM IS APPROVED FOR THE TREATMENT OF CATAPLEXY IN PATIENTS WITH NARCOLEPSY, AND THAT SAFETY OR EFFICACY HAS NOT BEEN ESTABLISHED FOR ANY OTHER INDICATION.
☐ I UNDERSTAND THAT THE SAFETY OF DOSES GREATER THAN 9gm/DAY HAS NOT BEEN ESTABLISHED

PATIENT INFORMATION

BEST TIME TO CONTACT PATIENT: ☐ DAY ☐ NIGHT
DAY #: _____ EVENING #: _____
INSURANCE COMPANY NAME: _____ PHONE #: _____
INSURED'S NAME: _____ RELATIONSHIP TO PATIENT: _____
IDENTIFICATION NUMBER: _____ POLICY/GROUP NUMBER: _____
PRESCRIPTION CARD: ☐ NO ☐ YES IF YES, CARRIER: _____ POLICY #: _____ GROUP: _____

PLEASE ATTACH COPIES OF PATIENT'S INSURANCE CARDS

FAX COMPLETED FORM TO XYREM SUCCESS PROGRAM (TOLL-FREE) 1-866-470-1744
FOR INFORMATION, CALL THE XYREM TEAM (TOLL FREE) AT 1-866-XYREM88 (1-866-997-3688)

FIG. 9

PATIENT ASSISTANCE APPLICATION REQUEST FORM

DATE:

TO: PATIENT ASSISTANCE ORGANIZATION
FROM: SDS

FAX #: 203-798-2291

PLEASE SEND A XYREM PATIENT ASSISTANCE PROGRAM APPLICATION TO:

PATIENT NAME _____

ADDRESS _____

_____

_____

TELEPHONE: ( ) _____

PATIENT DOSAGE: _____ (GRAMS) TWICE NIGHTLY FOR A TOTAL DOSAGE OF _____ (GRAMS)

_____ BOTTLES (THREE MONTHS SUPPLY)

BACKGROUND INFORMATION:

_____

_____

_____

_____

_____

_____

FIG. 10

1100

SENSITIVE DRUG PATIENT ASSISTANCE PROGRAM

VOUCHER REQUEST FOR MEDICATION

PATIENT INFORMATION
<FIRST NAME><LAST NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890
DOB: 01/01/1900
SSN: 123-45-6789
DRUG ALLOTMENT: 100%
LRD: 03/01/2001

PHYSICIAN INFORMATION
<PHYSICIAN NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890

CASE CODE: ********

FIRST SHIPMENT THIS YEAR

DRUG	QUANTITY
XYREEM 180ml btl	1

VALIDATION DATE:	03/01/2001
EXPIRATION DATE:	05/31/2001
ISSUE DATE:	03/15/2001

APPROVED _____

PHARMACY USE

NORD COPY

****

(DETACH HERE)

PATIENT INFORMATION
<FIRST NAME><LAST NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890
DOB: 01/01/1900
SSN: 123-45-6789
DRUG ALLOTMENT: 100%
LRD: 03/01/2001

PHYSICIAN INFORMATION
<PHYSICIAN NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890

CASE CODE: ********

FIRST SHIPMENT THIS YEAR

DRUG	QUANTITY
XYREM 180ml btl	1

VALIDATION DATE:	03/01/2001
EXPIRATION DATE:	05/31/2001
ISSUE DATE:	03/15/2001

APPROVED _____

PHARMACY USE

FIG. 11

SENSITIVE DRUG PHYSICIAN'S CERTIFICATE OF MEDICAL NEED

PATIENT INFORMATION

DATE: _____

NAME: _____
LAST FIRST M

DATE OF BIRTH: _____

DRUG BEING PRESCRIBED: XYREM

DIAGNOSIS/CONDITION FOR WHICH DRUG IS BEING PRESCRIBED: _____

ICD-9: _____

PHYSICIAN INFORMATION

PHYSICIAN'S NAME (PLEASE PRINT): _____

PHYSICIAN'S SIGNATURE: _____ DATE: _____

PLEASE FAX BACK TO SENSITIVE DRUG SUCCESS PROGRAM: (1-800-TOLL FREE NUMBER)

FIG. 12

ACTIVITY REPORTS

	REPORT FREQUENCY		
	WEEKLY	MONTHLY	QUARTERLY
SALES			
Rx BY ZIP (NEW AND TOTAL)	X	X	X
Rx BY PHYSICIAN BY ZIP	X	X	
$ BY ZIP	X	X	X
REGULATORY			
# OF PHYSICIAN REGISTRIES		X	
# OF DENIED PHYSICIAN REGISTRIES AND REASON		X	
# OF COMPLETED PATIENT REGISTRIES		X	
# OF PROBLEM IDENTIFICATION & MANAGEMENT RISK DIVERSION REPORTS COMPLETED	X		
# OF CYCLE COUNTS PERFORMED & ACCURACY OF EACH		X	
QUALITY ASSURANCE			
# OF PRODUCT DEFECTS/COMPLAINTS REPORTED, TYPE AND LOT #		X	
CALL CENTER			
# OF CALLS RECEIVED		X	
# OF CALLS INITIATED		X	
# OF CALLS ANSWERED IN 30 SECONDS, ETC.		X	
PERCENTAGE OF CALLS ANSWERED IN 30 SECONDS		X	
# OF ABANDONED CALLS		X	
% OF ABANDONED CALLS		X	
AVERAGE CALL LENGTH		X	
PHARMACY			
# OF FAXED Rx/ENROLLMENT FORMS		X	
# OF MAILED Rx/ENROLLEMENT FORMS		X	
# OF RxS SHIPPED W/IN 1, 2, 3, 4 ETC. DAYS (FROM THE TIME INITIAL RECEIPT TO SHIPMENT OF Rx)		X	
# OF PATIENT SUCCESS PACKETS SHIPPED		X	

FIG. 13A

ACTIVITY REPORTS

PHARMACY		X	
# OF PHYSICIAN SUCCESS PACKETS SHIPPED		X	
# OF COMPLETED SHIPMENTS		X	
# OF INCOMPLETE SHIPMENTS AND REASON		X	
# OF SHIPPING ERRORS		X	
# OF PAP SHIPMENTS		X	
# OF PAP APPLICATIONS		X	
# OF PAP APPROVALS		X	
# OF CANCELED ORDERS		X	
# OF USPS ERRORS		X	
INVENTORY		X	
# OF RETURNED PRODUCTS AND REASON		X	
# OF OUTDATED BOTTLES OF PRODUCT		X	
INVENTORY COUNTS OF CONSIGNMENT & PRODUCTION INVENTORY		X	
# OF UNITS RECEIVED		X	
LOTS RECEIVED		X	
REIMBURSEMENT		X	
# OF PENDED AND WHY		X	
# OF APPROVALS		X	
# OF DENIALS		X	
# OF REJECTIONS		X	
PAYOR TYPES		X	

FIG. 13B

ACTIVITY REPORTS

PATIENT CARE		X	
# OF ADVERSE EVENTS REPORTED AND TYPE		X	
# OF ADVERSE EVENTS SENT TO OMI		X	
# OF DOSING PROBLEMS AND TYPE		X	
# OF NONCOMPLIANCE EPISODES AND REASON		X	
# OF PATIENT COUNSELED AND REASON		X	
# OF PATIENTS DISCONTINUED AND REASON		X	
PATIENT CARE		X	
# OF PATIENTS REFERRED TO PHYSICIAN AND REASON		X	
# OF ACTIVE PATIENTS		X	
# OF NEW PATIENTS		X	
# OF RESTART PATIENTS		X	
# OF DISCONTINUED PATIENTS AND REASON		X	
DRUG INFORMATION		X	
# OF DRUG INFORMATION REQUESTS AND TYPE		X	
# OF CALLS TRIAGED TO OMI		X	

FIG. 13C

SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

FIELD OF THE INVENTION

The present invention relates to distribution of drugs, and in particular to the distribution of sensitive drugs.

BACKGROUND OF THE INVENTION

Sensitive drugs are controlled to minimize risk and ensure that they are not abused, or cause adverse reactions. Such sensitive drugs are approved for specific uses by the Food and Drug Administration, and must be prescribed by a licensed physician in order to be purchased by consumers. Some drugs, such as cocaine and other common street drugs are the object of abuse and illegal schemes to distribute for profit. Some schemes include Dr. shopping, diversion, and pharmacy thefts. A locked cabinet or safe is a requirement for distribution of some drugs.

Certain agents, such as gamma hydroxy buterate (GHB) are also abused, yet also are effective for therapeutic purposes such as treatment of daytime cataplexy in patients with narcolepsy. Some patients however, will obtain prescriptions from multiple doctors, and have them filled at different pharmacies. Still further, an unscrupulous physician may actually write multiple prescriptions for a patient, or multiple patients, who use cash to pay for the drugs. These patients will then sell the drug to dealers or others for profit.

There is a need for a distribution system and method that directly addresses these abuses. There is a further need for such a system and method that provides education and limits the potential for such abuse.

SUMMARY OF THE INVENTION

A drug distribution system and method utilizes a central pharmacy and database to track all prescriptions for a sensitive drug. Information is kept in a central database regarding all physicians allowed to prescribe the sensitive drug, and all patients receiving the drug. Abuses are identified by monitoring data in the database for prescription patterns by physicians and prescriptions obtained by patients. Further verification is made that the physician is eligible to prescribe the drug by consulting a separate database for a valid DEA license, and optionally state medical boards to determine whether any corrective or approved disciplinary actions relating to controlled substances have been brought against the physician. Multiple controls beyond those for traditional drugs are imposed on the distribution depending on the sensitivity of the drug.

Education is provided to both physician and patient. Prior to shipping the drug for the first time, the patient is contacted to ensure that product and abuse related educational materials have been received and/or read. The patient may provide the name of a designee to the central pharmacy who is authorized to accept shipment of the drug. Receipt of the initial drug shipment is confirmed by contacting the patient. Either a phone call or other communication to the patient within a set time after delivery may be made to ensure receipt. Further, a courier service's tracking system is used to confirm delivery in further embodiments. If a shipment is lost, an investigation is launched to find it.

In one embodiment, the drug may be shipped by the central pharmacy to another pharmacy for patient pick-up. The second pharmacy's ability to protect against diversion before shipping the drug must be confirmed. This ability may be checked through NTIS and State Boards of Pharmacy.

Prescription refills are permitted in the number specified in the original prescription. In addition, if a prescription refill is requested by the patient prior to the anticipated due date, such refills will be questioned. A lost, stolen, destroyed or spilled prescription/supply is documented and replaced to the extent necessary to honor the prescription, and will also cause a review or full investigation.

The exclusive central database contains all relevant data related to distribution of the drug and process of distributing it, including patient, physician and prescription information. Several queries and reports are run against the database to provide information which might reveal potential abuse of the sensitive drug, such as early refills.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a block diagram of a computer system for use in implementing the system and method of the present invention.

FIGS. **2**A, **2**B and **2**C are a flowchart describing a method for sensitive drug distribution at least partially utilizing a computer system such as that shown in FIG. **1**.

FIG. **3** is a flowchart of a physician success program at least partially implemented on a computer system such as that shown in FIG. **1**.

FIGS. **4**A and **4**B are a flowchart describing a method for handling refill requests at least partially utilizing a computer system such as that shown in FIG. **1**.

FIG. **5** is a flowchart of a process for requesting special reimbursement when a patient is uninsured or underinsured at least partially utilizing a computer system as that shown in FIG. **1**.

FIG. **6** is a flowchart of a process for inventory control at least partially utilizing a computer system such as that shown in FIG. **1**.

FIG. **7** is a block diagram of database fields.

FIG. **8** is a block diagram showing a list of queries against the database fields.

FIG. **9** is a copy of one example prescription and enrollment form.

FIG. **10** is a copy of one example of a NORD application request form for patient financial assistance.

FIG. **11** is a copy of one example voucher request for medication for use with the NORD application request form of FIG. **10**.

FIG. **12** is a copy of certificate of medical need.

FIGS. **13**A, **13**B and **13**C are descriptions of sample reports obtained by querying a central database having fields represented in FIG. **7**.

DETAILED DESCRIPTION OF THE INVENTION

In the following description, reference is made to the accompanying drawings that form a part hereof, and in which is shown by way of illustration specific embodiments in which the invention may be practiced. These embodiments are described in sufficient detail to enable those skilled in the art to practice the invention, and it is to be understood that other embodiments may be utilized and that structural, logical and electrical changes may be made without departing from the scope of the present invention. The following description is, therefore, not to be taken in a limited sense, and the scope of the present invention is defined by the appended claims.

The functions or algorithms described herein are implemented in software or a combination of software and human

implemented procedures in one embodiment. The software comprises computer executable instructions stored on computer readable media such as memory or other type of storage devices. The term "computer readable media" is also used to represent carrier waves on which the software is transmitted. Further, such functions correspond to modules, which are software, hardware, firmware of any combination thereof. Multiple functions are performed in one or more modules as desired, and the embodiments described are merely examples. The software is executed on a digital signal processor, ASIC, microprocessor, or other type of processor operating on a computer system, such as a personal computer, server or other computer system.

A sensitive drug is one which can be abused, or has addiction properties or other properties that render the drug sensitive. One example of such a drug is sodium oxybate, also known as gamma hydroxy butyrate (GHB $C_4H_7NaO_3$) which is useful for treatment of cataplexy in patients with narcolepsy. GHB is marketed under the trademark of Xyrem® (sodium oxybate oral solution), which trademark can be used interchangeably with GHB herein. Sensitive drugs also include narcotics or other drugs which require controls on their distribution and use to monitor behaviors to prevent abuse and adverse side effects.

In one embodiment, Xyrem® is subject to a restricted distribution program. One aspect of the program is to educate physicians and patients about the risks and benefits of Xyrem, including support via ongoing contact with patients and a toll free helpline. Initial prescriptions are filled only after a prescriber and patient have received and read the educational materials. Further, patient and prescribing physician registries are maintained and monitored to ensure proper distribution.

In a further embodiment, bulk sodium oxybate is manufactured at a single site, as is the finished drug product. Following manufacture of the drug product, it is stored at a facility compliant with FDA Schedule III regulations, where a consignment inventory is maintained. The inventory is owned by a company, and is managed by a central pharmacy, which maintains the consignment inventory. Xyrem® is distributed and dispensed through a primary and exclusive central pharmacy, and is not stocked in retail pharmacy outlets. It is distributed by overnight carriers, or by US mail in one embodiment to potentially invoke mail fraud laws if attempts of abuse occur.

FIG. **1** is a simplified block diagram of a computer system **100**, such as a personal computer for implementing at least a portion of the methods described herein. A central processing unit (CPU) **110** executes computer programs stored on a memory **120**. Memory **120** in one embodiment comprises one or more levels of cache as desired to speed execution of the program and access to data on which the programs operate. The CPU is directly coupled to memory **120** in one embodiment. Both CPU **110** and memory **120** are coupled to a bus **130**. A storage **140**, I/O **150** and communications **160** are also coupled to the bus **130**. Storage **140** is usually a long term storage device, such as a disk drive, tape drive, DVD, CD or other type of storage device. In one embodiment, storage **140** is used to house a database for use with the present invention. I/O **150** comprises keyboards, sound devices, displays and other mechanisms by which a user interacts with the computer system **100**. Communications **160** comprises a network, phone connection, local area network, wide area network or other mechanism for communicating with external devices. Such external devices comprise servers, other peer computers and other devices. In one embodiment, such external device comprises a database server that is used in place of the database on storage **140**. Other computer system architectures capable of executing software and interacting with a database and users may also be used. Appropriate security measures such as encryption are used to ensure confidentiality. Further, data integrity and backup measures are also used to prevent data loss.

FIGS. **2**A, **2**B and **2**C represent an initial prescription order entry process for a sensitive drug, such as Xyrem. At **202**, a medical doctor (MD) sends a Rx/enrollment form via mail, fax, email or other means to an intake/reimbursement specialist at **204**, who makes a copy of the RX/enrollment form that is stamped "copy". The original fax is forwarded to a pharmacy team. The enrollment form contains prescriber information, prescription information, checkboxes for the prescriber indicating they have read materials, educated the patient, understand the use in treatment, and understand certain safety information, and also contains patient information.

The prescriber information contains standard contact information as well as license number, DEA number and physician specialty. Patient and prescription information includes name, social security number, date of birth, gender, contact information, drug identification, patient's appropriate dosage, and number of refills allowed, along with a line for the prescriber's signature. Patient insurance information is also provided.

There are two workflows involved at the pharmacy team, intake reimbursement **206** and pharmacy workflow **208**, which may proceed in parallel or serially. The intake work flow **206** starts with an intake reimbursement specialist entering the patient and physician information into an application/database referred to as CHIPS, which is used to maintain a record of a client home infusion program (CHIP) for Xyrem®. A check is made to ensure the information is complete at **212**. If not, at **214**, an intake representative attempts to reach the MD or prescriber to obtain the missing information. If the missing information has not been obtained within a predetermined period of time, such as 24 hours at **216**, the Rx/Enrollment form is sent back to the MD with a rejection explanation. A note is entered in CHIPS that the application was rejected.

If the information is complete at **212**, the MD is contacted at **220** to verify receipt and accuracy of the patient's Rx. This contact is recorded in CHIPS, The intake and reimbursement specialist then sends a consent form and cover letter to the patient at **224**. The insurance provider is contacted at **226** to verify coverage and benefits. At **228**, a determination is made regarding coverage for the drug. If it is not available, it is determined at **230** whether the patient is willing and able to pay. If not, a process **232** is performed for handling patients who are uninsured or underinsured, In one embodiment, the process is referred to as a NORD process.

If the patient is willing and able to pay at **230**, the patient is informed of the cost of the product and is given payment options at **234**. At **236**, once payment is received, the intake reimbursement specialist submits a coverage approval form with the enrollment form to the pharmacy team as notification to process the patient's prescription. If coverage is approved at **228**, the intake reimbursement specialist also submits the coverage approval form at **238** with the enrollment form to the pharmacy tem as notification to process the patient's prescription. Processing of the prescription is described below.

Upon receipt and initial processing of the prescription enrollment form and sending an original to the pharmacy work flow block **208**, the patient is shipped a Xyrem® success packet via mail. In one embodiment, the Xyrem® success packet contains educational material for a patient that advises of the proper use, care and handling of the drug and conse-

quences of diversion at **268**. The medical doctor's credentials are checked to determine if the physician has a current DEA license to prescribe controlled substances and if he or she has had any actions related to misuse/misprescribing of controlled drugs against him or her, within a predetermined time, such as three months at **270**. If they have, a pharmacist holds the prescription until receiving a coverage approval form from the intake reimbursement specialist at **272**.

If the credentials have not been recently checked, the pharmacist verifies the credentials and enters all findings in the database at **274**. If the credentials are approved at **276**, the physician is indicated as approved in a physician screen populated by information from the database at **280**. The prescription is then held pending coverage approval at **282**.

If any disciplinary actions are identified, as referenced at block **278**, management of the pharmacy is notified and either approves processing of the prescription with continued monitoring of the physician, or processing of the prescription is not performed, and the physician is noted in the database as unapproved at **284**. The MD is contacted by a pharmacist at **286**, and informed that the patient's Rx cannot be processed. The enrollment form is then mailed back to the physician with cover letter reiteration that the prescription cannot be processed at **288**. The patient is also sent a letter at **290** indication that the prescription cannot be processed and the patient is instructed to contact their physician.

Actual filling of the approved prescription begins with receipt of the coverage approval form as indicated at **240**. The patient is contacted by the pharmacy, such as by a technician to complete a technician section of a patient counseling checklist. If a pharmacist verifies that the program materials were not read at **242**, the receipt of the material is confirmed at **244** and another call is scheduled to counsel the patient before the drug is shipped.

If the program materials were read at **242**, the checklist is completed at **246** and the technician transfers the patient to the pharmacist who reviews the entire checklist and completes remaining pharmacist specified sections. At **248**, the pharmacist indicates in the database that the patient counseling and checklist was successfully completed, indicating the date completed.

At **250**, the pharmacist schedules the patient's shipment for the next business day or the next business day that the patient or designee is able to sign for the package. Further, as indicated at **252**, the shipment must be sent to the patient's home address unless the patient is traveling or has moved. In that event, the pharmacist may determine that an exception may be made. The patient or the patient's designee who is at least 18 years old, must sign for the package upon delivery.

At **254**, the pharmacist enters the prescription order in the database, creating an order number. The pharmacist then verifies at **256** the prescription and attaches a verification label to the hard copy prescription. At **258**, a pick ticket is generated for the order and the order is forwarded to the pharmacy for fulfillment. The shipment is confirmed in the database at **260**, the original Rx is filed with the pharmacy Rx's in numerical order at **262**, and the order is shipped by USPS Express Mail **264**. Use of the US mail invokes certain criminal penalties for unauthorized diversion. Optionally, other mail services may be used. Potential changes in the law may also bring criminal penalties into play. Following shipment, the patient is called by the central pharmacy to confirm that the prescription was received.

As noted at **266**, for the sensitive drug, Xyrem, all inventory is cycle counted and reconciled with the database system quantities before shipments for the day are sent. This provides a very precise control of the inventor.

A physician success program materials request process begins at **310** in FIG. **3**. At **320**, the MD calls to the central pharmacy to request program materials. A special phone number is provided. MD demographics, DEA number, and data or request are entered into the database at **330**. At **340**, a request is made to ship the materials to the MD via a fulfillment website, or other mechanism. The request process ends at **350**.

A refill request process begins at **402** in FIGS. **4**A and **4**B. There are two different paths for refills. A first path beginning at **404** involves generating report from the central database of patients with a predetermined number of days or product remaining. A second path beginning at **406** is followed when patient calls to request an early refill.

In the first path, a copy of the report is provided to an intake reimbursement specialist at **408**. No sooner than 8 days before the medication depletion, a pharmacy technician contacts the patient at **410** to complete the pre-delivery checklist. At **412**, if the patient is not reached, a message is left mentioning the depletion, and a return number at **414**. A note is also entered into the database indicating the date the message was left at **416**.

If the patient is reached at **412**, the next shipment is scheduled at **418**, the prescription is entered into the database creating an order at **420**, the pharmacist verifies the prescription and attaches a verification label at **422** and the shipment is confirmed in the database at **424**. Note at **426** that the inventory is cycle counted and reconciled with the database quantities before the shipments for a day or other time period are sent. A pick ticket is generated for the order and the order is forwarded for fulfillment at **428**, with the first path ending at **430**.

The second path, beginning at **406** results in a note code being entered into the database on a patient screen indicating an early refill request at **432**. At **434**, a sensitive drug problem identification and management risk diversion report may be completed, documented and distributed. The pharmacist evaluates the patient's compliance with therapy or possible product diversion, misuse or over-use at **436**. In one embodiment, cash payers are also identified. The pharmacist then contacts the prescribing physician to alert them of the situation and confirm if the physician approves of the early refill at **438**. If the physician does not approve as indicated at **440**, the patient must wait until the next scheduled refill date to receive additional product as indicated at **442**, and the process ends at **444**.

If the physician approves at **440**, the pharmacist enters a note in the database on a patient screen that the physician approves the request at **446**. The pharmacist notifies an intake reimbursement specialist to contact the patient's insurance provider to verify coverage for the early refill at **448**. If the insurance provider will pay as determined at **450**, the specialist submits the coverage approval form as notification that the refill may be processed at **452**. At **454**, the pharmacy technician contacts the patient to schedule shipment of the product for the next business day, and the process of filling the order is continued at **456** by following the process beginning at **240**.

If the insurance provider will not pay at **450**, it is determined whether the patient is willing and/or able to pay at **458**. If not, the patient must wait until the next scheduled refill date to receive additional product at **460**. If it was determined at **458** that the patient was willing and able to pay, the patient is informed of the cost of the product and is given payment options at **462**. Once payment is received as indicated at **464**, the specialist submits a coverage approval form to the pharmacy team as notification that the refill request can be processed at **466**. At **468**, the pharmacy technician contacts the

patient to schedule shipment. The process of filling the order is continued at **470** by following the process beginning at **240**.

A process, referred to as a NORD process in one embodiment is used to determine whether donated, third party funds are available for paying for prescriptions where neither insurance will, nor the patient can pay. The process begins at **510** upon determining that a patient is uninsured or underinsured. A reimbursement specialist explains the NORD program to the patient and faxes an application request form to NORD for the patient. At **515**, the intake reimbursement specialist documents in the database that an application has been received through NORD. At **520**, NORD mails an application to the patient within one business day.

A determination is made at **525** by NORD whether the patient is approved. If not, at **530**, NORD sends a denial letter to the patient, and it is documented in the database at **540** that the patient was denied by NORD. If the patient is approved, NORD sends an acceptance letter to the patient and faxes a voucher to the central pharmacy (SDS in one embodiment) to indicate the approval at **545**. At **550**, an intake reimbursement specialist submits a coverage approval form to the pharmacy team as notification that the patient has been approved for coverage. The process of filling the order is continued at **555** by following the process beginning at **240**.

An inventory control process is illustrated in FIG. **6** beginning at **610**. Each week, a responsible person at the central pharmacy, such as the director of the pharmacy transfers inventory for the week's shipments to a segregated warehouse location for production inventory. At **620**, a purchase order is generated for the inventory transferred to the production location and is sent, such as by fax, to a controller, such as the controller of the company that obtained approval for distribution and use of the sensitive drug. At **630**, the controller invoices the central pharmacy for the product moved to production. The process ends at **640**.

The central database described above is a relational database running on the system of FIG. **1**, or a server based system having a similar architecture coupled to workstations via a network, as represented by communications **160**. The database is likely stored in storage **140**, and contains multiple fields of information as indicated at **700** in FIG. **7**. The organization and groupings of the fields are shown in one format for convenience. It is recognized that many different organizations or schemas may be utilized. In one embodiment, the groups of fields comprise prescriber fields **710**, patient fields **720**, prescription fields **730** and insurance fields **740**. For purposes of illustration, all the entries described with respect to the above processes are included in the fields. In further embodiments, no such groupings are made, and the data is organized in a different manner.

Several queries are illustrated at **800** in FIG. **8**. There may be many other queries as required by individual state reporting requirements. A first query at **810** is used to identify prescriptions written by physician. The queries may be written in structured query language, natural query languages or in any other manner compatible with the database. A second query **820** is used to pull information from the database related to prescriptions by patient name. A third query **830** is used to determine prescriptions by frequency, and a n^{th} query finds prescriptions by dose at **840**. Using query languages combined with the depth of data in the central database allows many other methods of investigating for potential abuse of the drugs. The central database ensures that all prescriptions, prescribers and patients are tracked and subject to such investigations. In further embodiments, the central database may be distributed among multiple computers provided a query operates over all data relating to such prescriptions, prescribers and patients for the drug.

An example of one prescription and enrollment form is shown at **900** in FIG. **9**. As previously indicated, several fields are included for prescriber information, prescription information and patient information.

FIG. **10** is a copy of one example NORD application request form **1000** used to request that an application be sent to a patient for financial assistance.

FIG. **11** is a copy of one example application **1100** for financial assistance as requested by form **1000**. The form requires both patient and physician information. Social security number information is also requested. The form provides information for approving the financial assistance and for tracking assistance provided.

FIG. **12** is a copy of one example voucher request **1200** for medication for use with the NORD application request form of FIG. **10**. In addition to patient and physician information, prescription information and diagnosis information is also provided.

FIGS. **13**A, **13**B and **13**C are descriptions of sample reports obtained by querying a central database having fields represented in FIG. **7**. The activities grouped by sales, regulatory, quality assurance, call center, pharmacy, inventory, reimbursement, patient care and drug information. Each report has an associated frequency or frequencies. The reports are obtained by running queries against the database, with the queries written in one of many query languages.

While the invention has been described with respect to a Schedule III drug, it is useful for other sensitive drugs that are DEA or Federally scheduled drugs in Schedule II-V, as well as still other sensitive drugs where multiple controls are desired for distribution and use.

The invention claimed is:

1. A computerized method of distributing a prescription drug under exclusive control of an exclusive central pharmacy, the method comprising:

receiving in a computer processor all prescription requests, for any and all patients being prescribed the prescription drug, only at the exclusive central pharmacy from any and all medical doctors allowed to prescribe the prescription drug, the prescription requests containing information identifying patients, the prescription drug, and various credentials of the any and all medical doctors;

requiring entering of the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations, such that all prescriptions for the prescription drug are processed only by the exclusive central pharmacy using only the exclusive computer database;

checking with the computer processor the credentials of the any and all doctors to determine the eligibility of the doctors to prescribe the prescription drug;

confirming with a patient that educational material has been read prior to shipping the prescription drug;

checking the exclusive computer database for potential abuse of the prescription drug;

mailing the prescription drug to the patient only if no potential abuse is found by the patient to whom the prescription drug is prescribed and the doctor prescribing the prescription drug;

confirming receipt by the patient of the prescription drug; and

generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.

2. A computerized method of distributing a prescription drug under exclusive control of an exclusive central pharmacy, the method comprising:

receiving in a computer processor all prescription requests, for any and all patients being prescribed the prescription drug, only at the exclusive central pharmacy from any and all medical doctors allowed to prescribe the prescription drug, the prescription requests containing information identifying patients, the prescription drug, and various credentials of the any and all medical doctors;

entering the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations, such that all prescriptions for the prescription drug are processed only by the exclusive central pharmacy using only the exclusive computer database;

checking with the computer processor the credentials of the any and all doctors to determine the eligibility of the doctors to prescribe the prescription drug;

checking the exclusive computer database for potential abuse of the prescription drug;

mailing the prescription drug to a patient only if no potential abuse is found by the patient to whom the prescription drug is prescribed and the doctor prescribing the prescription drug;

confirming receipt by the patient of the prescription drug; and

generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.

3. The method of claim **2** wherein the exclusive central pharmacy controls the exclusive computer database.

4. The method of claim **2** and further comprising selectively blocking shipment of the prescription drug to a patient.

5. The method of claim **2** wherein an abuse pattern is associated with a patient, and shipment is blocked upon such association.

6. The method of claim **2** wherein the prescription drug comprises gamma hydroxy butyrate (GHB).

7. A computerized method of distributing a prescription drug under control of an exclusive central pharmacy, the method comprising:

receiving in a computer processor prescription requests, for any and all patients being prescribed the prescription drug, only at the central pharmacy from any and all authorized prescribers allowed to prescribed the prescription drug, the prescription requests containing information identifying patients, the prescription drug, and various credentials of the any and all authorized prescribers;

entering the information into an exclusive computer database under exclusive control of the central pharmacy for analysis of potential abuse situations, wherein the use of the exclusive computer database is required for distribution of the prescription drug, such that all prescriptions for the prescription drug are processed only by the exclusive central pharmacy using only the exclusive computer database;

checking with the computer processor the credentials of the any and all authorized prescribers to determine the eligibility of the prescribers to prescribe the prescription drug;

confirming with a patient that educational material has been read prior to providing the prescription drug to the patient;

requiring checking of the exclusive computer database for potential abuse associated with the patient and the authorized prescriber;

providing the prescription drug to the patient only provided information in the exclusive computer database is not indicative of potential abuse by the patient to whom the prescription drug is prescribed and the authorized prescriber of the prescription drug;

confirming receipt by the patient of the prescription drug; and

generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.

8. A computerized method of distributing gamma hydroxy butyrate (GHB) under control of an exclusive central pharmacy, the method comprising:

receiving in a computer processor prescription requests for GHB, for any and all patients being prescribed GHB, only at the central pharmacy from any and all authorized prescribers allowed to prescribe GHB, the prescription requests for GHB containing information identifying patients and various credentials of the any and all authorized prescribers;

entering the information into an exclusive computer database under exclusive control of the central pharmacy for analysis of potential abuse situations, wherein the use of the exclusive computer database is required for distribution of GHB, such that all prescriptions for GHB are processed only by the exclusive central pharmacy using only the exclusive computer database;

checking with the computer processor the credentials of the any and all authorized prescribers to determine the eligibility of the prescribers to prescribe GHB;

confirming with the patient that GHB educational material has been read prior to providing GHB to the patient a first time;

requiring checking of the exclusive computer database for potential GHB abuse associated with the patient;

providing GHB to the patient only provided information in the exclusive computer database is not indicative of potential abuse by the patient to whom GHB is prescribed and the authorized prescriber of the GHB;

confirming receipt by the patient of the GHB; and

generating with the computer processor periodic reports via the exclusive computer database to evaluate potential GHB diversion patterns.

9. A computerized method of distributing gamma hydroxy butyrate (GHB) under control of an exclusive central pharmacy, the method comprising:

receiving in a computer processor prescription requests for GHB, for any and all patients being prescribed GHB, only at the central pharmacy from any and all authorized prescribers allowed to prescribe GHB, the prescription requests containing information identifying patients and various credentials of the any and all authorized prescribers;

entering the information into an exclusive computer database under exclusive control of the central pharmacy for analysis of potential abuse situations, wherein the use of the exclusive computer database is required for distribution of GHB, such that all prescriptions for GHB are processed only by the exclusive central pharmacy using only the exclusive computer database;

checking with the computer processor the credentials of the any and all authorized prescribers to determine the eligibility of the prescribers to prescribe GHB;

confirming with the patient that GHB educational material has been read prior to providing GHB to the patient a first time;

requiring checking of the exclusive computer database for potential GHB abuse associated with the patient;

mailing GHB to the patient only provided information in the exclusive computer database is not indicative of potential abuse by the patient to whom GHB is prescribed and the authorized prescriber of the GHB;

confirming receipt by the patient of the GHB; and

generating with the computer processor periodic reports via the exclusive computer database to evaluate potential GHB diversion patterns.

10. A computerized method of distributing gamma hydroxy butyrate (GHB) under control of an exclusive central pharmacy, the method comprising:

manufacturing GHB;

providing manufactured GHB only to the exclusive central pharmacy;

receiving in a computer processor all prescription requests for GHB, for any and all patients being prescribed GHB, only at the central pharmacy from any and all authorized prescribers allowed to prescribe GHB, the prescription requests containing information identifying patients and various credentials of the any and all authorized prescribers;

entering the information into an exclusive computer database under exclusive control of the central pharmacy for analysis of potential abuse situations, wherein the use of the exclusive computer database is required for distribution of GHB, such that all prescriptions for GHB are processed only by the exclusive central pharmacy using only the exclusive computer database;

checking with the computer processor the credentials of the any and all authorized prescribers to determine the eligibility of the prescribers to prescribe GHB;

confirming with the patient that GHB educational material has been read prior to providing GHB to the patient a first time;

requiring checking of the exclusive computer database for potential GHB abuse associated with the patient;

mailing GHB to the patient only provided information in the exclusive computer database is not indicative of potential abuse by the patient to whom GHB is prescribed and the doctor prescribing the GHB;

confirming receipt by the patient of the GHB; and

generating with the computer processor periodic reports via the exclusive computer database to evaluate potential GHB diversion patterns.

11. A computerized method of distributing a prescription drug under control of an exclusive central pharmacy, the method comprising:

receiving in a computer processor all prescription requests, for any and all patients being prescribed the prescription drug, only at the central pharmacy from any and all authorized prescribers allowed to prescribed the prescription drug, the prescription requests containing information identifying patients, the prescription drug, and various credentials of the any and all authorized prescribers;

entering the information into an exclusive computer database under exclusive control of the central pharmacy for analysis of potential abuse situations, wherein the use of the exclusive computer database is required for distribution of the prescription drug, such that all prescriptions for the prescription drug are processed only by the exclusive central pharmacy using only the exclusive computer database;

checking with the computer processor the credentials of the any and all authorized prescribers to determine the eligibility of the prescribers to prescribe the prescription drug;

confirming with the patient that educational material has been read prior to providing the prescription drug to the patient;

requiring checking of the exclusive computer database for potential abuse by the patient to whom the prescription drug is prescribed and the authorized prescriber allowed to prescribe the prescription drug;

providing the prescription drug to the patient only provided information in the exclusive computer database is not indicative of potential abuse by the patient to whom the prescription drug is prescribed and the authorized prescriber allowed to prescribe the prescription drug; and

confirming receipt by the patient of the prescription drug.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,668,730 B2
APPLICATION NO. : 10/322348
DATED : February 23, 2010
INVENTOR(S) : Reardan et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page:

The first or sole Notice should read --

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 547 days.

Signed and Sealed this

Seventh Day of December, 2010

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

EXHIBIT B

US007765106B2

(12) **United States Patent**
Reardan et al.

(10) **Patent No.: US 7,765,106 B2**
(45) **Date of Patent: *Jul. 27, 2010**

(54) **SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD**

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(73) Assignee: **JPI Commercial, LLC**, Palo Alto, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1645 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/979,665**

(22) Filed: **Nov. 2, 2004**

(65) **Prior Publication Data**

US 2005/0090425 A1 Apr. 28, 2005

Related U.S. Application Data

(62) Division of application No. 10/322,348, filed on Dec. 17, 2002, now Pat. No. 7,668,730.

(51) **Int. Cl.**
G06Q 10/00 (2006.01)

(52) **U.S. Cl.** **705/2**; 705/3

(58) **Field of Classification Search** 705/2, 705/3

See application file for complete search history.

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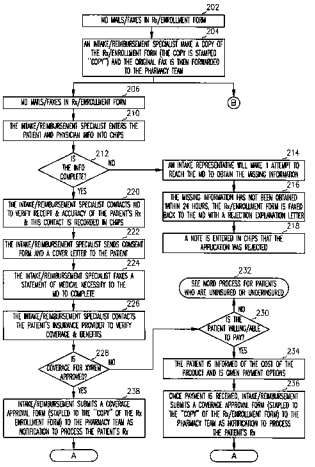
Assistant Examiner—Lena Najarian
(74) *Attorney, Agent, or Firm*—Schwegman, Lundberg & Woessner, P.A.

(57) **ABSTRACT**

A drug distribution system and method utilizes a central pharmacy and database to track all prescriptions for a sensitive drug. Information is kept in the database regarding all physicians allowed to prescribe the sensitive drug, and all patients receiving the drug. Abuses are identified by monitoring data in the database for prescription patterns by physicians and prescriptions obtained by patients. Further verification is made that the physician is eligible to prescribe the drug by consulting a separate database, and optionally whether any actions are taken against the physician. Multiple controls beyond those for normal drugs are imposed on the distribution depending on the sensitivity of the drug.

8 Claims, 16 Drawing Sheets



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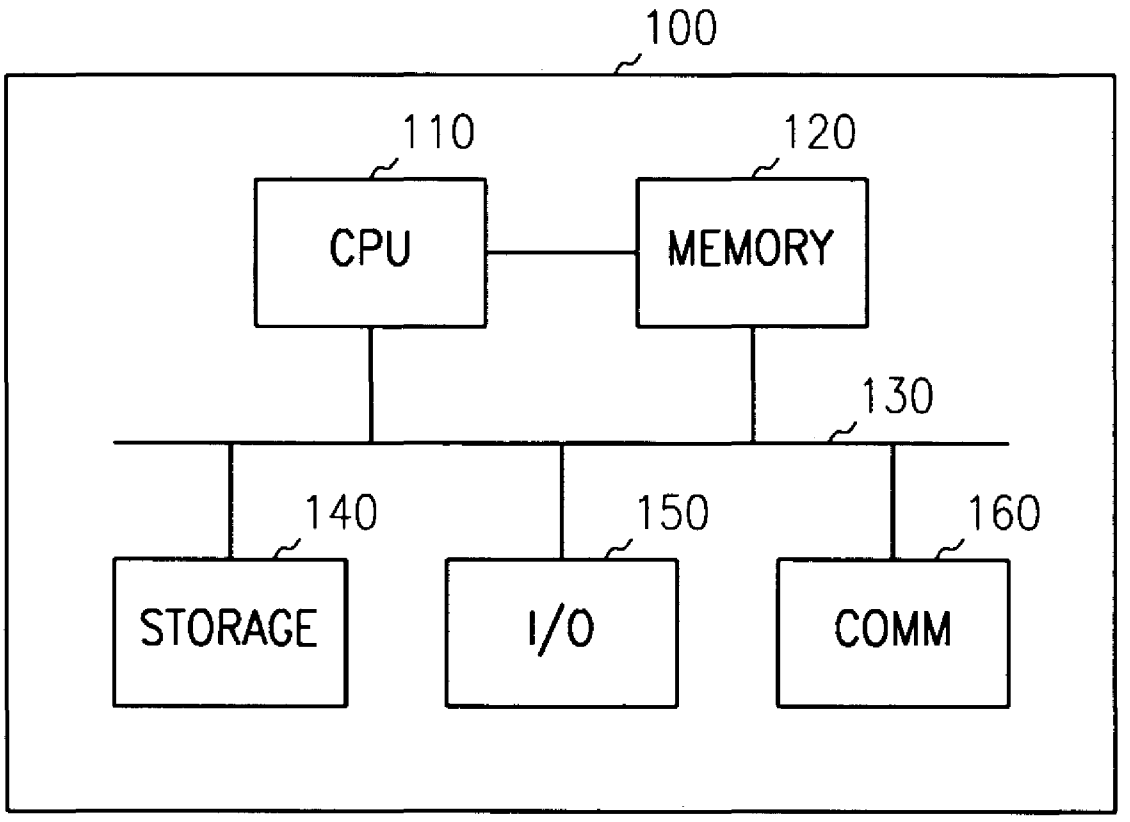


FIG. 1

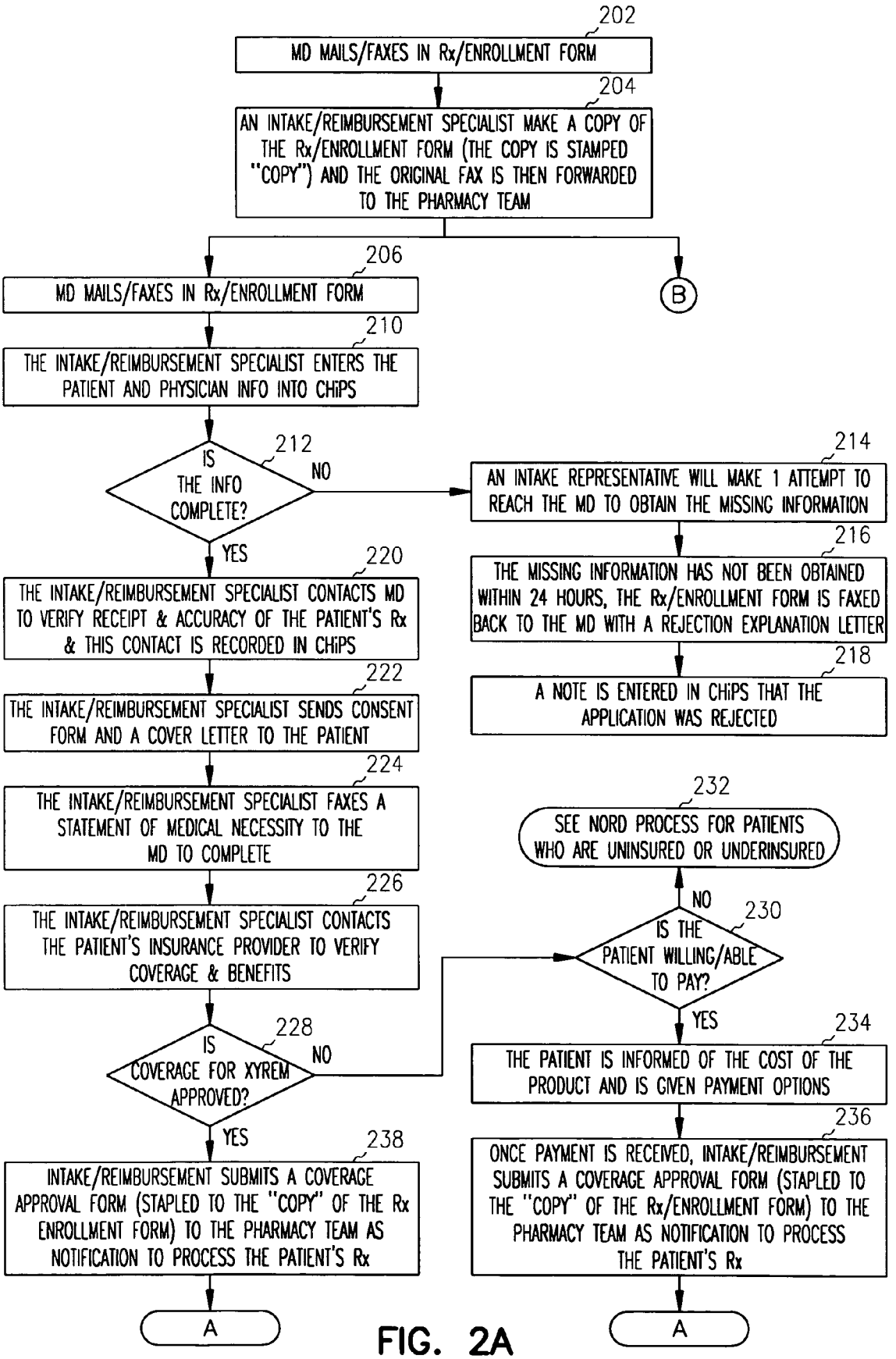

202
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
204
AN INTAKE/REIMBURSEMENT SPECIALIST MAKE A COPY OF THE Rx/ENROLLMENT FORM (THE COPY IS STAMPED "COPY") AND THE ORIGINAL FAX IS THEN FORWARDED TO THE PHARMACY TEAM
206
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
B
210
THE INTAKE/REIMBURSEMENT SPECIALIST ENTERS THE PATIENT AND PHYSICIAN INFO INTO CHiPS
212
IS THE INFO COMPLETE?
NO
YES
214
AN INTAKE REPRESENTATIVE WILL MAKE 1 ATTEMPT TO REACH THE MD TO OBTAIN THE MISSING INFORMATION
216
THE MISSING INFORMATION HAS NOT BEEN OBTAINED WITHIN 24 HOURS, THE Rx/ENROLLMENT FORM IS FAXED BACK TO THE MD WITH A REJECTION EXPLANATION LETTER
218
A NOTE IS ENTERED IN CHiPS THAT THE APPLICATION WAS REJECTED
220
THE INTAKE/REIMBURSEMENT SPECIALIST CONTACTS MD TO VERIFY RECEIPT & ACCURACY OF THE PATIENT'S Rx & THIS CONTACT IS RECORDED IN CHiPS
222
THE INTAKE/REIMBURSEMENT SPECIALIST SENDS CONSENT FORM AND A COVER LETTER TO THE PATIENT
224
THE INTAKE/REIMBURSEMENT SPECIALIST FAXES A STATEMENT OF MEDICAL NECESSITY TO THE MD TO COMPLETE
226
THE INTAKE/REIMBURSEMENT SPECIALIST CONTACTS THE PATIENT'S INSURANCE PROVIDER TO VERIFY COVERAGE & BENEFITS
228
IS COVERAGE FOR XYREM APPROVED?
NO
YES
232
SEE NORD PROCESS FOR PATIENTS WHO ARE UNINSURED OR UNDERINSURED
230
IS THE PATIENT WILLING/ABLE TO PAY?
NO
YES
234
THE PATIENT IS INFORMED OF THE COST OF THE PRODUCT AND IS GIVEN PAYMENT OPTIONS
236
ONCE PAYMENT IS RECEIVED, INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM (STAPLED TO THE "COPY" OF THE Rx/ENROLLMENT FORM) TO THE PHARMACY TEAM AS NOTIFICATION TO PROCESS THE PATIENT'S Rx
238
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM (STAPLED TO THE "COPY" OF THE Rx ENROLLMENT FORM) TO THE PHARMACY TEAM AS NOTIFICATION TO PROCESS THE PATIENT'S Rx
A
A

FIG. 2A

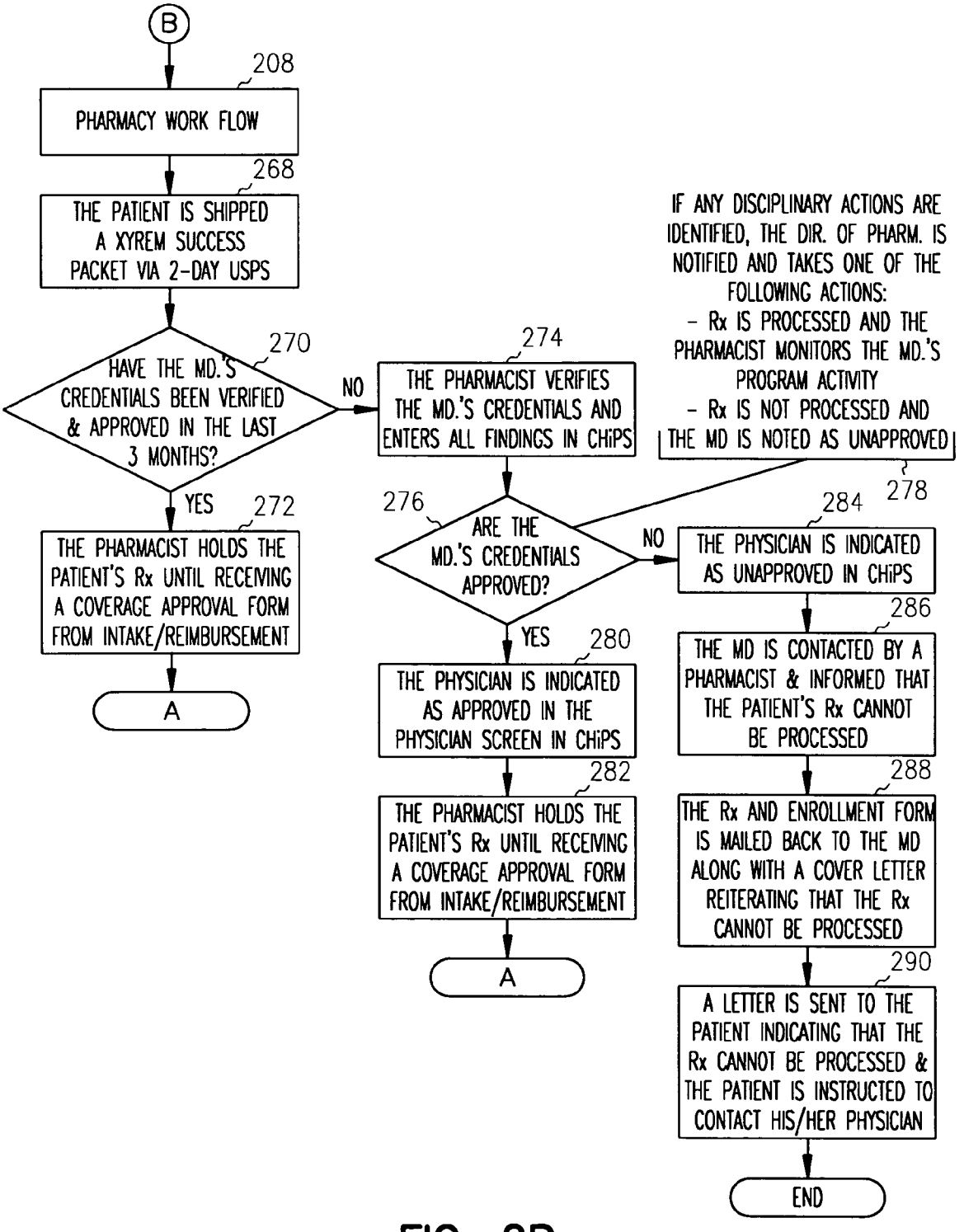

B
208
PHARMACY WORK FLOW
268
THE PATIENT IS SHIPPED A XYREM SUCCESS PACKET VIA 2-DAY USPS
270
HAVE THE MD.'S CREDENTIALS BEEN VERIFIED & APPROVED IN THE LAST 3 MONTHS?
NO
YES
272
THE PHARMACIST HOLDS THE PATIENT'S Rx UNTIL RECEIVING A COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT
A
274
THE PHARMACIST VERIFIES THE MD.'S CREDENTIALS AND ENTERS ALL FINDINGS IN CHiPS
276
ARE THE MD.'S CREDENTIALS APPROVED?
NO
YES
280
THE PHYSICIAN IS INDICATED AS APPROVED IN THE PHYSICIAN SCREEN IN CHiPS
282
THE PHARMACIST HOLDS THE PATIENT'S Rx UNTIL RECEIVING A COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT
A
IF ANY DISCIPLINARY ACTIONS ARE IDENTIFIED, THE DIR. OF PHARM. IS NOTIFIED AND TAKES ONE OF THE FOLLOWING ACTIONS:
- Rx IS PROCESSED AND THE PHARMACIST MONITORS THE MD.'S PROGRAM ACTIVITY
- Rx IS NOT PROCESSED AND THE MD IS NOTED AS UNAPPROVED
278
284
THE PHYSICIAN IS INDICATED AS UNAPPROVED IN CHiPS
286
THE MD IS CONTACTED BY A PHARMACIST & INFORMED THAT THE PATIENT'S Rx CANNOT BE PROCESSED
288
THE Rx AND ENROLLMENT FORM IS MAILED BACK TO THE MD ALONG WITH A COVER LETTER REITERATING THAT THE Rx CANNOT BE PROCESSED
290
A LETTER IS SENT TO THE PATIENT INDICATING THAT THE Rx CANNOT BE PROCESSED & THE PATIENT IS INSTRUCTED TO CONTACT HIS/HER PHYSICIAN
END

FIG. 2B

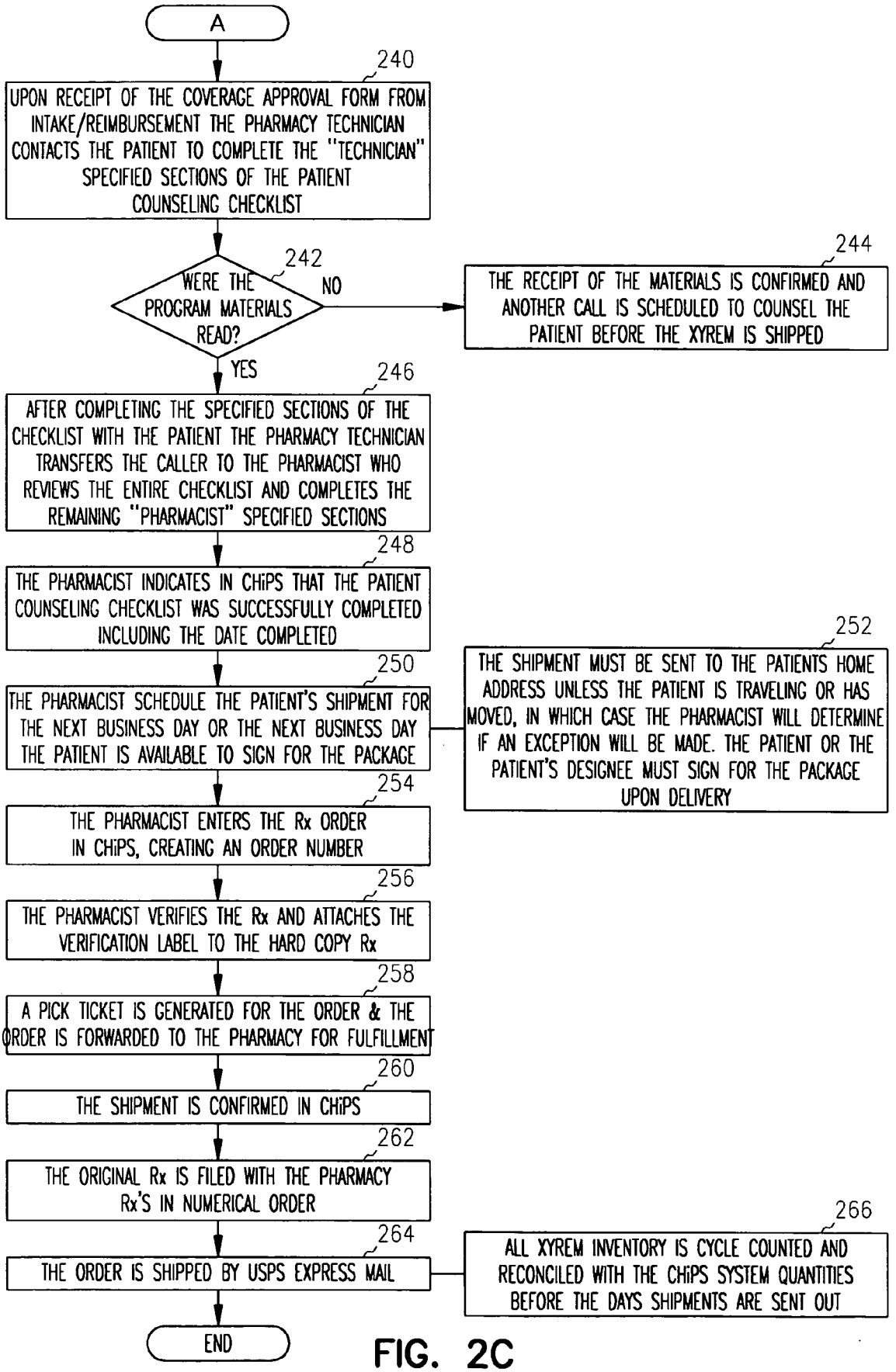

A
240
UPON RECEIPT OF THE COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE THE "TECHNICIAN" SPECIFIED SECTIONS OF THE PATIENT COUNSELING CHECKLIST
242
WERE THE PROGRAM MATERIALS READ?
NO
244
THE RECEIPT OF THE MATERIALS IS CONFIRMED AND ANOTHER CALL IS SCHEDULED TO COUNSEL THE PATIENT BEFORE THE XYREM IS SHIPPED
YES
246
AFTER COMPLETING THE SPECIFIED SECTIONS OF THE CHECKLIST WITH THE PATIENT THE PHARMACY TECHNICIAN TRANSFERS THE CALLER TO THE PHARMACIST WHO REVIEWS THE ENTIRE CHECKLIST AND COMPLETES THE REMAINING "PHARMACIST" SPECIFIED SECTIONS
248
THE PHARMACIST INDICATES IN CHIPS THAT THE PATIENT COUNSELING CHECKLIST WAS SUCCESSFULLY COMPLETED INCLUDING THE DATE COMPLETED
250
THE PHARMACIST SCHEDULE THE PATIENT'S SHIPMENT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
252
THE SHIPMENT MUST BE SENT TO THE PATIENTS HOME ADDRESS UNLESS THE PATIENT IS TRAVELING OR HAS MOVED, IN WHICH CASE THE PHARMACIST WILL DETERMINE IF AN EXCEPTION WILL BE MADE. THE PATIENT OR THE PATIENT'S DESIGNEE MUST SIGN FOR THE PACKAGE UPON DELIVERY
254
THE PHARMACIST ENTERS THE Rx ORDER IN CHIPS, CREATING AN ORDER NUMBER
256
THE PHARMACIST VERIFIES THE Rx AND ATTACHES THE VERIFICATION LABEL TO THE HARD COPY Rx
258
A PICK TICKET IS GENERATED FOR THE ORDER & THE ORDER IS FORWARDED TO THE PHARMACY FOR FULFILLMENT
260
THE SHIPMENT IS CONFIRMED IN CHIPS
262
THE ORIGINAL Rx IS FILED WITH THE PHARMACY Rx'S IN NUMERICAL ORDER
264
THE ORDER IS SHIPPED BY USPS EXPRESS MAIL
266
ALL XYREM INVENTORY IS CYCLE COUNTED AND RECONCILED WITH THE CHIPS SYSTEM QUANTITIES BEFORE THE DAYS SHIPMENTS ARE SENT OUT
END

FIG. 2C

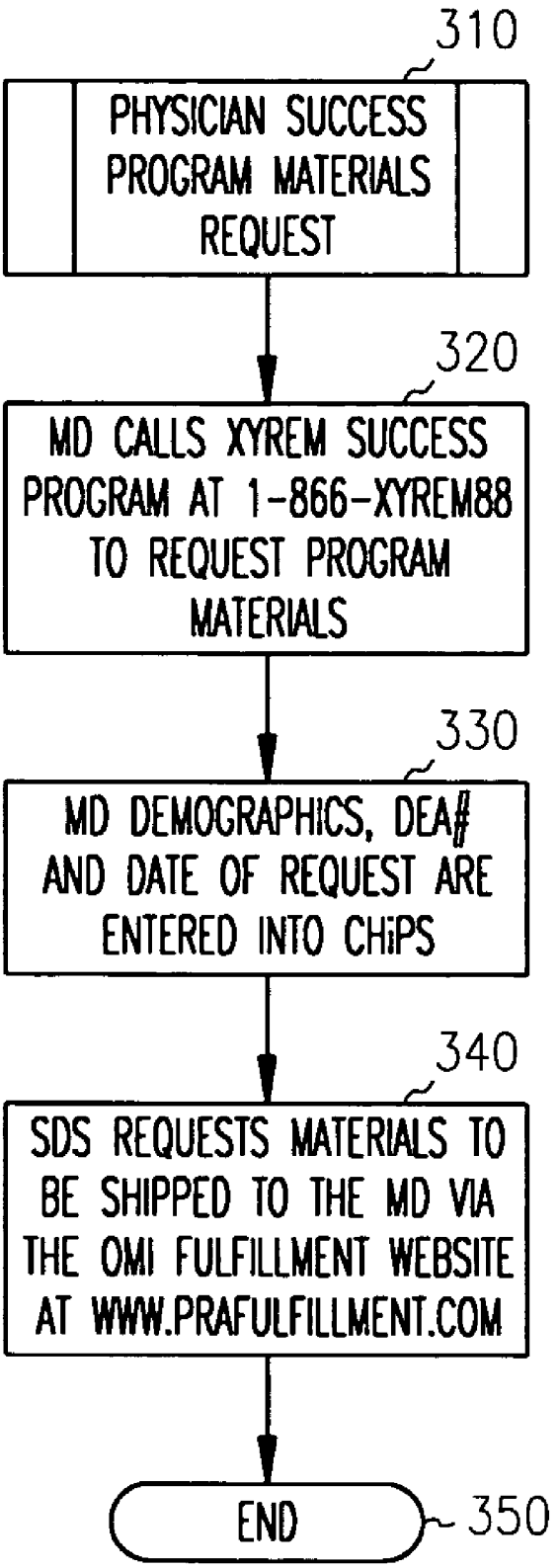

310
PHYSICIAN SUCCESS PROGRAM MATERIALS REQUEST
320
MD CALLS XYREM SUCCESS PROGRAM AT 1-866-XYREM88 TO REQUEST PROGRAM MATERIALS
330
MD DEMOGRAPHICS, DEA# AND DATE OF REQUEST ARE ENTERED INTO CHIPS
340
SDS REQUESTS MATERIALS TO BE SHIPPED TO THE MD VIA THE OMI FULFILLMENT WEBSITE AT WWW.PRAFULFILLMENT.COM
END
350

FIG. 3

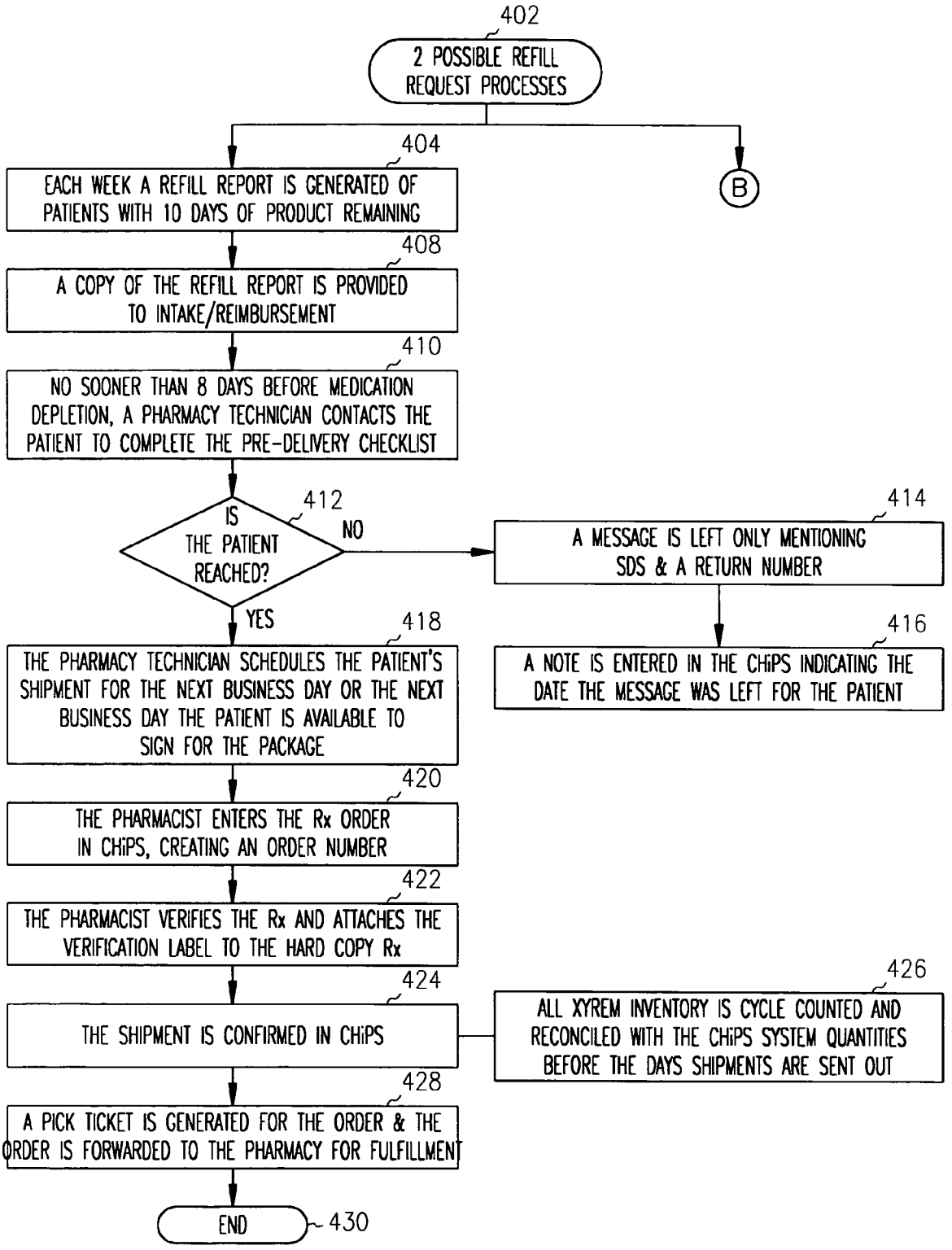

402
2 POSSIBLE REFILL REQUEST PROCESSES
404
EACH WEEK A REFILL REPORT IS GENERATED OF PATIENTS WITH 10 DAYS OF PRODUCT REMAINING
B
408
A COPY OF THE REFILL REPORT IS PROVIDED TO INTAKE/REIMBURSEMENT
410
NO SOONER THAN 8 DAYS BEFORE MEDICATION DEPLETION, A PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE THE PRE-DELIVERY CHECKLIST
412
IS THE PATIENT REACHED?
NO
414
A MESSAGE IS LEFT ONLY MENTIONING SDS & A RETURN NUMBER
416
A NOTE IS ENTERED IN THE CHiPS INDICATING THE DATE THE MESSAGE WAS LEFT FOR THE PATIENT
YES
418
THE PHARMACY TECHNICIAN SCHEDULES THE PATIENT'S SHIPMENT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
420
THE PHARMACIST ENTERS THE Rx ORDER IN CHiPS, CREATING AN ORDER NUMBER
422
THE PHARMACIST VERIFIES THE Rx AND ATTACHES THE VERIFICATION LABEL TO THE HARD COPY Rx
424
THE SHIPMENT IS CONFIRMED IN CHiPS
426
ALL XYREM INVENTORY IS CYCLE COUNTED AND RECONCILED WITH THE CHiPS SYSTEM QUANTITIES BEFORE THE DAYS SHIPMENTS ARE SENT OUT
428
A PICK TICKET IS GENERATED FOR THE ORDER & THE ORDER IS FORWARDED TO THE PHARMACY FOR FULFILLMENT
END
430

FIG. 4A

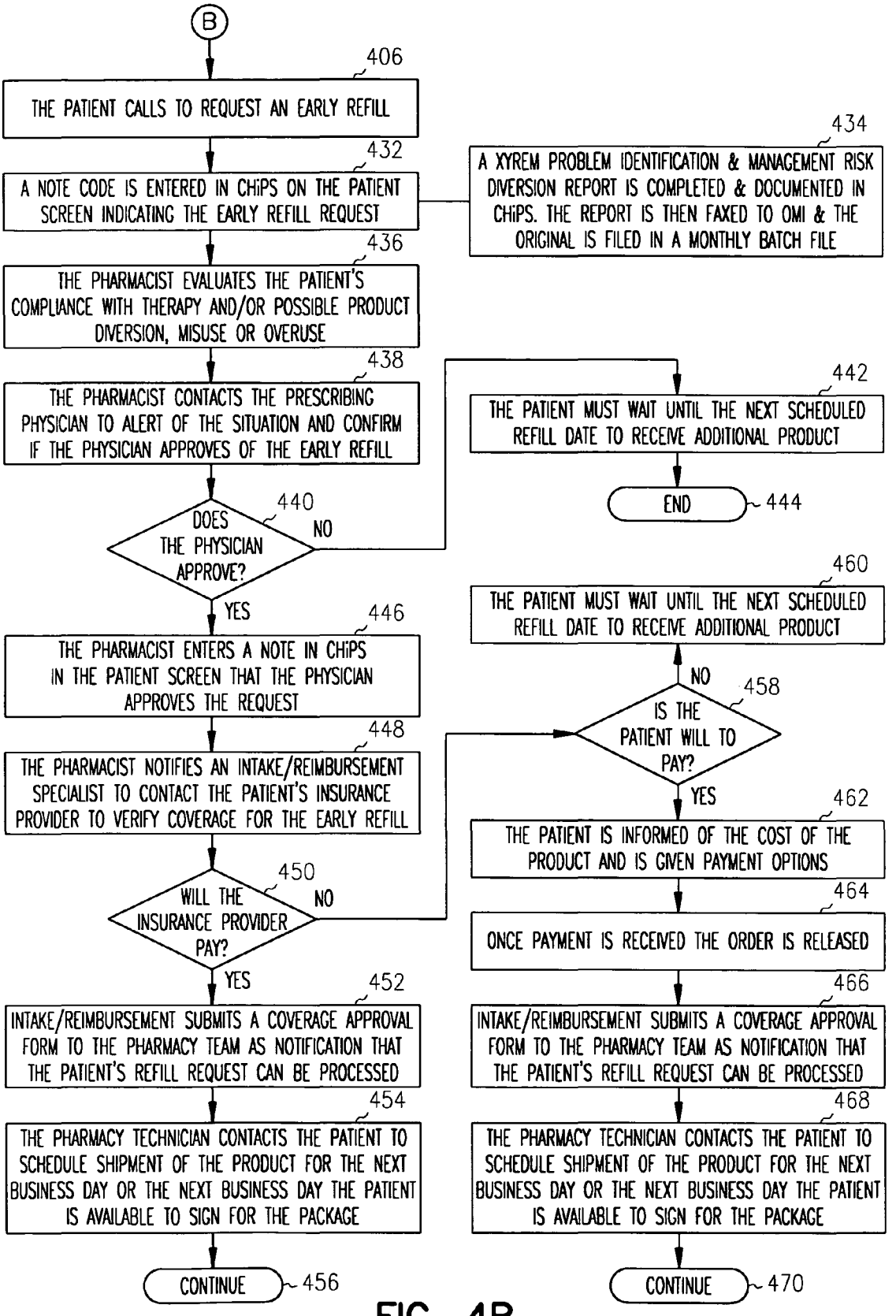

B
406
THE PATIENT CALLS TO REQUEST AN EARLY REFILL
432
A NOTE CODE IS ENTERED IN CHIPS ON THE PATIENT SCREEN INDICATING THE EARLY REFILL REQUEST
434
A XYREM PROBLEM IDENTIFICATION & MANAGEMENT RISK DIVERSION REPORT IS COMPLETED & DOCUMENTED IN CHIPS. THE REPORT IS THEN FAXED TO OMI & THE ORIGINAL IS FILED IN A MONTHLY BATCH FILE
436
THE PHARMACIST EVALUATES THE PATIENT'S COMPLIANCE WITH THERAPY AND/OR POSSIBLE PRODUCT DIVERSION, MISUSE OR OVERUSE
438
THE PHARMACIST CONTACTS THE PRESCRIBING PHYSICIAN TO ALERT OF THE SITUATION AND CONFIRM IF THE PHYSICIAN APPROVES OF THE EARLY REFILL
440
DOES THE PHYSICIAN APPROVE?
NO
442
THE PATIENT MUST WAIT UNTIL THE NEXT SCHEDULED REFILL DATE TO RECEIVE ADDITIONAL PRODUCT
END
444
YES
446
THE PHARMACIST ENTERS A NOTE IN CHIPS IN THE PATIENT SCREEN THAT THE PHYSICIAN APPROVES THE REQUEST
448
THE PHARMACIST NOTIFIES AN INTAKE/REIMBURSEMENT SPECIALIST TO CONTACT THE PATIENT'S INSURANCE PROVIDER TO VERIFY COVERAGE FOR THE EARLY REFILL
450
WILL THE INSURANCE PROVIDER PAY?
NO
460
THE PATIENT MUST WAIT UNTIL THE NEXT SCHEDULED REFILL DATE TO RECEIVE ADDITIONAL PRODUCT
458
IS THE PATIENT WILL TO PAY?
NO
YES
462
THE PATIENT IS INFORMED OF THE COST OF THE PRODUCT AND IS GIVEN PAYMENT OPTIONS
464
ONCE PAYMENT IS RECEIVED THE ORDER IS RELEASED
YES
452
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT'S REFILL REQUEST CAN BE PROCESSED
466
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT'S REFILL REQUEST CAN BE PROCESSED
454
THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO SCHEDULE SHIPMENT OF THE PRODUCT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
468
THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO SCHEDULE SHIPMENT OF THE PRODUCT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
CONTINUE
456
CONTINUE
470

FIG. 4B

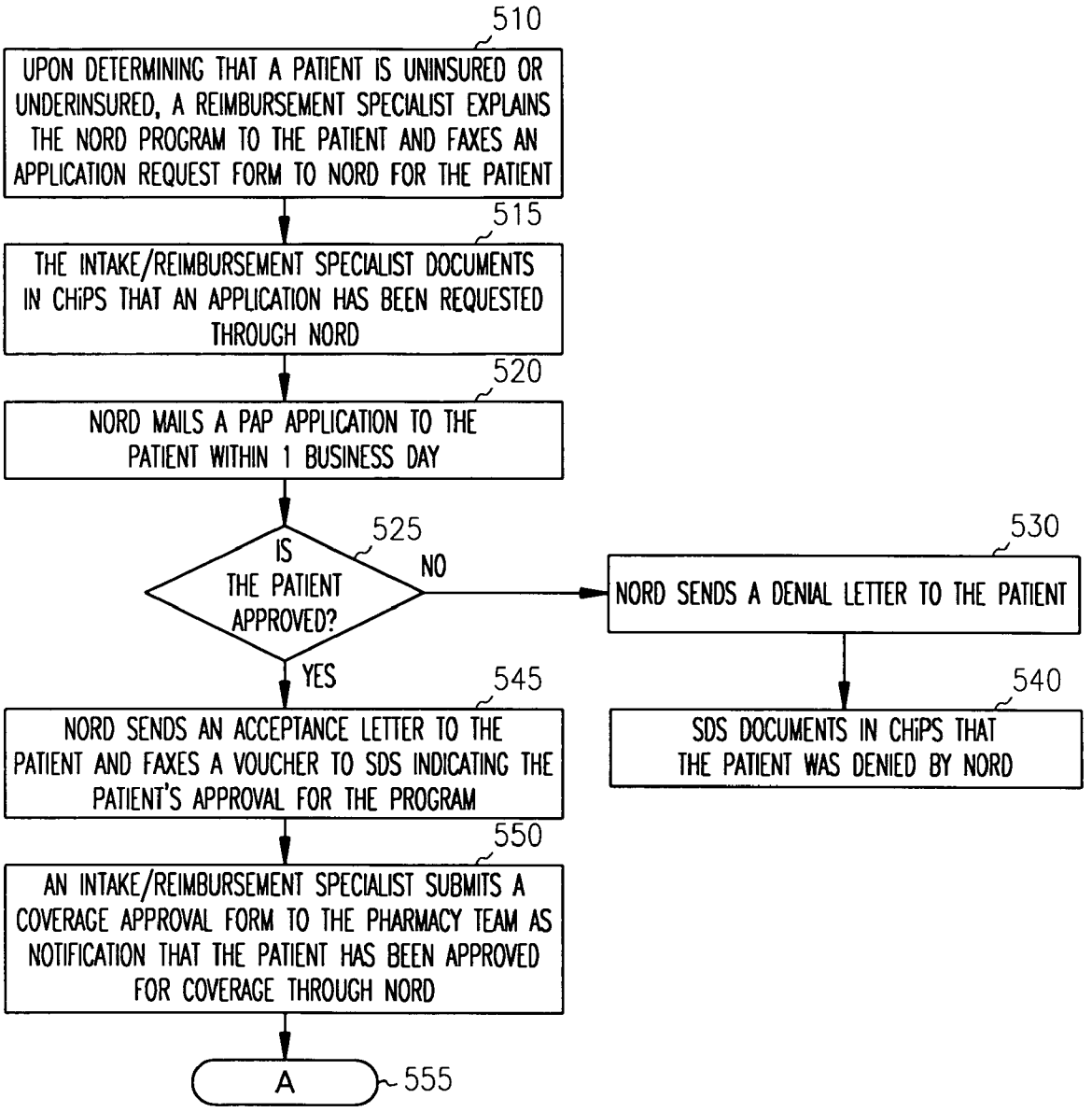

510
UPON DETERMINING THAT A PATIENT IS UNINSURED OR UNDERINSURED, A REIMBURSEMENT SPECIALIST EXPLAINS THE NORD PROGRAM TO THE PATIENT AND FAXES AN APPLICATION REQUEST FORM TO NORD FOR THE PATIENT
515
THE INTAKE/REIMBURSEMENT SPECIALIST DOCUMENTS IN CHIPS THAT AN APPLICATION HAS BEEN REQUESTED THROUGH NORD
520
NORD MAILS A PAP APPLICATION TO THE PATIENT WITHIN 1 BUSINESS DAY
525
IS THE PATIENT APPROVED?
NO
530
NORD SENDS A DENIAL LETTER TO THE PATIENT
YES
545
NORD SENDS AN ACCEPTANCE LETTER TO THE PATIENT AND FAXES A VOUCHER TO SDS INDICATING THE PATIENT'S APPROVAL FOR THE PROGRAM
540
SDS DOCUMENTS IN CHIPS THAT THE PATIENT WAS DENIED BY NORD
550
AN INTAKE/REIMBURSEMENT SPECIALIST SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT HAS BEEN APPROVED FOR COVERAGE THROUGH NORD
A
555

FIG. 5

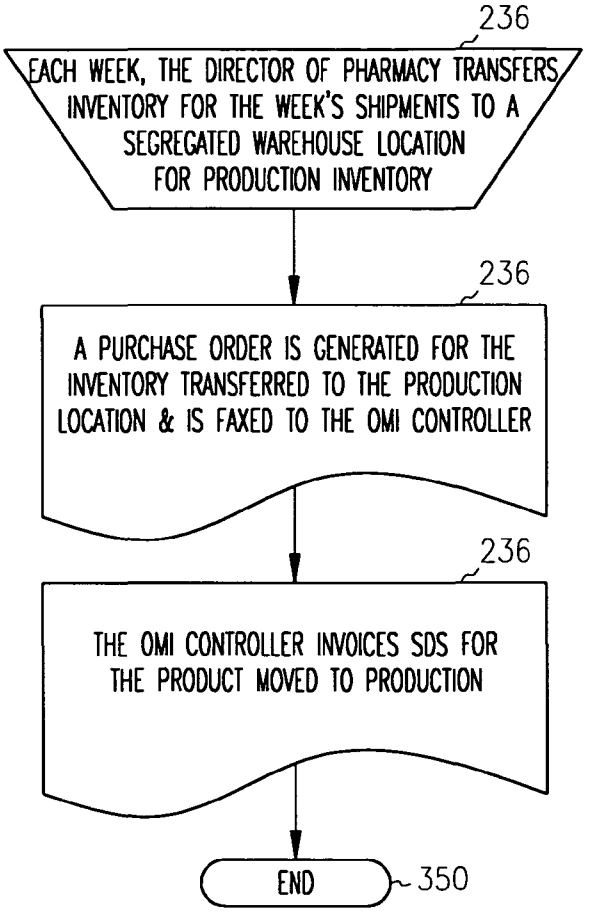


FIG. 6

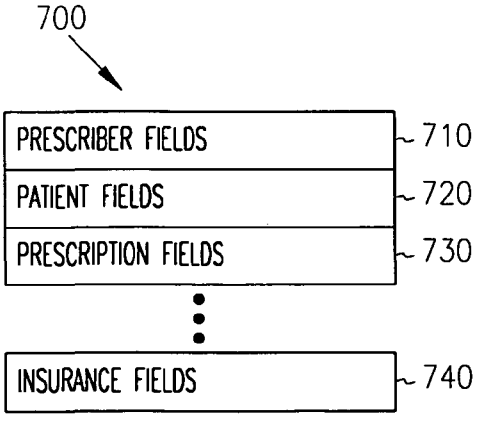


FIG. 7

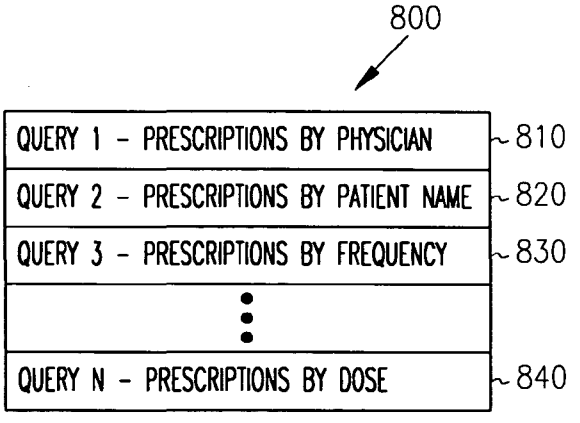


FIG. 8

900

PRESCRIPTION AND ENROLLMENT FORM

PRESCRIBER INFORMATION

PRESCRIBER'S NAME: _____ OFFICE CONTACT: _____
STREET ADDRESS: _____
CITY: _____ STATE: _____ ZIP: _____
PHONE: _____ FAX: _____
LICENSE NUMBER: _____ DEA NUMBER: _____
MD SPECIALTY: _____

PRESCRIPTION FORM

PATIENT NAME: _____ SS#: _____ DOB: _____ SEX M / F
ADDRESS: _____
CITY: _____ STATE: _____ ZIP: _____
Rx: XYREM ORAL SOLUTION (500 mg/mL) 180 ML BOTTLE QUANTITY: _____ MONTHS SUPPLY
SIG: TAKE _____ GMS P.O. DILUTED IN 60 mL WATER AT H.S. AND THEN AGAIN 2 1/2 TO 4 HOURS LATER
REFILLS (CIRCLE ONE): 0 1 2 (MAXIMUM OF 3 MONTH SUPPLY)
_____ DATE: _____/_____/_____
PRESCRIBER'S SIGNATURE

PHYSICIAN DECLARATION–PLEASE CHECK EACH BOX | TO BE COMPLETED AT INITIAL PRESCRIPTION ONLY

☐ I HAVE READ THE MATERIALS IN THE XYREM PHYSICIAN SUCCESS PROGRAM
☐ I VERIFY THAT THE PATIENT HAS BEEN EDUCATED WITH RESPECT TO XYREM PREPARATION, DOSING AND SCHEDULING.
☐ I UNDERSTAND THAT XYREM IS APPROVED FOR THE TREATMENT OF CATAPLEXY IN PATIENTS WITH NARCOLEPSY, AND THAT SAFETY OR EFFICACY HAS NOT BEEN ESTABLISHED FOR ANY OTHER INDICATION.
☐ I UNDERSTAND THAT THE SAFETY OF DOSES GREATER THAN 9gm/DAY HAS NOT BEEN ESTABLISHED

PATIENT INFORMATION

BEST TIME TO CONTACT PATIENT: ☐ DAY ☐ NIGHT
DAY #: _____ EVENING #: _____
INSURANCE COMPANY NAME: _____ PHONE #: _____
INSURED'S NAME: _____ RELATIONSHIP TO PATIENT: _____
IDENTIFICATION NUMBER: _____ POLICY/GROUP NUMBER: _____
PRESCRIPTION CARD: ☐ NO ☐ YES IF YES, CARRIER: _____ POLICY #: _____ GROUP: _____

PLEASE ATTACH COPIES OF PATIENT'S INSURANCE CARDS

FAX COMPLETED FORM TO XYREM SUCCESS PROGRAM (TOLL-FREE) 1-866-470-1744
FOR INFORMATION, CALL THE XYREM TEAM (TOLL FREE) AT 1-866-XYREM88 (1-866-997-3688)

FIG. 9

1000

PATIENT ASSISTANCE APPLICATION REQUEST FORM

DATE:

TO: PATIENT ASSISTANCE ORGANIZATION
FROM: SDS

FAX #: 203-798-2291

PLEASE SEND A XYREM PATIENT ASSISTANCE PROGRAM APPLICATION TO:

PATIENT NAME _____

ADDRESS _____

_____

_____

TELEPHONE: ( ) _____

PATIENT DOSAGE: _____ (GRAMS) TWICE NIGHTLY FOR A TOTAL DOSAGE OF _____ (GRAMS)

_____ BOTTLES (THREE MONTHS SUPPLY)

BACKGROUND INFORMATION:

_____

_____

_____

_____

_____

_____

FIG. 10

1100

SENSITIVE DRUG PATIENT ASSISTANCE PROGRAM

VOUCHER REQUEST FOR MEDICATION

PATIENT INFORMATION
<FIRST NAME><LAST NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890
DOB: 01/01/1900
SSN: 123-45-6789
DRUG ALLOTMENT: 100%
LRD: 03/01/2001

PHYSICIAN INFORMATION
<PHYSICIAN NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890

CASE CODE: ********

FIRST SHIPMENT THIS YEAR

DRUG	QUANTITY
XYREEM 180ml btl	1

VALIDATION DATE:	03/01/2001
EXPIRATION DATE:	05/31/2001
ISSUE DATE:	03/15/2001

APPROVED _____

PHARMACY USE

NORD COPY

****

(DETACH HERE)

PATIENT INFORMATION
<FIRST NAME><LAST NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890
DOB: 01/01/1900
SSN: 123-45-6789
DRUG ALLOTMENT: 100%
LRD: 03/01/2001

PHYSICIAN INFORMATION
<PHYSICIAN NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890

CASE CODE: ********

FIRST SHIPMENT THIS YEAR

DRUG	QUANTITY
XYREM 180ml btl	1

VALIDATION DATE:	03/01/2001
EXPIRATION DATE:	05/31/2001
ISSUE DATE:	03/15/2001

APPROVED _____

PHARMACY USE

FIG. 11

SENSITIVE DRUG PHYSICIAN'S CERTIFICATE
OF MEDICAL NEED

PATIENT INFORMATION

DATE: _____

NAME: _____
LAST FIRST M

DATE OF BIRTH: _____

DRUG BEING PRESCRIBED: XYREM

DIAGNOSIS/CONDITION FOR WHICH DRUG IS BEING PRESCRIBED: _____

ICD-9: _____

PHYSICIAN INFORMATION

PHYSICIAN'S NAME (PLEASE PRINT): _____

PHYSICIAN'S SIGNATURE: _____ DATE: _____

PLEASE FAX BACK TO SENSITIVE DRUG SUCCESS PROGRAM: (1-800-TOLL FREE NUMBER)

FIG. 12

ACTIVITY REPORTS

	REPORT FREQUENCY		
	WEEKLY	MONTHLY	QUARTERLY
SALES			
Rx BY ZIP (NEW AND TOTAL)	X	X	X
Rx BY PHYSICIAN BY ZIP	X	X	
$ BY ZIP	X	X	X
REGULATORY			
# OF PHYSICIAN REGISTRIES		X	
# OF DENIED PHYSICIAN REGISTRIES AND REASON		X	
# OF COMPLETED PATIENT REGISTRIES		X	
# OF PROBLEM IDENTIFICATION & MANAGEMENT RISK DIVERSION REPORTS COMPLETED	X		
# OF CYCLE COUNTS PERFORMED & ACCURACY OF EACH		X	
QUALITY ASSURANCE			
# OF PRODUCT DEFECTS/COMPLAINTS REPORTED, TYPE AND LOT #		X	
CALL CENTER			
# OF CALLS RECEIVED		X	
# OF CALLS INITIATED		X	
# OF CALLS ANSWERED IN 30 SECONDS, ETC.		X	
PERCENTAGE OF CALLS ANSWERED IN 30 SECONDS		X	
# OF ABANDONED CALLS		X	
% OF ABANDONED CALLS		X	
AVERAGE CALL LENGTH		X	
PHARMACY			
# OF FAXED Rx/ENROLLMENT FORMS		X	
# OF MAILED Rx/ENROLLEMENT FORMS		X	
# OF RxS SHIPPED W/IN 1, 2, 3, 4 ETC. DAYS (FROM THE TIME INITIAL RECEIPT TO SHIPMENT OF Rx)		X	
# OF PATIENT SUCCESS PACKETS SHIPPED		X	

FIG. 13A

ACTIVITY REPORTS

PHARMACY		X	
# OF PHYSICIAN SUCCESS PACKETS SHIPPED		X	
# OF COMPLETED SHIPMENTS		X	
# OF INCOMPLETE SHIPMENTS AND REASON		X	
# OF SHIPPING ERRORS		X	
# OF PAP SHIPMENTS		X	
# OF PAP APPLICATIONS		X	
# OF PAP APPROVALS		X	
# OF CANCELED ORDERS		X	
# OF USPS ERRORS		X	
INVENTORY		X	
# OF RETURNED PRODUCTS AND REASON		X	
# OF OUTDATED BOTTLES OF PRODUCT		X	
INVENTORY COUNTS OF CONSIGNMENT & PRODUCTION INVENTORY		X	
# OF UNITS RECEIVED		X	
LOTS RECEIVED		X	
REIMBURSEMENT		X	
# OF PENDED AND WHY		X	
# OF APPROVALS		X	
# OF DENIALS		X	
# OF REJECTIONS		X	
PAYOR TYPES		X	

FIG. 13B

ACTIVITY REPORTS

PATIENT CARE		X	
# OF ADVERSE EVENTS REPORTED AND TYPE		X	
# OF ADVERSE EVENTS SENT TO OMI		X	
# OF DOSING PROBLEMS AND TYPE		X	
# OF NONCOMPLIANCE EPISODES AND REASON		X	
# OF PATIENT COUNSELED AND REASON		X	
# OF PATIENTS DISCONTINUED AND REASON		X	
PATIENT CARE		X	
# OF PATIENTS REFERRED TO PHYSICIAN AND REASON		X	
# OF ACTIVE PATIENTS		X	
# OF NEW PATIENTS		X	
# OF RESTART PATIENTS		X	
# OF DISCONTINUED PATIENTS AND REASON		X	
DRUG INFORMATION		X	
# OF DRUG INFORMATION REQUESTS AND TYPE		X	
# OF CALLS TRIAGED TO OMI		X	

FIG. 13C

SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

RELATED APPLICATIONS

This application is a divisional application of U.S. patent application Ser. No. 10/322,348, filed Dec. 17, 2002, now U.S. Pat. No. 7,668,730 which application is incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to distribution of drugs, and in particular to the distribution of sensitive drugs.

BACKGROUND OF THE INVENTION

Sensitive drugs are controlled to minimize ensure that they are not abuse and adverse reactions. Such sensitive drugs are approved for specific uses by the Food and Drug Administration, and must be prescribed by a licensed physician in order to be purchased by consumers. Some drugs, such as cocaine and other common street drugs are the object of abuse and illegal schemes to distribute for profit. Some schemes include Dr. shopping, diversion, and pharmacy thefts. A locked cabinet or safe is a requirement for distribution of some drugs.

Certain agents, such as gamma hydroxy buterate (GHB) are also abused, yet also are effective for theraputic purposes such as treatment of daytime cataplexy in patients with narcolepsy. Some patients however, will obtain prescriptions from multiple doctors, and have them filled at different pharmacies. Still further, an unscrupulous physician may actually write multiple prescriptions for a patient, or multiple patients, who use cash to pay for the drugs. These patients will then sell the drug to dealers or others for profit.

There is a need for a distribution system and method that directly addresses these abuses. There is a further need for such a system and method that provides education and limits the potential for such abuse.

SUMMARY OF THE INVENTION

A drug distribution system and method utilizes a central pharmacy and database to track all prescriptions for a sensitive drug. Information is kept in a central database regarding all physicians allowed to prescribe the sensitive drug, and all patients receiving the drug. Abuses are identified by monitoring data in the database for prescription patterns by physicians and prescriptions obtained by patients. Further verification is made that the physician is eligible to prescribe the drug by consulting a separate database for a valid DEA license, and optionally state medical boards to determine whether any corrective or approved disciplinary actions relating to controlled substances have been brought against the physician. Multiple controls beyond those for traditional drugs are imposed on the distribution depending on the sensitivity of the drug.

Education is provided to both physician and patient. Prior to shipping the drug for the first time, the patient is contacted to ensure that product and abuse related educational materials have been received and/or read. The patient may provide the name of a designee to the central pharmacy who is authorized to accept shipment of the drug. Receipt of the initial drug shipment is confirmed by contacting the patient. Either a phone call or other communication to the patient within a set time after delivery may be made to ensure receipt. Further, a courier service's tracking system is used to confirm delivery in further embodiments. If a shipment is lost, an investigation is launched to find it.

In one embodiment, the drug may be shipped by the central pharmacy to another pharmacy for patient pick-up. The second pharmacy's ability to protect against diversion before shipping the drug must be confirmed. This ability may be checked through NTIS and State Boards of Pharmacy.

Prescription refills are permitted in the number specified in the original prescription. In addition, if a prescription refill is requested by the patient prior to the anticipated due date, such refills will be questioned. A lost, stolen, destroyed or spilled prescription/supply is documented and replaced to the extent necessary to honor the prescription, and will also cause a review or full investigation.

The exclusive central database contains all relevant data related to distribution of the drug and process of distributing it, including patient, physician and prescription information. Several queries and reports are run against the database to provide information which might reveal potential abuse of the sensitive drug, such as early refills.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a block diagram of a computer system for use in implementing the system and method of the present invention.

FIGS. **2**A, **2**B and **2**C are a flowchart describing a method for sensitive drug distribution at least partially utilizing a computer system such as that shown in FIG. **1**.

FIG. **3** is a flowchart of a physician success program at least partially implemented on a computer system such as that shown in FIG. **1**.

FIGS. **4**A and **4**B are a flowchart describing a method for handling refill requests at least partially utilizing a computer system such as that shown in FIG. **1**.

FIG. **5** is a flowchart of a process for requesting special reimbursement when a patient is uninsured or underinsured at least partially utilizing a computer system as that shown in FIG. **1**.

FIG. **6** is a flowchart of a process for inventory control at least partially utilizing a computer system such as that shown in FIG. **1**.

FIG. **7** is a block diagram of database fields.

FIG. **8** is a block diagram showing a list of queries against the database fields.

FIG. **9** is a copy of one example prescription and enrollment form.

FIG. **10** is a copy of one example of a NORD application request form for patient financial assistance.

FIG. **11** is a copy of one example voucher request for medication for use with the NORD application request form of FIG. **10**.

FIG. **12** is a copy of certificate of medical need.

FIGS. **13**A, **13**B and **13**C are descriptions of sample reports obtained by querying a central database having fields represented in FIG. **7**.

DETAILED DESCRIPTION OF THE INVENTION

In the following description, reference is made to the accompanying drawings that form a part hereof, and in which is shown by way of illustration specific embodiments in which the invention may be practiced. These embodiments are described in sufficient detail to enable those skilled in the art to practice the invention, and it is to be understood that other embodiments may be utilized and that structural, logical

and electrical changes may be made without departing from the scope of the present invention. The following description is, therefore, not to be taken in a limited sense, and the scope of the present invention is defined by the appended claims.

The functions or algorithms described herein are implemented in software or a combination of software and human implemented procedures in one embodiment. The software comprises computer executable instructions stored on computer readable media such as memory or other type of storage devices. The term "computer readable media" is also used to represent carrier waves on which the software is transmitted. Further, such functions correspond to modules, which are software, hardware, firmware of any combination thereof. Multiple functions are performed in one or more modules as desired, and the embodiments described are merely examples. The software is executed on a digital signal processor, ASIC, microprocessor, or other type of processor operating on a computer system, such as a personal computer, server or other computer system.

A sensitive drug is one which can be abused, or has addiction properties or other properties that render the drug sensitive. One example of such a drug is sodium oxybate, also known as gamma hydroxy butyrate (GHB $C_4H_7NaO_3$) which is useful for treatment of cataplexy in patients with narcolepsy. GHB is marketed under the trademark of Xyrem® (sodium oxybate oral solution), which trademark can be used interchangeably with GHB herein. Sensitive drugs also include narcotics or other drugs which require controls on their distribution and use to monitor behaviors to prevent abuse and adverse side effects.

In one embodiment, Xyrem® is subject to a restricted distribution program. One aspect of the program is to educate physicians and patients about the risks and benefits of Xyrem, including support via ongoing contact with patients and a toll free helpline. Initial prescriptions are filled only after a prescriber and patient have received and read the educational materials. Further, patient and prescribing physician registries are maintained and monitored to ensure proper distribution.

In a further embodiment, bulk sodium oxybate is manufactured at a single site, as is the finished drug product. Following manufacture of the drug product, it is stored at a facility compliant with FDA Schedule III regulations, where a consignment inventory is maintained. The inventory is owned by a company, and is managed by a central pharmacy, which maintains the consignment inventory. Xyrem® is distributed and dispensed through a primary and exclusive central pharmacy, and is not stocked in retail pharmacy outlets. It is distributed by overnight carriers, or by US mail in one embodiment to potentially invoke mail fraud laws if attempts of abuse occur.

FIG. **1** is a simplified block diagram of a computer system **100**, such as a personal computer for implementing at least a portion of the methods described herein. A central processing unit (CPU) **110** executes computer programs stored on a memory **120**. Memory **120** in one embodiment comprises one or more levels of cache as desired to speed execution of the program and access to data on which the programs operate. The CPU is directly coupled to memory **120** in one embodiment. Both CPU **110** and memory **120** are coupled to a bus **130**. A storage **140**, I/O **150** and communications **160** are also coupled to the bus **130**. Storage **140** is usually a long term storage device, such as a disk drive, tape drive, DVD, CD or other type of storage device. In one embodiment, storage **140** is used to house a database for use with the present invention. I/O **150** comprises keyboards, sound devices, displays and other mechanisms by which a user interacts with the computer system **100**. Communications **160** comprises a network, phone connection, local area network, wide area network or other mechanism for communicating with external devices. Such external devices comprise servers, other peer computers and other devices. In one embodiment, such external device comprises a database server that is used in place of the database on storage **140**. Other computer system architectures capable of executing software and interacting with a database and users may also be used. Appropriate security measures such as encryption are used to ensure confidentiality. Further, data integrity and backup measures are also used to prevent data loss.

FIGS. **2**A, **2**B and **2**C represent an initial prescription order entry process for a sensitive drug, such as Xyrem. At **202**, a medical doctor (MD) sends a Rx/enrollment form via mail, fax, email or other means to an intake/reimbursement specialist at **204**, who makes a copy of the RX/enrollment form that is stamped "copy". The original fax is forwarded to a pharmacy team. The enrollment form contains prescriber information, prescription information, checkboxes for the prescriber indicating they have read materials, educated the patient, understand the use in treatment, and understand certain safety information, and also contains patient information.

The prescriber information contains standard contact information as well as license number, DEA number and physician specialty. Patient and prescription information includes name, social security number, date of birth, gender, contact information, drug identification, patient's appropriate dosage, and number of refills allowed, along with a line for the prescriber's signature. Patient insurance information is also provided.

There are two workflows involved at the pharmacy team, intake reimbursement **206** and pharmacy workflow **208**, which may proceed in parallel or serially. The intake work flow **206** starts with an intake reimbursement specialist entering the patient and physician information into an application/database referred to as CHIPS, which is used to maintain a record of a client home infusion program (CHIP) for Xyrem®. A check is made to ensure the information is complete at **212**. If not, at **214**, an intake representative attempts to reach the MD or prescriber to obtain the missing information. If the missing information has not been obtained within a predetermined period of time, such as 24 hours at **216**, the Rx/Enrollment form is sent back to the MD with a rejection explanation. A note is entered in CHIPS that the application was rejected.

If the information is complete at **212**, the MD is contacted at **220** to verify receipt and accuracy of the patient's Rx. This contact is recorded in CHIPS. The intake and reimbursement specialist then sends a consent form and a cover letter to the patient at **224**. The insurance provider is contacted at **226** to verify coverage and benefits. At **228**, a determination is made regarding coverage for the drug. If it is not available, it is determined at **230** whether the patient is willing and able to pay. If not, a process is performed for handling patients who are uninsured or underinsured. In one embodiment, the process is referred to as a NORD process.

If the patient is willing and able to pay at **230**, the patient is informed of the cost of the product and is given payment options at **234**. At **236**, once payment is received, the intake reimbursement specialist submits a coverage approval form with the enrollment form to the pharmacy team as notification to process the patient's prescription. If coverage is approved at **228**, the intake reimbursement specialist also submits the coveral approval form with the enrollment form to the pharmacy team as notification to process the patient's prescription. Processing of the prescription is described below.

Upon receipt and initial processing of the prescription enrollment form and sending an original to the pharmacy work flow block **208**, the patient is shipped a Xyrem® success packet via mail. In one embodiment, the Xyrem® success packet contains educational material for a patient that advises of the proper use, care and handling of the drug and consequences of diversion at **268**. The medical doctor's credentials are checked to determine if the physician has a current DEA license to prescribe controlled substances and if he or she has had any actions related to misuse/misprescribing of controlled drugs against him or her, within a predetermined time, such as three months at **270**. If they have, a pharmacist holds the prescription until receiving a coverage approval form from the intake reimbursement specialist at **272**.

If the credentials have not been recently checked, the pharmacist verifies the credentials and enters all findings in the database at **274**. If the credentials are approved at **276**, the physician is indicated as approved in a physician screen populated by information from the database at **280**. The prescription is then held pending coverage approval at **282**.

If any disciplinary actions are identified, as referenced at block **278**, management of the pharmacy is notified and either approves processing of the prescription with continued monitoring of the physician, or processing of the prescription is not performed, and the physician is noted in the database as unapproved at **284**. The enrollment form is then mailed back to the physician with a cover letter reiterating that the prescription cannot be processed at **288**. The patient is also sent a letter at **290** indicating that the prescription cannot be processed and the patient is instructed to contact their physician.

Actual filling of the approved prescription begins with receipt of the coverage approval form as indicated at **240**. The patient is contacted by the pharmacy, such as by a technician to complete a technician section of a patient counseling checklist. If a pharmacist verifies that the program materials were not read at **242**, the receipt of the material is confirmed at **244** and another call is scheduled to counsel the patient before the drug is shipped.

If the program materials, were read at **242**, the checklist is completed at **246** and the technician transfers the patient to the pharmacist who reviews the entire checklist and completes remaining pharmacist specified sections. At **248**, the pharmacists indicates in the database that the patient counseling and checklist was successfully completed, indicating the date completed.

At **250**, the pharmacist schedules the patient's shipment for the next business day or the next business day that the patient or designee is able to sign for the package. Further, as indicated at **252**, the shipment must be sent to the patient's home address unless the patient is traveling or has moved. In that event, the pharmacist may determine that an exception may be made. The patient or the patient's designee who is at least 18 years old, must sign for the package upon delivery.

At **254**, the pharmacist enters the prescription order in the database, creating an order number. The pharmacist then verifies at **256** the prescription and attaches a verification label to the hard copy prescription. At **258**, a pick ticket is generated for the order and the order is forwarded to the pharmacy for fulfillment. The shipment is confirmed in the database at **260**, and the order is shipped by USPS Express Mail. Use of the US mail invokes certain criminal penalties for unauthorized diversion. Optionally, other mail services may be used. Potential changes in the law may also bring criminal penalties into play. Following shipment, the patient is called by the central pharmacy to confirm that the prescription was received.

As noted at **266**, for the sensitive drug, Xyrem, all inventory is cycle counted an reconciled with the database system quantities before shipments for the day are sent. This provides a very precise control of the inventor.

A physician success program materials request process begins at **310** in FIG. **3**. At **320**, the MD calls to the central pharmacy to request program materials. A special phone number is provided. MD demographics, DEA number, and data or request are entered into the database at **330**. At **340**, a request is made to ship the materials to the MD via a fulfillment website, or other mechanism. The request process ends at **350**.

A refill request process begins at **302** in FIGS. **4**A and **4**B. There are two different paths for refills. A first path beginning at **404** involves generating a report from the central database of patients with a predetermined number of days or product remaining. A second path beginning at **406** is followed when a patient calls to request an early refill.

In the first path, a copy of the report is provided to an intake reimbursement specialist at **408**. No sooner than 8 days before the medication depletion, a pharmacy technician contacts the patient at **410** to complete the pre-delivery checklist. At **412**, if the patient is not reached, a message is left mentioning the depletion, and a return number at **414**. A note is also entered into the database indicating the date the message was left at **416**.

If the patient is reached at **412**, the next shipment is scheduled at **418**, the prescription is entered into the database creating an order at **420**, the pharmacist verifies the prescription and attaches a verification label at **422** and the shipment is confirmed in the database at **424**. Note at **426** that the inventory is cycle counted and reconciled with the database quantities before the shipments for a day or other time period are sent. A pick ticket is generated for the order and the order is forwarded for fulfillment at **428**, with the first path ending at **430**.

The second path, beginning at **406** results in a note code being entered into the database on a patient screen indicating an early refill request at **432**. The pharmacist evaluates the patient's compliance with therapy or possible product diversion, misuse or over-use at **436**. In one embodiment, cash payers are also identified. The pharmacist then contacts the prescribing physician to alert them of the situation and confirm if the physician approves of the early refill at **438**. If the physician does not approve as indicated at **440**, the patient must wait until the next scheduled refill date to receive additional product as indicated at **442**, and the process ends at **444**.

If the physician approves at **440**, the pharmacist enters a note in the database on a patient screen that the physician approves the request at **446**. The pharmacist notifies an intake reimbursement specialist to contact the patient's insurance provider to verify coverage for the early refill at **448**. If the insurance provider will pay as determined at **450**, the specialist submits the coverage approval form as notification that the refill may be processed at **452**. At **454**, the pharmacy technician contacts the patient to schedule shipment of the product for the next business day, and the process of filling the order is continued at **456** by following the process beginning at **240**.

If the insurance provider will not pay at **450**, it is determined whether the patient is willing and/or able to pay at **458**. If not, the patient must wait until the next scheduled refill date to receive additional product at **460**. If it was determined at **458** that the patient was willing and able to pay, the patient is informed of the cost of the product and is given payment options at **462**. Once payment is received as indicated at **464**, the specialist submits a coverage approval form to the pharmacy team as notification that the refill request can be pro-

cessed at **466**. At **468**, the pharmacy technician contacts the patient to schedule shipment. The process of filling the order is continued at **470** by following the process beginning at **240**.

A process, referred to as a NORD process in one embodiment is used to determine whether donated, third party funds are available for paying for prescriptions where neither insurance will, nor the patient can pay. The process begins at **510** upon determining that a patient is uninsured or underinsured. A reimbursement specialist explains the NORD program to the patient and faxes an application request form to NORD for the patient. At **515**, the intake reimbursement specialist documents in the database that an application has been received through NORD. At **520**, NORD mails an application to the patient within one business day.

A determination is made at **525** by NORD whether the patient is approved. If not, at **530**, NORD sends a denial letter to the patient, and it is documented in the database at **540** that the patient was denied by NORD. If the patient is approved, NORD sends an acceptance letter to the patient and faxes a voucher to the central pharmacy (SDS in one embodiment) to indicate the approval at **545**. At **550**, an intake reimbursement specialist submits a coverage approval form to the pharmacy team as notification that the patient has been approved for coverage. The process of filling the order is continued at **555** by following the process beginning at **240**.

An inventory control process is illustrated in FIG. **6** beginning at **610**. Each week, a responsible person at the central pharmacy, such as the director of the pharmacy transfers inventory for the week's shipments to a segregated warehouse location for production inventory. At **620**, a purchase order is generated for the inventory transferred to the production location and is sent, such as by fax, to a controller, such as the controller of the company that obtained approval for distribution and use of the sensitive drug. At **630**, the controller invoices the central pharmacy for the product moved to production. The process ends at **640**.

The central database described above is a relational database running on the system of FIG. **1**, or a server based system having a similar architecture coupled to workstations via a network, as represented by communications **160**. The database is likely stored in storage **140**, and contains multiple fields of information as indicated at **700** in FIG. **7**. The organization and groupings of the fields are shown in one format for convenience. It is recognized that many different organizations or schemas may be utilized. In one embodiment, the groups of fields comprise prescriber fields **710**, patient fields **720**, prescription fields **730** and insurance fields **740**. For purposes of illustration, all the entries described with respect to the above processes are included in the fields. In further embodiments, no such groupings are made, and the data is organized in a different manner.

Several queries are illustrated at **800** in FIG. **8**. There may be many other queries as required by individual state reporting requirements. A first query at **810** is used to identify prescriptions written by physician. The queries may be written in structured query language, natural query languages or in any other manner compatible with the database. A second query **820** is used to pull information from the database related to prescriptions by patient name. A third query **830** is used to determine prescriptions by frequency, and a n^{th} query finds prescriptions by dose at **840**. Using query languages combined with the depth of data in the central database allows many other methods of investigating for potential abuse of the drugs. The central database ensures that all prescriptions, prescribers and patients are tracked and subject to such investigations. In further embodiments, the central database may be distributed among multiple computers provided a query operates over all data relating to such prescriptions, prescribers and patients for the drug.

An example of one prescription and enrollment form is shown at **900** in FIG. **9**. As previously indicated, several fields are included for prescriber information, prescription information and patient information.

FIG. **10** is a copy of one example NORD application request form **1000** used to request that an application be sent to a patient for financial assistance.

FIG. **11** is a copy of one example application **1100** for financial assistance as requested by form **1000**. The form requires both patient and physician information. Social security number information is also requested. The form provides information for approving the financial assistance and for tracking assistance provided.

FIG. **12** is a copy of one example voucher request for medication for use with the NORD application request form of FIG. **10**. In addition to patient and physician information, prescription information and diagnosis information is also provided.

FIGS. **13**A, **13**B and **13**C are descriptions of sample reports obtained by querying a central database having fields represented in FIG. **7**. The activities grouped by sales, regulatory, quality assurance, call center, pharmacy, inventory, reimbursement, patient care and drug information. Each report has an associated frequency or frequencies. The reports are obtained by running queries against the database, with the queries written in one of many query languages.

While the invention has been described with respect to a Schedule III drug, it is useful for other sensitive drugs that are DEA or Federally scheduled drugs in Schedule II-V, as well as still other sensitive drugs where multiple controls are desired for distribution and use.

The invention claimed is:

1. A therapeutic method for treating a patient with a prescription drug that is effective for therapeutic purposes, but is also a drug that has potential to be abused, misused, or diverted, comprising:

receiving, only into an exclusive central computer system, all prescriptions for any and all patients being prescribed the prescription drug and from any and all doctors allowed to prescribe the prescription drug, the prescriptions containing information identifying the patient, the prescription drug, and various credentials of the medical doctor who is prescribing the prescription drug;

requiring entering of the information into an exclusive computer database associated with the exclusive central computer system for analysis of potential abuse, misuse, or diversion of the prescription drug, such that all prescriptions for the prescription drug are processed for authorization only using the exclusive central computer system and the exclusive computer database;

controlling the distribution of said prescription drug using the exclusive central computer system that tracks all prescriptions of said prescription drug and analyzes for the potential abuse, misuse, or diversion of the prescription drug by determining current and anticipated patterns of potential prescription abuse, misuse, or diversion of said prescription drug from periodic reports generated by the exclusive central computer system and the exclusive computer database based on prescription data from a medical doctor, wherein said prescription data contain information identifying the patient, the drug prescribed, and credentials of the doctor; and selecting multiple controls for distribution using said exclusive central computer system, the controls selected

from the group consisting of communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; verifying the home address of the patient; shipping via US postal service or a commercial shipping service; receiving the name of an at least 18 year old designee to receive the drug; confirming receipt of an initial shipment of the drug to the patient; returning the drug to a pharmacy after two attempts to deliver; launching an investigation when a shipment is lost; shipping to another pharmacy for delivery; requiring manufacture at a single location; authorizing release of inventory in a controlled manner; questioning early refills; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; limiting the prescription to a one month supply; requiring rewriting of the prescription periodically; and making the database available to the DEA for checking for abuse, misuse, or diversion patterns in the data, for cash payments, and for inappropriate questions;

authorizing the filling, using the exclusive central computer system, of a prescription for the prescription drug that has been subjected to said multiple controls and has been approved for shipment to the patient;

noting, based on one or more of the analysis of the potential abuse, misuse, or diversion of the prescription drug and the periodic reports, that there is a potential for abuse, misuse, or diversion by the patient to whom the prescription drug is prescribed; and

delivering the prescription drug to the patient in order to treat the patient with the prescription drug.

2. The method of claim **1** , wherein the controls for distribution are communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; or requiring rewriting of the prescription periodically.

3. A therapeutic method for treating a narcoleptic patient with sodium oxybate for daytime cataplexy comprising:

receiving, only into an exclusive central computer system, all prescriptions for any and all patients being prescribed sodium oxybate and from any and all medical doctors allowed to prescribe sodium oxybate, the prescriptions containing information relating to the patient, sodium oxybate, and various credentials of the medical doctor who is prescribing the sodium oxybate;

requiring entering of the information into an exclusive computer database associated with the exclusive central computer system for analysis of potential abuse, misuse, or diversion, such that all prescriptions for sodium oxybate are processed for authorization only using the exclusive central computer system and the exclusive computer database;

controlling the distribution of sodium oxybate using the exclusive central computer system that tracks all prescriptions of sodium oxybate and analyzes for the potential abuse, misuse, or diversion by determining current and anticipated patterns of potential prescription abuse, misuse, or diversion of sodium oxybate from periodic reports generated by the exclusive central computer system based on prescription data from a medical doctor, wherein said prescription data contain information identifying the patient, sodium oxybate as the drug prescribed, and credentials of the doctor; and selecting multiple controls for distribution using said exclusive central computer system, the controls selected from the group consisting of communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying the physician is eligible to prescribe sodium oxybate by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; verifying the home address of the patient; shipping via US postal service or a commercial shipping service; receiving the name of an at least 18 year old designee to receive the drug; confirming receipt of an initial shipment of the drug to the patient; returning the drug to a pharmacy after two attempts to deliver; launching an investigation when a shipment is lost; shipping to another pharmacy for delivery; requiring manufacture at a single location; authorizing release of inventory in a controlled manner; questioning early refills; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; limiting the prescription to a one month supply; requiring rewriting of the prescription periodically; and making the database available to the DEA for checking for abuse, misuse, or diversion patterns in the data, for cash payments, and for inappropriate questions;

authorizing the filling, using the exclusive central computer system, of a prescription for sodium oxybate that has been subjected to said multiple controls and has been approved for shipment to the patient;

noting, based on one or more of the analysis of the potential abuse, misuse, or diversion of the prescription drug and the periodic reports, that there is a potential for abuse, misuse, or diversion by the patient to whom the prescription drug is prescribed; and

delivering the sodium oxybate to the patient in order to treat the patient with the sodium oxybate.

4. The method of claim **3**, wherein the controls for distribution are communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying patient registry information; providing comprehensive education information to the

patient; verifying the patient has received and/or reviewed the educational materials; or requiring rewriting of the prescription periodically.

5. A therapeutic method for treating a patient with a prescription drug that is effective for therapeutic purposes, but is also a drug that has potential to be abused, misused, or diverted, comprising:

receiving, only into an exclusive computer database in a computer system, from any and all medical doctors allowed to prescribe the prescription drug and any and all patients being prescribed the prescription drug, all prescriptions for the prescription drug, the prescriptions containing information identifying the patient, the prescription drug, and various credentials of the medical doctor who is prescribing the prescription drug;

requiring entering of the information into the exclusive computer database for analysis of potential abuse, misuse, or diversion of the prescription drug, such that all prescriptions for the prescription drug are processed for authorization only via the exclusive computer database;

controlling the distribution of said prescription drug with the computer system that tracks all prescriptions of said prescription drug and analyzes for the potential abuse, misuse, or diversion of the prescription drug by determining current and anticipated patterns of potential prescription abuse, misuse, or diversion of said prescription drug from periodic reports generated by the computer system based on prescription data from a medical doctor, wherein said prescription data contain information identifying the patient, the drug prescribed, and credentials of the doctor; and selecting multiple controls for distribution of the prescription drug, the controls selected from the group consisting of communicating prescriptions from a physician to the exclusive computer database; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; verifying the home address of the patient; shipping via US postal service or a commercial shipping service; receiving the name of an at least 18 year old designee to receive the drug; confirming receipt of an initial shipment of the drug to the patient; returning the drug to a pharmacy after two attempts to deliver; launching an investigation when a shipment is lost; shipping to another pharmacy for delivery; requiring manufacture at a single location; authorizing the release of inventory in a controlled manner; questioning early refills; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; limiting the prescription to a one month supply; requiring rewriting of the prescription periodically; and making the database available to the DEA for checking for abuse, misuse, or diversion patterns in the data, for cash payments, and for inappropriate questions;

authorizing the filling, using the exclusive computer database, of a prescription for the prescription drug that has been subjected to said multiple controls and has been approved for shipment to the patient;

noting, based on one or more of the analysis of the potential abuse, misuse, or diversion of the prescription drug and the periodic reports, that there is a potential for abuse, misuse, or diversion by the patient to whom the prescription drug is prescribed; and

delivering the prescription drug to the patient in order to treat the patient with the prescription drug.

6. The method of claim **5**, wherein the controls for distribution are communicating prescriptions from a physician to the exclusive computer database; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; or requiring rewriting of the prescription periodically.

7. A therapeutic method for treating a patient with a prescription drug that is effective for therapeutic purposes, but is also a drug that has potential to be abused, misused, or diverted, comprising:

receiving, only into an exclusive central computer system, all prescriptions for any and all patients being prescribed the prescription drug and any and all medical doctors allowed to prescribed the prescription drug, the prescriptions containing information identifying the patient, the prescription drug, and various credentials of the medical doctor who is writing the prescription;

requiring entering of the information into an exclusive computer database associated with the exclusive central computer system for analysis of potential abuse, misuse, or diversion of the prescription drug, such that all prescriptions for the prescription drug are processed for authorization only using the exclusive central computer system and the exclusive computer database;

controlling the distribution of said prescription drug using the exclusive central computer system that tracks all prescriptions of said prescription drug and analyzes for the potential abuse, misuse, or diversion of the prescription drug by determining current and anticipated patterns of potential prescription abuse, misuse, or diversion of said prescription drug from periodic reports generated by the exclusive central computer system and the exclusive computer database based on prescription data from a medical doctor, wherein said prescription data contain information identifying the patient, the drug prescribed, and credentials of the doctor; and selecting multiple controls for distribution using the exclusive central computer system, the controls selected from the group consisting of communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information;

verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials;

verifying the home address of the patient; shipping via US postal service or a commercial shipping service; receiving the name of an at least 18 year old designee to receive the drug; confirming receipt of an initial shipment of the drug to the patient; returning the drug to a pharmacy after two attempts to deliver; launching an investigation when a shipment is lost; shipping to another pharmacy for delivery; requiring manufacture at a single location; authorizing release of inventory in a controlled manner; questioning early refills; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; limiting the prescription to a one month supply; requiring rewriting of the prescription periodically; and making the database available to the DEA for checking for abuse, misuse, or diversion patterns in the data, for cash payments, and for inappropriate questions;

authorizing the filling, using the exclusive central computer system, of a prescription for the prescription drug that has been subjected to said multiple controls and has been approved for shipment to the patient;

noting, based on one or more of the analysis of the potential abuse, misuse, or diversion of the prescription drug and the periodic reports, that there is a potential for abuse, misuse, or diversion by the patient to whom the prescription drug is prescribed; and

delivering the prescription drug to the patient in order to treat the patient with the prescription drug.

8. The method of claim **7**, wherein the controls for distribution are communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; or requiring rewriting of the prescription periodically.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,765,106 B2
APPLICATION NO. : 10/979665
DATED : July 27, 2010
INVENTOR(S) : Dayton T. Reardan et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 12, lines 20-67, column 13, lines 1-20, column 14, lines 1-7, in Claim 7, delete "7. A therapeutic method for treating a patient with a prescription drug that is effective for therapeutic purposes, but is also a drug that has potential to be abused, misused, or diverted, comprising:

receiving, only into an exclusive central computer system, all prescriptions for any and all patients being prescribed the prescription drug and any and all medical doctors allowed to prescribed the prescription drug, the prescriptions containing information identifying the patient, the prescription drug, and various credentials of the medical doctor who is writing the prescription;

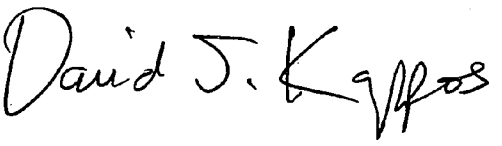
requiring entering of the information into an exclusive computer database associated with the exclusive central computer system for analysis of potential abuse, misuse, or diversion of the prescription drug, such that all prescriptions for the prescription drug are processed for authorization only using the exclusive central computer system and the exclusive computer database;

controlling the distribution of said prescription drug using the exclusive central computer system that tracks all prescriptions of said prescription drug and analyzes for the potential abuse, misuse, or diversion of the prescription drug by determining current and anticipated patterns of potential prescription abuse, misuse, or diversion of said prescription drug from periodic reports generated by the exclusive central computer system and the exclusive computer database based on prescription data from a medical doctor, wherein said prescription data contain information identifying the patient, the drug prescribed, and credentials of the doctor; and selecting multiple controls for distribution using the exclusive central computer system, the controls selected from the group consisting of communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information;

verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; verifying the home address of the patient; shipping via US postal service or a commercial shipping service; receiving the name of an at least 18 year old designee to receive the drug;

Signed and Sealed this

Twenty-third Day of November, 2010



David J. Kappos
Director of the United States Patent and Trademark Office

confirming receipt of an initial shipment of the drug to the patient; returning the drug to a pharmacy after two attempts to deliver; launching an investigation when a shipment is lost; shipping to another pharmacy for delivery; requiring manufacture at a single location; authorizing release of inventory in a controlled manner; questioning early refills; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; limiting the prescription to a one month supply; requiring rewriting of the prescription periodically; and making the database available to the DEA for checking for abuse, misuse, or diversion patterns in the data, for cash payments, and for inappropriate questions;

authorizing the filling, using the exclusive central computer system, of a prescription for the prescription drug that has been subjected to said multiple controls and has been approved for shipment to the patient;

noting, based on one or more of the analysis of the potential abuse, misuse, or diversion of the prescription drug and the periodic reports, that there is a potential for abuse, misuse, or diversion by the patient to whom the prescription drug is prescribed; and

delivering the prescription drug to the patient in order to treat the patient with the prescription drug." and

insert -- 7. A therapeutic method for treating a patient with a prescription drug that is effective for therapeutic purposes, but is also a drug that has potential to be abused, misused, or diverted, comprising:

receiving, only into an exclusive central computer system, all prescriptions for any and all patients being prescribed the prescription drug and any and all medical doctors allowed to prescribed the prescription drug, the prescriptions containing information identifying the patient, the prescription drug, and various credentials of the medical doctor who is writing the prescription;

requiring entering of the information into an exclusive computer database associated with the exclusive central computer system for analysis of potential abuse, misuse, or diversion of the prescription drug, such that all prescriptions for the prescription drug are processed for authorization only using the exclusive central computer system and the exclusive computer database;

controlling the distribution of said prescription drug using the exclusive central computer system that tracks all prescriptions of said prescription drug and analyzes for the potential abuse, misuse, or diversion of the prescription drug by determining current and anticipated patterns of potential prescription abuse, misuse, or diversion of said prescription drug from periodic reports generated by the exclusive central computer system and the exclusive computer database based on prescription data from a medical doctor, wherein said prescription data contain information identifying the patient, the drug prescribed, and credentials of the doctor; and selecting multiple controls for distribution using the exclusive central computer system, the controls selected from the group consisting of communicating prescriptions from a physician to the exclusive central computer system; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has received and/or reviewed the educational materials; verifying the home address of the patient; shipping via US postal service or a commercial shipping service; receiving the name of an at least 18 year old designee to receive the drug; confirming receipt of

an initial shipment of the drug to the patient; returning the drug to a pharmacy after two attempts to deliver; launching an investigation when a shipment is lost; shipping to another pharmacy for delivery; requiring manufacture at a single location; authorizing release of inventory in a controlled manner; questioning early refills; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; limiting the prescription to a one month supply; requiring rewriting of the prescription periodically; and making the database available to the DEA for checking for abuse, misuse, or diversion patterns in the data, for cash payments, and for inappropriate questions;

authorizing the filling, using the exclusive central computer system, of a prescription for the prescription drug that has been subjected to said multiple controls and has been approved for shipment to the patient;

noting, based on one or more of the analysis of the potential abuse, misuse, or diversion of the prescription drug and the periodic reports, that there is a potential for abuse, misuse, or diversion by the patient to whom the prescription drug is prescribed; and

delivering the prescription drug to the patient in order to treat the patient with the prescription drug. --, therefor.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,765,106 B2
APPLICATION NO. : 10/979665
DATED : July 27, 2010
INVENTOR(S) : Dayton T. Reardan et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Delete the Title Page showing an illustrative figure, and substitute the attached Title Page therefor.

Delete Sheet 2 of 16 showing Fig. 2A, and substitute the attached sheet therefor.

On Sheet 10 of 16, in Figure 9, line 23, after "ESTABLISHED" insert -- . --.

In column 1, line 27, delete "buterate" and insert -- butyrate --, therefor.

In column 1, line 28, delete "theraputic" and insert -- therapeutic --, therefor.

In column 4, line 65, delete "coveral" and insert -- coverage --, therefor.

Signed and Sealed this
Fifteenth Day of February, 2011

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

(12) **United States Patent**
Reardan et al.

(10) **Patent No.: US 7,765,106 B2**
(45) **Date of Patent: *Jul. 27, 2010**

(54) **SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD**

(75) Inventors: **Dayton T. Reardan**, Excelsior, MN (US); **Patti A. Engel**, Eagan, MN (US); **Bob Gagne**, St. Paul, MN (US)

(73) Assignee: **JPI Commercial, LLC**, Palo Alto, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1645 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/979,665**

(22) Filed: **Nov. 2, 2004**

(65) **Prior Publication Data**

US 2005/0090425 A1 Apr. 28, 2005

Related U.S. Application Data

(62) Division of application No. 10/322,348, filed on Dec. 17, 2002, now Pat. No. 7,668,730.

(51) **Int. Cl.**
G06Q 10/00 (2006.01)

(52) **U.S. Cl.** **705/2**; 705/3

(58) **Field of Classification Search** 705/2, 705/3

See application file for complete search history.

(56) **References Cited**

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5,845,255	A	12/1998	Mayaud	705/3
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6,952,681	B2	10/2005	McQuade et al.	
7,058,584	B2	6/2006	Kosinski et al.	

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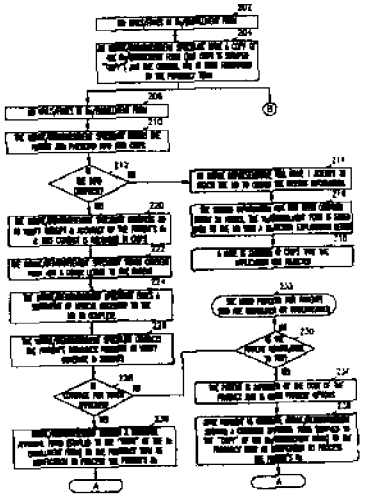
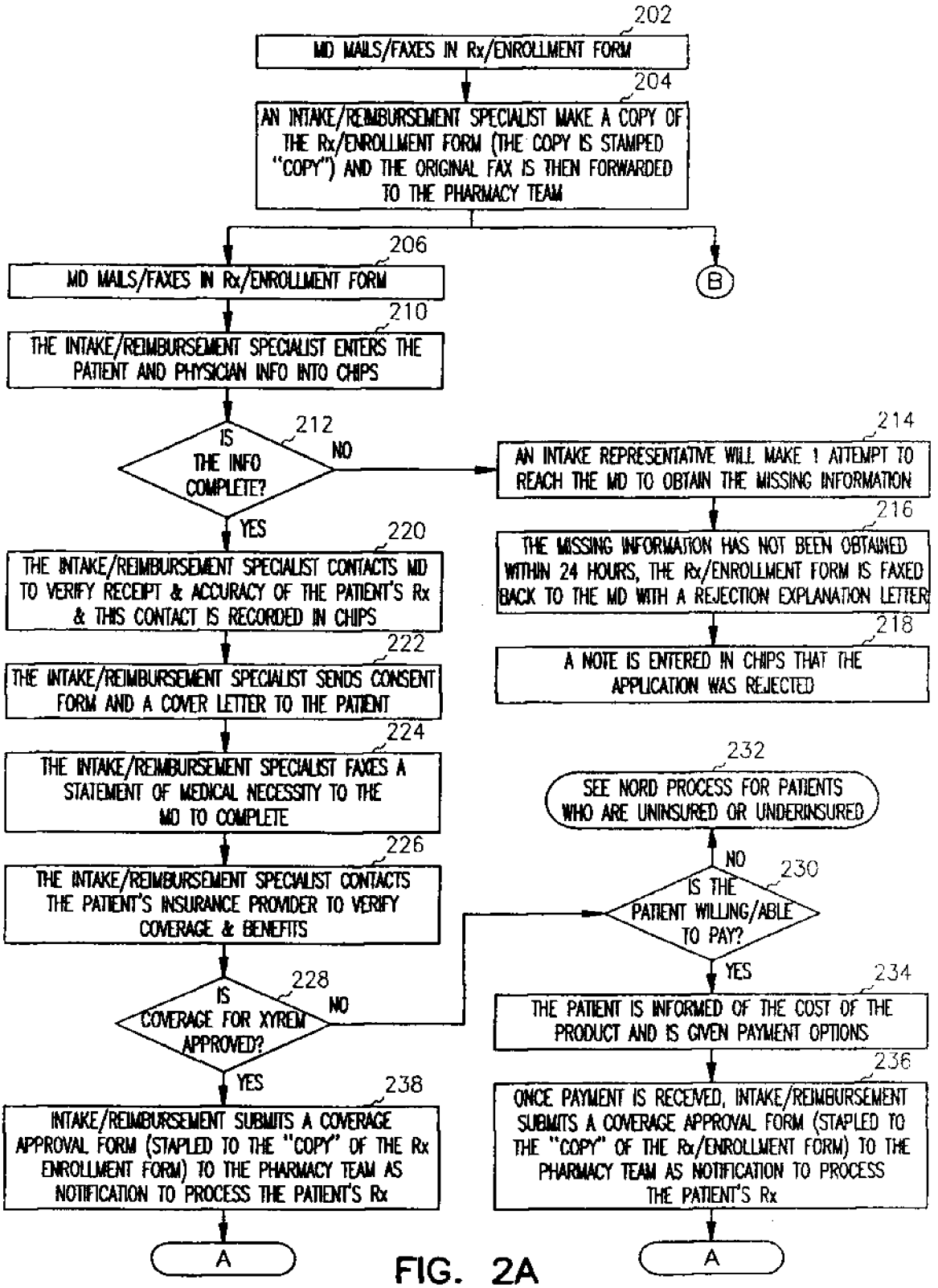
Primary Examiner—Gerald J. O'Connor
Assistant Examiner—Lena Najarian
(74) *Attorney, Agent, or Firm*— Schwegman, Lundberg & Woessner, P.A.

(57) **ABSTRACT**

A drug distribution system and method utilizes a central pharmacy and database to track all prescriptions for a sensitive drug. Information is kept in the database regarding all physicians allowed to prescribe the sensitive drug, and all patients receiving the drug. Abuses are identified by monitoring data in the database for prescription patterns by physicians and prescriptions obtained by patients. Further verification is made that the physician is eligible to prescribe the drug by consulting a separate database, and optionally whether any actions are taken against the physician. Multiple controls beyond those for normal drugs are imposed on the distribution depending on the sensitivity of the drug.

8 Claims, 16 Drawing Sheets

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A
A

FIG. 2A

EXHIBIT C

US007765107B2

(12) **United States Patent**
Reardan et al.

(10) **Patent No.: US 7,765,107 B2**
(45) **Date of Patent: *Jul. 27, 2010**

(54) **SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD**

(75) Inventors: **Dayton T. Reardan**, Excelsior, MN (US); **Patti A. Engel**, Eagan, MN (US); **Bob Gagne**, St. Paul, MN (US)

(73) Assignee: **JPI Commercial, LLC.**, Palo Alto, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1369 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/097,985**

(22) Filed: **Apr. 1, 2005**

(65) **Prior Publication Data**

US 2005/0216309 A1 Sep. 29, 2005

Related U.S. Application Data

(62) Division of application No. 10/322,348, filed on Dec. 17, 2002, now Pat. No. 7,668,730.

(51) **Int. Cl.**
G06Q 10/00 (2006.01)

(52) **U.S. Cl.** **705/2**; 705/3

(58) **Field of Classification Search** 705/2, 705/3

See application file for complete search history.

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6,347,329	B1		2/2002	Evans
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Primary Examiner—Gerald J. O'Connor
Assistant Examiner—Lena Najarian
(74) *Attorney, Agent, or Firm*—Schwegman, Lundberg & Woessner, P.A.

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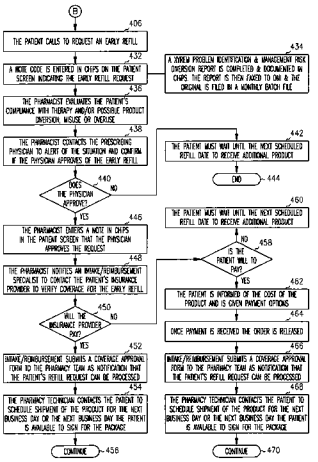
6 Claims, 16 Drawing Sheets



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"U.S. Appl. No. 11/097,651 , Non-Final Office Action mailed Mar. 3, 2010", 19 Pgs.

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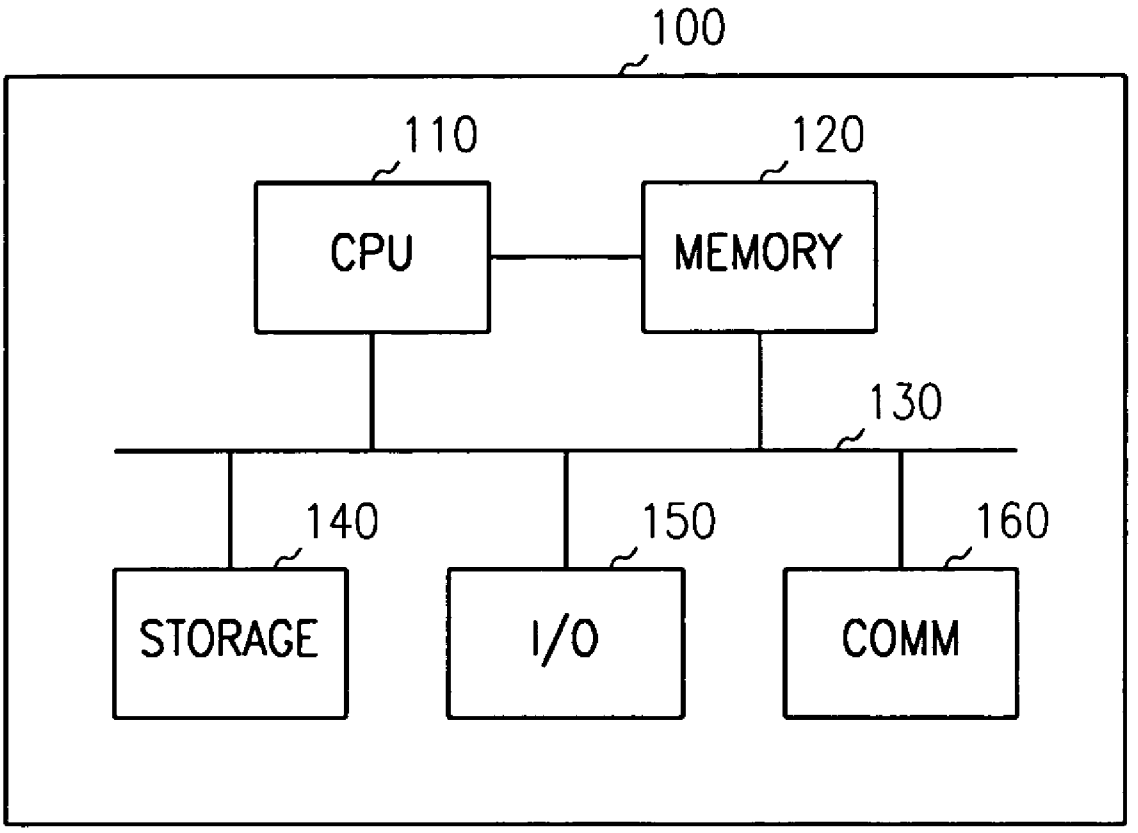
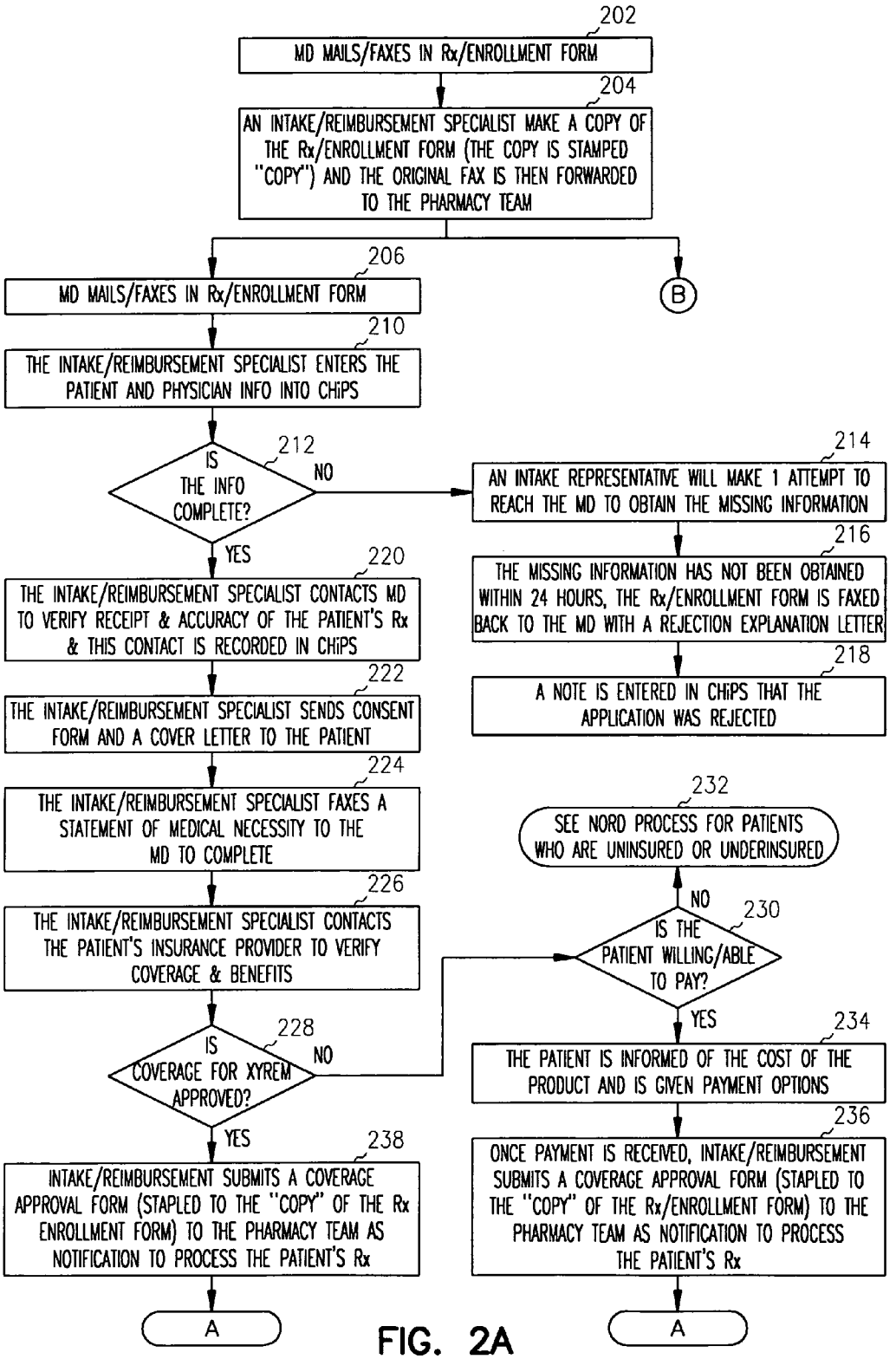


FIG. 1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A
A

FIG. 2A

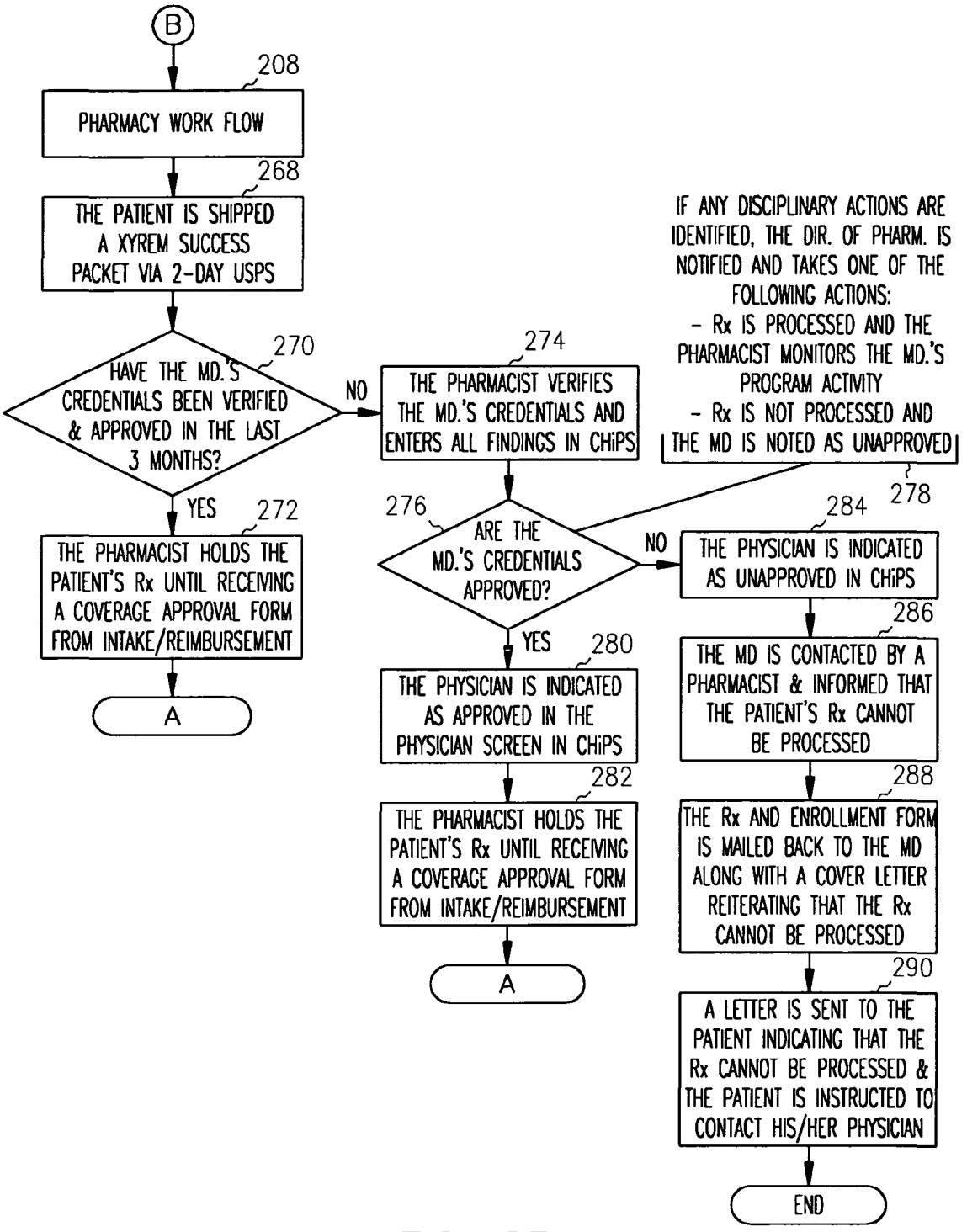
B
208
PHARMACY WORK FLOW
268
THE PATIENT IS SHIPPED A XYREM SUCCESS PACKET VIA 2-DAY USPS
270
HAVE THE MD.'S CREDENTIALS BEEN VERIFIED & APPROVED IN THE LAST 3 MONTHS?
NO
YES
272
THE PHARMACIST HOLDS THE PATIENT'S Rx UNTIL RECEIVING A COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT
A
274
THE PHARMACIST VERIFIES THE MD.'S CREDENTIALS AND ENTERS ALL FINDINGS IN CHiPS
276
ARE THE MD.'S CREDENTIALS APPROVED?
NO
YES
280
THE PHYSICIAN IS INDICATED AS APPROVED IN THE PHYSICIAN SCREEN IN CHiPS
282
THE PHARMACIST HOLDS THE PATIENT'S Rx UNTIL RECEIVING A COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT
A
IF ANY DISCIPLINARY ACTIONS ARE IDENTIFIED, THE DIR. OF PHARM. IS NOTIFIED AND TAKES ONE OF THE FOLLOWING ACTIONS:
- Rx IS PROCESSED AND THE PHARMACIST MONITORS THE MD.'S PROGRAM ACTIVITY
- Rx IS NOT PROCESSED AND THE MD IS NOTED AS UNAPPROVED
278
284
THE PHYSICIAN IS INDICATED AS UNAPPROVED IN CHiPS
286
THE MD IS CONTACTED BY A PHARMACIST & INFORMED THAT THE PATIENT'S Rx CANNOT BE PROCESSED
288
THE Rx AND ENROLLMENT FORM IS MAILED BACK TO THE MD ALONG WITH A COVER LETTER REITERATING THAT THE Rx CANNOT BE PROCESSED
290
A LETTER IS SENT TO THE PATIENT INDICATING THAT THE Rx CANNOT BE PROCESSED & THE PATIENT IS INSTRUCTED TO CONTACT HIS/HER PHYSICIAN
END

FIG. 2B

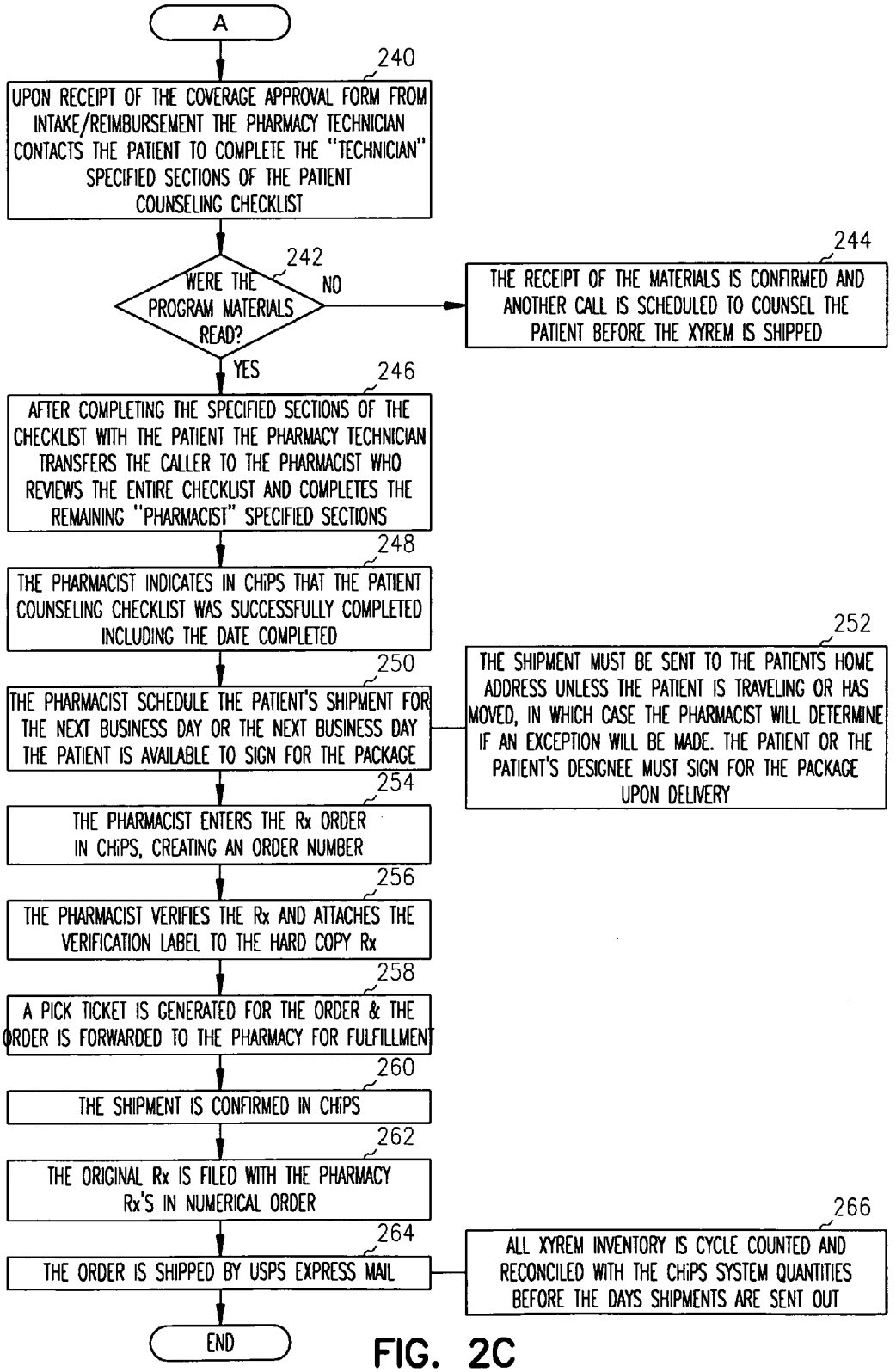
A
240
UPON RECEIPT OF THE COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE THE "TECHNICIAN" SPECIFIED SECTIONS OF THE PATIENT COUNSELING CHECKLIST
242
WERE THE PROGRAM MATERIALS READ?
NO
244
THE RECEIPT OF THE MATERIALS IS CONFIRMED AND ANOTHER CALL IS SCHEDULED TO COUNSEL THE PATIENT BEFORE THE XYREM IS SHIPPED
YES
246
AFTER COMPLETING THE SPECIFIED SECTIONS OF THE CHECKLIST WITH THE PATIENT THE PHARMACY TECHNICIAN TRANSFERS THE CALLER TO THE PHARMACIST WHO REVIEWS THE ENTIRE CHECKLIST AND COMPLETES THE REMAINING "PHARMACIST" SPECIFIED SECTIONS
248
THE PHARMACIST INDICATES IN CHIPS THAT THE PATIENT COUNSELING CHECKLIST WAS SUCCESSFULLY COMPLETED INCLUDING THE DATE COMPLETED
250
THE PHARMACIST SCHEDULE THE PATIENT'S SHIPMENT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
252
THE SHIPMENT MUST BE SENT TO THE PATIENTS HOME ADDRESS UNLESS THE PATIENT IS TRAVELING OR HAS MOVED, IN WHICH CASE THE PHARMACIST WILL DETERMINE IF AN EXCEPTION WILL BE MADE. THE PATIENT OR THE PATIENT'S DESIGNEE MUST SIGN FOR THE PACKAGE UPON DELIVERY
254
THE PHARMACIST ENTERS THE Rx ORDER IN CHIPS, CREATING AN ORDER NUMBER
256
THE PHARMACIST VERIFIES THE Rx AND ATTACHES THE VERIFICATION LABEL TO THE HARD COPY Rx
258
A PICK TICKET IS GENERATED FOR THE ORDER & THE ORDER IS FORWARDED TO THE PHARMACY FOR FULFILLMENT
260
THE SHIPMENT IS CONFIRMED IN CHIPS
262
THE ORIGINAL Rx IS FILED WITH THE PHARMACY Rx'S IN NUMERICAL ORDER
264
THE ORDER IS SHIPPED BY USPS EXPRESS MAIL
266
ALL XYREM INVENTORY IS CYCLE COUNTED AND RECONCILED WITH THE CHIPS SYSTEM QUANTITIES BEFORE THE DAYS SHIPMENTS ARE SENT OUT
END

FIG. 2C

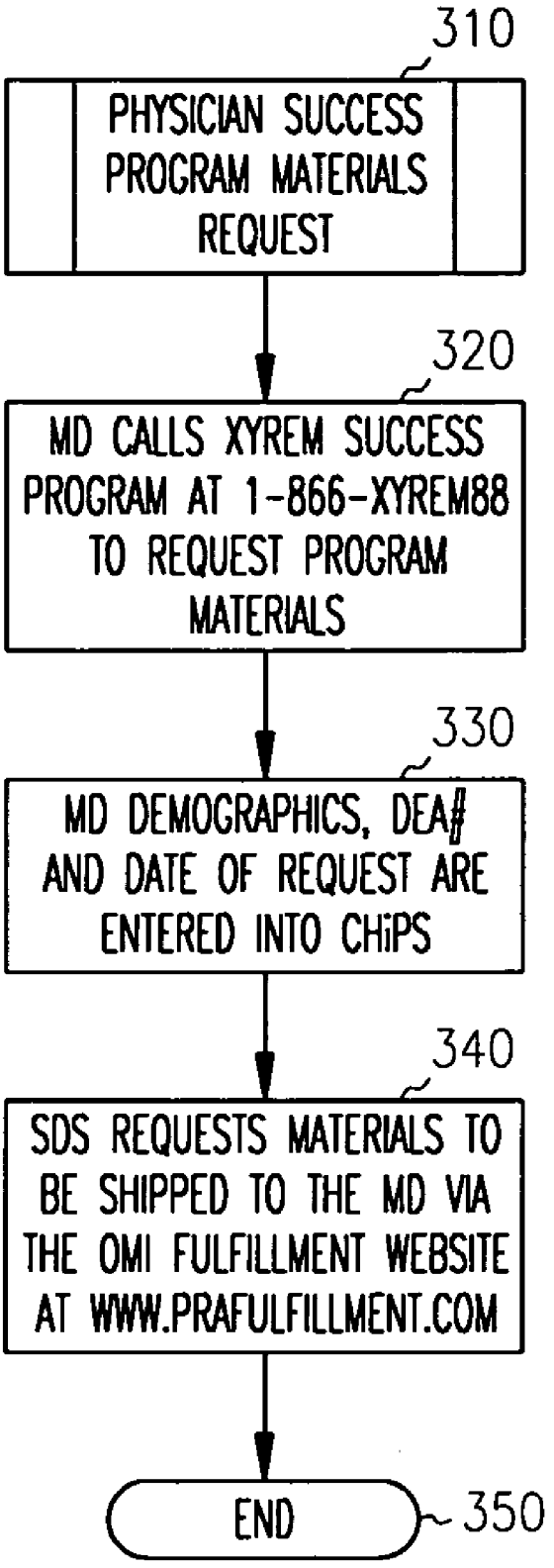
310
PHYSICIAN SUCCESS PROGRAM MATERIALS REQUEST
320
MD CALLS XYREM SUCCESS PROGRAM AT 1-866-XYREM88 TO REQUEST PROGRAM MATERIALS
330
MD DEMOGRAPHICS, DEA# AND DATE OF REQUEST ARE ENTERED INTO CHIPS
340
SDS REQUESTS MATERIALS TO BE SHIPPED TO THE MD VIA THE OMI FULFILLMENT WEBSITE AT WWW.PRAFULFILLMENT.COM
END
350

FIG. 3

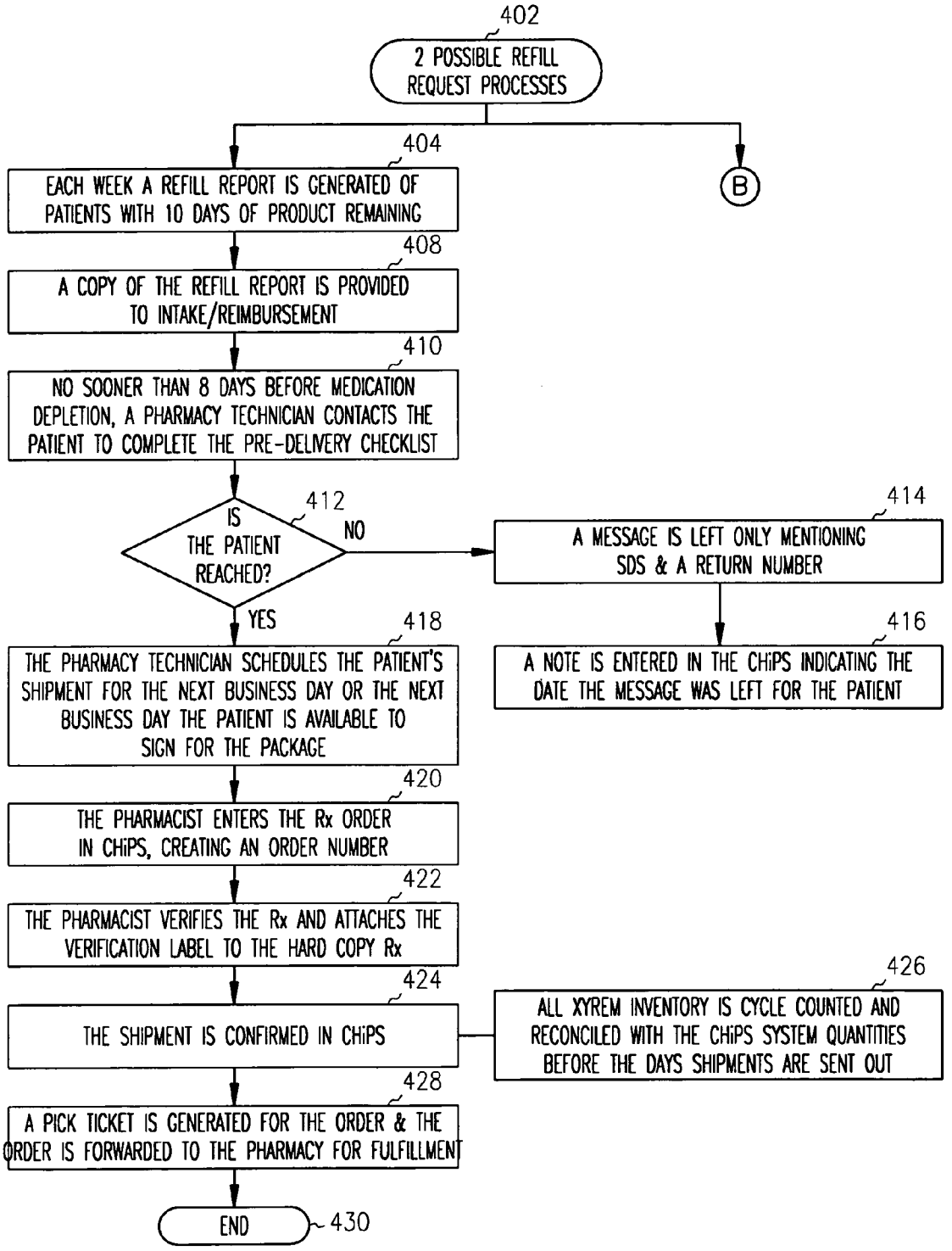
402
2 POSSIBLE REFILL REQUEST PROCESSES
404
EACH WEEK A REFILL REPORT IS GENERATED OF PATIENTS WITH 10 DAYS OF PRODUCT REMAINING
B
408
A COPY OF THE REFILL REPORT IS PROVIDED TO INTAKE/REIMBURSEMENT
410
NO SOONER THAN 8 DAYS BEFORE MEDICATION DEPLETION, A PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE THE PRE-DELIVERY CHECKLIST
412
IS THE PATIENT REACHED?
NO
414
A MESSAGE IS LEFT ONLY MENTIONING SDS & A RETURN NUMBER
416
A NOTE IS ENTERED IN THE CHIPS INDICATING THE DATE THE MESSAGE WAS LEFT FOR THE PATIENT
YES
418
THE PHARMACY TECHNICIAN SCHEDULES THE PATIENT'S SHIPMENT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
420
THE PHARMACIST ENTERS THE Rx ORDER IN CHIPS, CREATING AN ORDER NUMBER
422
THE PHARMACIST VERIFIES THE Rx AND ATTACHES THE VERIFICATION LABEL TO THE HARD COPY Rx
424
THE SHIPMENT IS CONFIRMED IN CHIPS
426
ALL XYREM INVENTORY IS CYCLE COUNTED AND RECONCILED WITH THE CHIPS SYSTEM QUANTITIES BEFORE THE DAYS SHIPMENTS ARE SENT OUT
428
A PICK TICKET IS GENERATED FOR THE ORDER & THE ORDER IS FORWARDED TO THE PHARMACY FOR FULFILLMENT
END
430

FIG. 4A

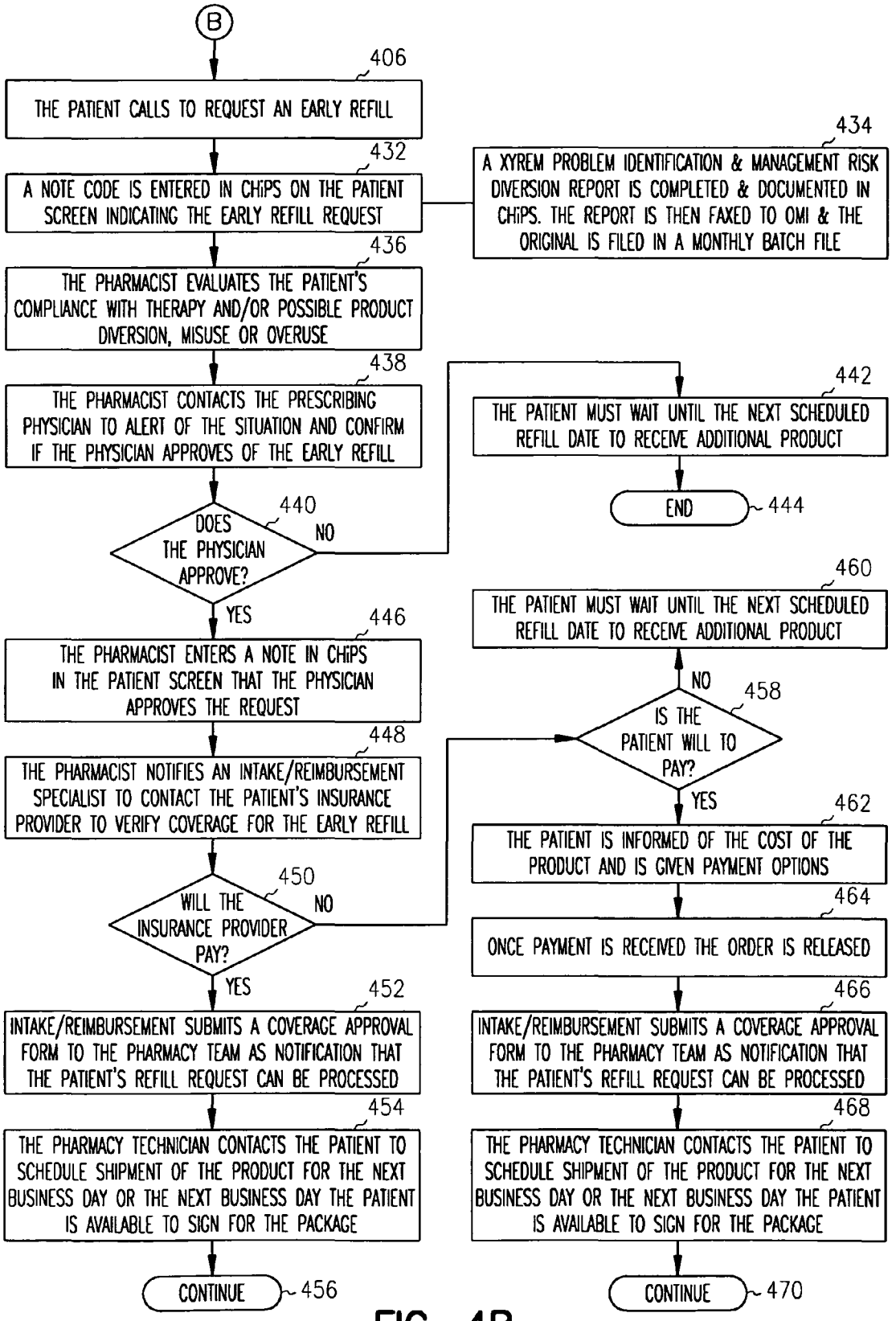
B
406
THE PATIENT CALLS TO REQUEST AN EARLY REFILL
432
A NOTE CODE IS ENTERED IN CHIPS ON THE PATIENT SCREEN INDICATING THE EARLY REFILL REQUEST
434
A XYREM PROBLEM IDENTIFICATION & MANAGEMENT RISK DIVERSION REPORT IS COMPLETED & DOCUMENTED IN CHIPS. THE REPORT IS THEN FAXED TO OMI & THE ORIGINAL IS FILED IN A MONTHLY BATCH FILE
436
THE PHARMACIST EVALUATES THE PATIENT'S COMPLIANCE WITH THERAPY AND/OR POSSIBLE PRODUCT DIVERSION, MISUSE OR OVERUSE
438
THE PHARMACIST CONTACTS THE PRESCRIBING PHYSICIAN TO ALERT OF THE SITUATION AND CONFIRM IF THE PHYSICIAN APPROVES OF THE EARLY REFILL
440
DOES THE PHYSICIAN APPROVE?
NO
442
THE PATIENT MUST WAIT UNTIL THE NEXT SCHEDULED REFILL DATE TO RECEIVE ADDITIONAL PRODUCT
END
444
YES
446
THE PHARMACIST ENTERS A NOTE IN CHIPS IN THE PATIENT SCREEN THAT THE PHYSICIAN APPROVES THE REQUEST
448
THE PHARMACIST NOTIFIES AN INTAKE/REIMBURSEMENT SPECIALIST TO CONTACT THE PATIENT'S INSURANCE PROVIDER TO VERIFY COVERAGE FOR THE EARLY REFILL
450
WILL THE INSURANCE PROVIDER PAY?
NO
460
THE PATIENT MUST WAIT UNTIL THE NEXT SCHEDULED REFILL DATE TO RECEIVE ADDITIONAL PRODUCT
458
IS THE PATIENT WILL TO PAY?
NO
YES
462
THE PATIENT IS INFORMED OF THE COST OF THE PRODUCT AND IS GIVEN PAYMENT OPTIONS
464
ONCE PAYMENT IS RECEIVED THE ORDER IS RELEASED
YES
452
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT'S REFILL REQUEST CAN BE PROCESSED
466
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT'S REFILL REQUEST CAN BE PROCESSED
454
THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO SCHEDULE SHIPMENT OF THE PRODUCT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
468
THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO SCHEDULE SHIPMENT OF THE PRODUCT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
CONTINUE
456
CONTINUE
470

FIG. 4B

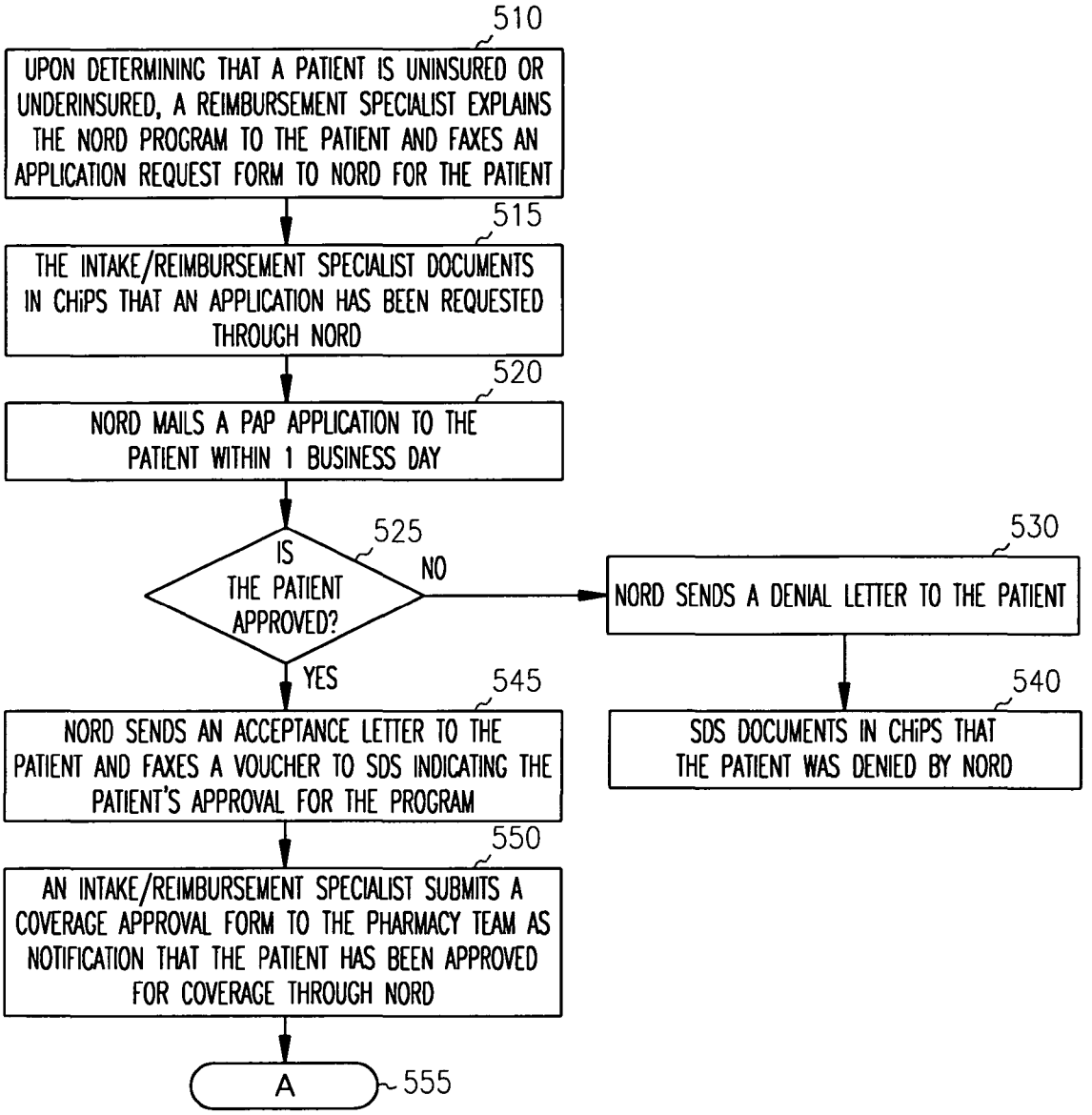
510
UPON DETERMINING THAT A PATIENT IS UNINSURED OR UNDERINSURED, A REIMBURSEMENT SPECIALIST EXPLAINS THE NORD PROGRAM TO THE PATIENT AND FAXES AN APPLICATION REQUEST FORM TO NORD FOR THE PATIENT
515
THE INTAKE/REIMBURSEMENT SPECIALIST DOCUMENTS IN CHiPS THAT AN APPLICATION HAS BEEN REQUESTED THROUGH NORD
520
NORD MAILS A PAP APPLICATION TO THE PATIENT WITHIN 1 BUSINESS DAY
525
IS THE PATIENT APPROVED?
NO
530
NORD SENDS A DENIAL LETTER TO THE PATIENT
YES
545
NORD SENDS AN ACCEPTANCE LETTER TO THE PATIENT AND FAXES A VOUCHER TO SDS INDICATING THE PATIENT'S APPROVAL FOR THE PROGRAM
540
SDS DOCUMENTS IN CHiPS THAT THE PATIENT WAS DENIED BY NORD
550
AN INTAKE/REIMBURSEMENT SPECIALIST SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT HAS BEEN APPROVED FOR COVERAGE THROUGH NORD
A
555

FIG. 5

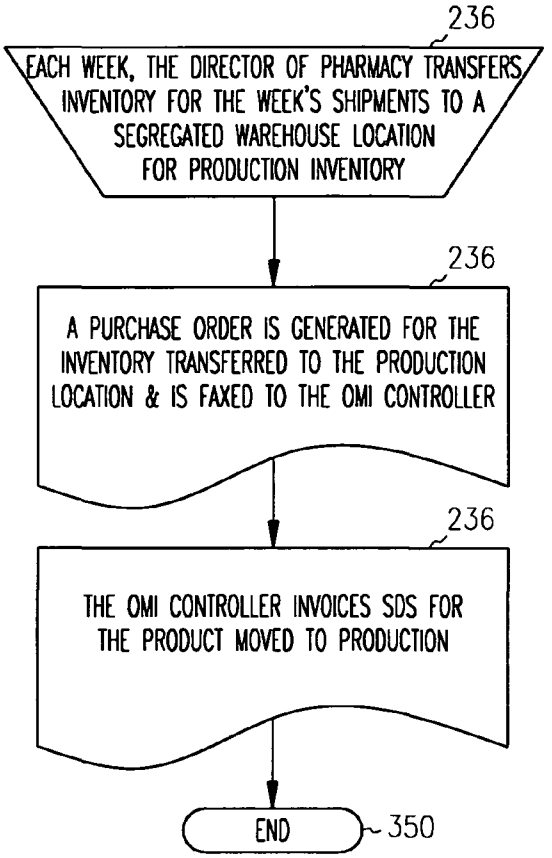

FIG. 6

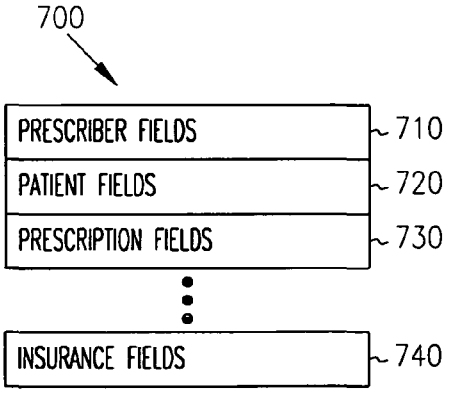

FIG. 7

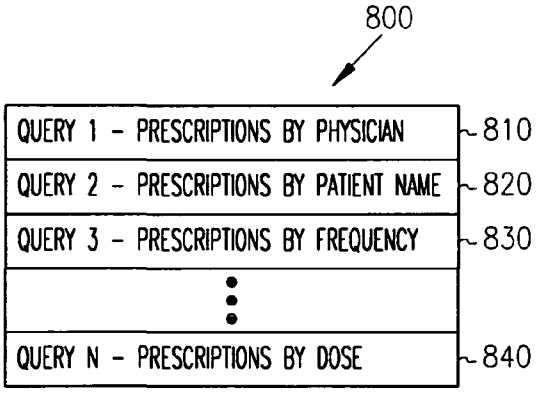

FIG. 8

900

PRESCRIPTION AND ENROLLMENT FORM

PRESCRIBER INFORMATION

PRESCRIBER'S NAME: _____ OFFICE CONTACT: _____
STREET ADDRESS: _____
CITY: _____ STATE: _____ ZIP: _____
PHONE: _____ FAX: _____
LICENSE NUMBER: _____ DEA NUMBER: _____
MD SPECIALTY: _____

PRESCRIPTION FORM

PATIENT NAME: _____ SS#: _____ DOB: _____ SEX M / F
ADDRESS: _____
CITY: _____ STATE: _____ ZIP: _____
Rx: XYREM ORAL SOLUTION (500 mg/mL) 180 Ml. BOTTLE QUANTITY: _____ MONTHS SUPPLY
SIG: TAKE _____ GMS P.O. DILUTED IN 60 mL WATER AT H.S. AND THEN AGAIN 2 1/2 TO 4 HOURS LATER
REFILLS (CIRCLE ONE): 0 1 2 (MAXIMUM OF 3 MONTH SUPPLY)
_____ DATE: _____/_____/_____
PRESCRIBER'S SIGNATURE

PHYSICIAN DECLARATION-PLEASE CHECK EACH BOX | TO BE COMPLETED AT INITIAL PRESCRIPTION ONLY

☐ I HAVE READ THE MATERIALS IN THE XYREM PHYSICIAN SUCCESS PROGRAM
☐ I VERIFY THAT THE PATIENT HAS BEEN EDUCATED WITH RESPECT TO XYREM PREPARATION, DOSING AND SCHEDULING.
☐ I UNDERSTAND THAT XYREM IS APPROVED FOR THE TREATMENT OF CATAPLEXY IN PATIENTS WITH NARCOLEPSY, AND THAT SAFETY OR EFFICACY HAS NOT BEEN ESTABLISHED FOR ANY OTHER INDICATION.
☐ I UNDERSTAND THAT THE SAFETY OF DOSES GREATER THAN 9gm/DAY HAS NOT BEEN ESTABLISHED

PATIENT INFORMATION

BEST TIME TO CONTACT PATIENT: ☐ DAY ☐ NIGHT
DAY #: _____ EVENING #: _____
INSURANCE COMPANY NAME: _____ PHONE #: _____
INSURED'S NAME: _____ RELATIONSHIP TO PATIENT: _____
IDENTIFICATION NUMBER: _____ POLICY/GROUP NUMBER: _____
PRESCRIPTION CARD: ☐ NO ☐ YES IF YES, CARRIER: _____ POLICY #: _____ GROUP: _____
PLEASE ATTACH COPIES OF PATIENT'S INSURANCE CARDS

FAX COMPLETED FORM TO XYREM SUCCESS PROGRAM (TOLL-FREE) 1-866-470-1744
FOR INFORMATION, CALL THE XYREM TEAM (TOLL FREE) AT 1-866-XYREM88 (1-866-997-3688)

FIG. 9

1000

PATIENT ASSISTANCE APPLICATION REQUEST FORM

DATE:

TO: PATIENT ASSISTANCE ORGANIZATION
FROM: SDS

FAX #: 203-798-2291

PLEASE SEND A XYREM PATIENT ASSISTANCE PROGRAM APPLICATION TO:

PATIENT NAME _____

ADDRESS _____

_____

_____

TELEPHONE: ( ) _____

PATIENT DOSAGE: _____ (GRAMS) TWICE NIGHTLY FOR A TOTAL DOSAGE OF _____ (GRAMS)

_____ BOTTLES (THREE MONTHS SUPPLY)

BACKGROUND INFORMATION:

_____

_____

_____

_____

_____

_____

FIG. 10

1100

SENSITIVE DRUG PATIENT ASSISTANCE PROGRAM

VOUCHER REQUEST FOR MEDICATION

PATIENT INFORMATION
<FIRST NAME><LAST NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890
DOB: 01/01/1900
SSN: 123-45-6789
DRUG ALLOTMENT: 100%
LRD: 03/01/2001

PHYSICIAN INFORMATION
<PHYSICIAN NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890

CASE CODE: ********

FIRST SHIPMENT THIS YEAR

DRUG	QUANTITY
XYREEM 180ml btl	1

VALIDATION DATE: 03/01/2001
EXPIRATION DATE: 05/31/2001
ISSUE DATE: 03/15/2001

APPROVED _____

PHARMACY USE

NORD COPY

****

(DETACH HERE)

PATIENT INFORMATION
<FIRST NAME><LAST NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890
DOB: 01/01/1900
SSN: 123-45-6789
DRUG ALLOTMENT: 100%
LRD: 03/01/2001

PHYSICIAN INFORMATION
<PHYSICIAN NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890

CASE CODE: ********

FIRST SHIPMENT THIS YEAR

DRUG	QUANTITY
XYREM 180ml btl	1

VALIDATION DATE: 03/01/2001
EXPIRATION DATE: 05/31/2001
ISSUE DATE: 03/15/2001

APPROVED _____

PHARMACY USE

FIG. 11

1200

SENSITIVE DRUG PHYSICIAN'S CERTIFICATE
OF MEDICAL NEED

PATIENT INFORMATION

DATE: _____

NAME: _____
LAST FIRST M

DATE OF BIRTH: _____

DRUG BEING PRESCRIBED: XYREM

DIAGNOSIS/CONDITION FOR WHICH DRUG IS BEING PRESCRIBED: _____

ICD-9: _____

PHYSICIAN INFORMATION

PHYSICIAN'S NAME (PLEASE PRINT): _____

PHYSICIAN'S SIGNATURE: _____ DATE: _____

PLEASE FAX BACK TO SENSITIVE DRUG SUCCESS PROGRAM: (1-800-TOLL FREE NUMBER)

FIG. 12

ACTIVITY REPORTS

	REPORT FREQUENCY		
	WEEKLY	MONTHLY	QUARTERLY
SALES			
Rx BY ZIP (NEW AND TOTAL)	X	X	X
Rx BY PHYSICIAN BY ZIP	X	X	
$ BY ZIP	X	X	X
REGULATORY			
# OF PHYSICIAN REGISTRIES		X	
# OF DENIED PHYSICIAN REGISTRIES AND REASON		X	
# OF COMPLETED PATIENT REGISTRIES		X	
# OF PROBLEM IDENTIFICATION & MANAGEMENT RISK DIVERSION REPORTS COMPLETED	X		
# OF CYCLE COUNTS PERFORMED & ACCURACY OF EACH		X	
QUALITY ASSURANCE			
# OF PRODUCT DEFECTS/COMPLAINTS REPORTED, TYPE AND LOT #		X	
CALL CENTER			
# OF CALLS RECEIVED		X	
# OF CALLS INITIATED		X	
# OF CALLS ANSWERED IN 30 SECONDS, ETC.		X	
PERCENTAGE OF CALLS ANSWERED IN 30 SECONDS		X	
# OF ABANDONED CALLS		X	
% OF ABANDONED CALLS		X	
AVERAGE CALL LENGTH		X	
PHARMACY			
# OF FAXED Rx/ENROLLMENT FORMS		X	
# OF MAILED Rx/ENROLLEMENT FORMS		X	
# OF RxS SHIPPED W/IN 1, 2, 3, 4 ETC. DAYS (FROM THE TIME INITIAL RECEIPT TO SHIPMENT OF Rx)		X	
# OF PATIENT SUCCESS PACKETS SHIPPED		X	

FIG. 13A

ACTIVITY REPORTS

PHARMACY		X	
# OF PHYSICIAN SUCCESS PACKETS SHIPPED		X	
# OF COMPLETED SHIPMENTS		X	
# OF INCOMPLETE SHIPMENTS AND REASON		X	
# OF SHIPPING ERRORS		X	
# OF PAP SHIPMENTS		X	
# OF PAP APPLICATIONS		X	
# OF PAP APPROVALS		X	
# OF CANCELED ORDERS		X	
# OF USPS ERRORS		X	
INVENTORY		X	
# OF RETURNED PRODUCTS AND REASON		X	
# OF OUTDATED BOTTLES OF PRODUCT		X	
INVENTORY COUNTS OF CONSIGNMENT & PRODUCTION INVENTORY		X	
# OF UNITS RECEIVED		X	
LOTS RECEIVED		X	
REIMBURSEMENT		X	
# OF PENDED AND WHY		X	
# OF APPROVALS		X	
# OF DENIALS		X	
# OF REJECTIONS		X	
PAYOR TYPES		X	

FIG. 13B

ACTIVITY REPORTS

PATIENT CARE		X	
# OF ADVERSE EVENTS REPORTED AND TYPE		X	
# OF ADVERSE EVENTS SENT TO OMI		X	
# OF DOSING PROBLEMS AND TYPE		X	
# OF NONCOMPLIANCE EPISODES AND REASON		X	
# OF PATIENT COUNSELED AND REASON		X	
# OF PATIENTS DISCONTINUED AND REASON		X	
PATIENT CARE		X	
# OF PATIENTS REFERRED TO PHYSICIAN AND REASON		X	
# OF ACTIVE PATIENTS		X	
# OF NEW PATIENTS		X	
# OF RESTART PATIENTS		X	
# OF DISCONTINUED PATIENTS AND REASON		X	
DRUG INFORMATION		X	
# OF DRUG INFORMATION REQUESTS AND TYPE		X	
# OF CALLS TRIAGED TO OMI		X	

FIG. 13C

SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

RELATED APPLICATION

This application is a divisional application of U.S. patent application Ser. No. 10/322,348, filed Dec. 17, 2002, now U.S. Pat. No. 7,668,730 which application is incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to distribution of drugs, and in particular to the distribution of sensitive drugs.

BACKGROUND OF THE INVENTION

Sensitive drugs are controlled to minimize risk and ensure that they are not abused, or cause adverse reactions. Such sensitive drugs are approved for specific uses by the Food and Drug Administration, and must be prescribed by a licensed physician in order to be purchased by consumers. Some drugs, such as cocaine and other common street drugs are the object of abuse and illegal schemes to distribute for profit. Some schemes include Dr. shopping, diversion, and pharmacy thefts. A locked cabinet or safe is a requirement for distribution of some drugs.

Certain agents, such as gamma hydroxy buterate (GHB) are also abused, yet also are effective for therapeutic purposes such as treatment of daytime cataplexy in patients with narcolepsy. Some patients however, will obtain prescriptions from multiple doctors, and have them filled at different pharmacies. Still further, an unscrupulous physician may actually write multiple prescriptions for a patient, or multiple patients, who use cash to pay for the drugs. These patients will then sell the drug to dealers or others for profit.

There is a need for a distribution system and method that directly addresses these abuses. There is a further need for such a system and method that provides education and limits the potential for such abuse.

SUMMARY OF THE INVENTION

A drug distribution system and method utilizes a central pharmacy and database to track all prescriptions for a sensitive drug. Information is kept in a central database regarding all physicians allowed to prescribe the sensitive drug, and all patients receiving the drug. Abuses are identified by monitoring data in the database for prescription patterns by physicians and prescriptions obtained by patients. Further verification is made that the physician is eligible to prescribe the drug by consulting a separate database for a valid DEA license, and optionally state medical boards to determine whether any corrective or approved disciplinary actions relating to controlled substances have been brought against the physician. Multiple controls beyond those for traditional drugs are imposed on the distribution depending on the sensitivity of the drug.

Education is provided to both physician and patient. Prior to shipping the drug for the first time, the patient is contacted to ensure that product and abuse related educational materials have been received and/or read. The patient may provide the name of a designee to the central pharmacy who is authorized to accept shipment of the drug. Receipt of the initial drug shipment is confirmed by contacting the patient. Either a phone call or other communication to the patient within a set time after delivery may be made to ensure receipt. Further, a courier service's tracking system is used to confirm delivery in further embodiments. If a shipment is lost, an investigation is launched to find it.

In one embodiment, the drug may be shipped by the central pharmacy to another pharmacy for patient pick-up. The second pharmacy's ability to protect against diversion before shipping the drug must be confirmed. This ability may be checked through NTIS and State Boards of Pharmacy.

Prescription refills are permitted in the number specified in the original prescription. In addition, if a prescription refill is requested by the patient prior to the anticipated due date, such refills will be questioned. A lost, stolen, destroyed or spilled prescription/supply is documented and replaced to the extent necessary to honor the prescription, and will also cause a review or full investigation.

The exclusive central database contains all relevant data related to distribution of the drug and process of distributing it, including patient, physician and prescription information. Several queries and reports are run against the database to provide information which might reveal potential abuse of the sensitive drug, such as early refills.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a block diagram of a computer system for use in implementing the system and method of the present invention.

FIGS. **2**A, **2**B and **2**C are a flowchart describing a method for sensitive drug distribution at least partially utilizing a computer system such as that shown in FIG. **1**.

FIG. **3** is a flowchart of a physician success program at least partially implemented on a computer system such as that shown in FIG. **1**.

FIGS. **4**A and **4**B are a flowchart describing a method for handling refill requests at least partially utilizing a computer system such as that shown in FIG. **1**.

FIG. **5** is a flowchart of a process for requesting special reimbursement when a patient is uninsured or underinsured at least partially utilizing a computer system as that shown in FIG. **1**.

FIG. **6** is a flowchart of a process for inventory control at least partially utilizing a computer system such as that shown in FIG. **1**.

FIG. **7** is a block diagram of database fields.

FIG. **8** is a block diagram showing a list of queries against the database fields.

FIG. **9** is a copy of one example prescription and enrollment form.

FIG. **10** is a copy of one example of a NORD application request form for patient financial assistance.

FIG. **11** is a copy of one example voucher request for medication for use with the NORD application request form of FIG. **10**.

FIG. **12** is a copy of certificate of medical need.

FIGS. **13**A, **13**B and **13**C are descriptions of sample reports obtained by querying a central database having fields represented in FIG. **7**.

DETAILED DESCRIPTION OF THE INVENTION

In the following description, reference is made to the accompanying drawings that form a part hereof, and in which is shown by way of illustration specific embodiments in which the invention may be practiced. These embodiments are described in sufficient detail to enable those skilled in the art to practice the invention, and it is to be understood that other embodiments may be utilized and that structural, logical

and electrical changes may be made without departing from the scope of the present invention. The following description is, therefore, not to be taken in a limited sense, and the scope of the present invention is defined by the appended claims.

The functions or algorithms described herein are implemented in software or a combination of software and human implemented procedures in one embodiment. The software comprises computer executable instructions stored on computer readable media such as memory or other type of storage devices. The term "computer readable media" is also used to represent carrier waves on which the software is transmitted. Further, such functions correspond to modules, which are software, hardware, firmware of any combination thereof. Multiple functions are performed in one or more modules as desired, and the embodiments described are merely examples. The software is executed on a digital signal processor, ASIC, microprocessor, or other type of processor operating on a computer system, such as a personal computer, server or other computer system.

A sensitive drug is one which can be abused, or has addiction properties or other properties that render the drug sensitive. One example of such a drug is sodium oxybate, also known as gamma hydroxy butyrate (GHB $C_4H_7NaO_3$) which is useful for treatment of cataplexy in patients with narcolepsy. GHB is marketed under the trademark of Xyrem® (sodium oxybate oral solution), which trademark can be used interchangeably with GHB herein. Sensitive drugs also include narcotics or other drugs which require controls on their distribution and use to monitor behaviors to prevent abuse and adverse side effects.

In one embodiment, Xyrem® is subject to a restricted distribution program. One aspect of the program is to educate physicians and patients about the risks and benefits of Xyrem, including support via ongoing contact with patients and a toll free helpline. Initial prescriptions are filled only after a prescriber and patient have received and read the educational materials. Further, patient and prescribing physician registries are maintained and monitored to ensure proper distribution.

In a further embodiment, bulk sodium oxybate is manufactured at a single site, as is the finished drug product. Following manufacture of the drug product, it is stored at a facility compliant with FDA Schedule III regulations, where a consignment inventory is maintained. The inventory is owned by a company, and is managed by a central pharmacy, which maintains the consignment inventory. Xyrem® is distributed and dispensed through a primary and exclusive central pharmacy, and is not stocked in retail pharmacy outlets. It is distributed by overnight carriers, or by US mail in one embodiment to potentially invoke mail fraud laws if attempts of abuse occur.

FIG. **1** is a simplified block diagram of a computer system **100**, such as a personal computer for implementing at least a portion of the methods described herein. A central processing unit (CPU) **110** executes computer programs stored on a memory **120**. Memory **120** in one embodiment comprises one or more levels of cache as desired to speed execution of the program and access to data on which the programs operate. The CPU is directly coupled to memory **120** in one embodiment. Both CPU **110** and memory **120** are coupled to a bus **130**. A storage **140**, I/O **150** and communications **160** are also coupled to the bus **130**. Storage **140** is usually a long term storage device, such as a disk drive, tape drive, DVD, CD or other type of storage device. In one embodiment, storage **140** is used to house a database for use with the present invention. I/O **150** comprises keyboards, sound devices, displays and other mechanisms by which a user interacts with the computer system **100**. Communications **160** comprises a network, phone connection, local area network, wide area network or other mechanism for communicating with external devices. Such external devices comprise servers, other peer computers and other devices. In one embodiment, such external device comprises a database server that is used in place of the database on storage **140**. Other computer system architectures capable of executing software and interacting with a database and users may also be used. Appropriate security measures such as encryption are used to ensure confidentiality. Further, data integrity and backup measures are also used to prevent data loss.

FIGS. **2**A, **2**B and **2**C represent an initial prescription order entry process for a sensitive drug, such as Xyrem. At **202**, a medical doctor (MD) sends a Rx/enrollment form via mail, fax, email or other means to an intake/reimbursement specialist at **204**, who makes a copy of the RX/enrollment form that is stamped "copy". The original fax is forwarded to a pharmacy team. The enrollment form contains prescriber information, prescription information, checkboxes for the prescriber indicating they have read materials, educated the patient, understand the use in treatment, and understand certain safety information, and also contains patient information.

The prescriber information contains standard contact information as well as license number, DEA number and physician specialty. Patient and prescription information includes name, social security number, date of birth, gender, contact information, drug identification, patient's appropriate dosage, and number of refills allowed, along with a line for the prescriber's signature. Patient insurance information is also provided.

There are two workflows involved at the pharmacy team, intake reimbursement **206** and pharmacy workflow **208**, which may proceed in parallel or serially. The intake work flow **206** starts with an intake reimbursement specialist entering the patient and physician information into an application/database referred to as CHIPS, which is used to maintain a record of a client home infusion program (CHIP) for Xyrem®. A check is made to ensure the information is complete at **212**. If not, at **214**, an intake representative attempts to reach the MD or prescriber to obtain the missing information. If the missing information has not been obtained within a predetermined period of time, such as 24 hours at **216**, the Rx/Enrollment form is sent back to the MD with a rejection explanation. A note is entered in CHIPS that the application was rejected.

If the information is complete at **212**, the MD is contacted at **220** to verify receipt and accuracy of the patient's Rx. This contact is recorded in CHIPS. The intake and reimbursement specialist then sends a consent form and a cover letter to the patient at **224**. The insurance provider is contacted at **226** to verify coverage and benefits. At **228**, a determination is made regarding coverage for the drug. If it is not available, it is determined at **230** whether the patient is willing and able to pay. If not, a process is performed for handling patients who are uninsured or underinsured. In one embodiment, the process is referred to as a NORD process.

If the patient is willing and able to pay at **230**, the patient is informed of the cost of the product and is given payment options at **234**. At **236**, once payment is received, the intake reimbursement specialist submits a coverage approval form with the enrollment form to the pharmacy team as notification to process the patient's prescription. If coverage is approved at **228**, the intake reimbursement specialist also submits the coverage approval form with the enrollment form to the pharmacy team as notification to process the patient's prescription. Processing of the prescription is described below.

Upon receipt and initial processing of the prescription enrollment form and sending an original to the pharmacy work flow block **208**, the patient is shipped a Xyrem® success packet via mail. In one embodiment, the Xyrem® success packet contains educational material for a patient that advises of the proper use, care and handling of the drug and consequences of diversion at **268**. The medical doctor's credentials are checked to determine if the physician has a current DEA license to prescribe controlled substances and if he or she has had any actions related to misuse/misprescribing of controlled drugs against him or her, within a predetermined time, such as three months at **270**. If they have, a pharmacist holds the prescription until receiving a coverage approval form from the intake reimbursement specialist at **272**.

If the credentials have not been recently checked, the pharmacist verifies the credentials and enters all findings in the database at **274**. If the credentials are approved at **276**, the physician is indicated as approved in a physician screen populated by information from the database at **280**. The prescription is then held pending coverage approval at **282**.

If any disciplinary actions are identified, as referenced at block **278**, management of the pharmacy is notified and either approves processing of the prescription with continued monitoring of the physician, or processing of the prescription is not performed, and the physician is noted in the database as unapproved at **284**. The enrollment form is then mailed back to the physician with a cover letter reiterating that the prescription cannot be processed at **288**. The patient is also sent a letter at **290** indicating that the prescription cannot be processed and the patient is instructed to contact their physician.

Actual filling of the approved prescription begins with receipt of the coverage approval form as indicated at **240**. The patient is contacted by the pharmacy, such as by a technician to complete a technician section of a patient counseling checklist. If a pharmacist verifies that the program materials were not read at **242**, the receipt of the material is confirmed at **244** and another call is scheduled to counsel the patient before the drug is shipped.

If the program materials were read at **242**, the checklist is completed at **246** and the technician transfers the patient to the pharmacist who reviews the entire checklist and completes remaining pharmacist specified sections. At **248**, the pharmacist indicates in the database that the patient counseling and checklist was successfully completed, indicating the date completed.

At **250**, the pharmacist schedules the patient's shipment for the next business day or the next business day that the patient or designee is able to sign for the package. Further, as indicated at **252**, the shipment must be sent to the patient's home address unless the patient is traveling or has moved. In that event, the pharmacist may determine that an exception may be made. The patient or the patient's designee who is at least 18 years old, must sign for the package upon delivery.

At **254**, the pharmacist enters the prescription order in the database, creating an order number. The pharmacist then verifies at **256** the prescription and attaches a verification label to the hard copy prescription. At **258**, a pick ticket is generated for the order and the order is forwarded to the pharmacy for fulfillment. The shipment is confirmed in the database at **260**, and the order is shipped by USPS Express Mail. Use of the US mail invokes certain criminal penalties for unauthorized diversion. Optionally, other mail services may be used. Potential changes in the law may also bring criminal penalties into play. Following shipment, the patient is called by the central pharmacy to confirm that the prescription was received.

As noted at **266**, for the sensitive drug, Xyrem, all inventory is cycle counted and reconciled with the database system quantities before shipments for the day are sent. This provides a very precise control of the inventor.

A physician success program materials request process begins at **310** in FIG. **3**. At **320**, the MD calls to the central pharmacy to request program materials. A special phone number is provided. MD demographics, DEA number, and data or request are entered into the database at **330**. At **340**, a request is made to ship the materials to the MD via a fulfillment website, or other mechanism. The request process ends at **350**.

A refill request process begins at **302** in FIGS. **4**A and **4**B. There are two different paths for refills. A first path beginning at **404** involves generating a report from the central database of patients with a predetermined number of days or product remaining. A second path beginning at **406** is followed when a patient calls to request an early refill.

In the first path, a copy of the report is provided to an intake reimbursement specialist at **408**. No sooner than **8** days before the medication depletion, a pharmacy technician contacts the patient at **410** to complete the pre-delivery checklist. At **412**, if the patient is not reached, a message is left mentioning the depletion, and a return number at **414**. A note is also entered into the database indicating the date the message was left at **416**.

If the patient is reached at **412**, the next shipment is scheduled at **418**, the prescription is entered into the database creating an order at **420**, the pharmacist verifies the prescription and attaches a verification label at **422** and the shipment is confirmed in the database at **424**. Note at **426** that the inventory is cycle counted and reconciled with the database quantities before the shipments for a day or other time period are sent. A pick ticket is generated for the order and the order is forwarded for fulfillment at **428**, with the first path ending at **430**.

The second path, beginning at **406** results in a note code being entered into the database on a patient screen indicating an early refill request at **432**. The pharmacist evaluates the patient's compliance with therapy or possible product diversion, misuse or over-use at **436**. In one embodiment, cash payers are also identified. The pharmacist then contacts the prescribing physician to alert them of the situation and confirm if the physician approves of the early refill at **438**. If the physician does not approve as indicated at **440**, the patient must wait until the next scheduled refill date to receive additional product as indicated at **442**, and the process ends at **444**.

If the physician approves at **440**, the pharmacist enters a note in the database on a patient screen that the physician approves the request at **446**. The pharmacist notifies an intake reimbursement specialist to contact the patient's insurance provider to verify coverage for the early refill at **448**. If the insurance provider will pay as determined at **450**, the specialist submits the coverage approval form as notification that the refill may be processed at **452**. At **454**, the pharmacy technician contacts the patient to schedule shipment of the product for the next business day, and the process of filling the order is continued at **456** by following the process beginning at **240**.

If the insurance provider will not pay at **450**, it is determined whether the patient is willing and/or able to pay at **458**. If not, the patient must wait until the next scheduled refill date to receive additional product at **460**. If it was determined at **458** that the patient was willing and able to pay, the patient is informed of the cost of the product and is given payment options at **462**. Once payment is received as indicated at **464**, the specialist submits a coverage approval form to the pharmacy team as notification that the refill request can be pro-

cessed at **466**. At **468**, the pharmacy technician contacts the patient to schedule shipment. The process of filling the order is continued at **470** by following the process beginning at **240**.

A process, referred to as a NORD process in one embodiment is used to determine whether donated, third party funds are available for paying for prescriptions where neither insurance will, nor the patient can pay. The process begins at **510** upon determining that a patient is uninsured or underinsured. A reimbursement specialist explains the NORD program to the patient and faxes an application request form to NORD for the patient. At **515**, the intake reimbursement specialist documents in the database that an application has been received through NORD. At **520**, NORD mails an application to the patient within one business day.

A determination is made at **525** by NORD whether the patient is approved. If not, at **530**, NORD sends a denial letter to the patient, and it is documented in the database at **540** that the patient was denied by NORD. If the patient is approved, NORD sends an acceptance letter to the patient and faxes a voucher to the central pharmacy (SDS in one embodiment) to indicate the approval at **545**. At **550**, an intake reimbursement specialist submits a coverage approval form to the pharmacy team as notification that the patient has been approved for coverage. The process of filling the order is continued at **555** by following the process beginning at **240**.

An inventory control process is illustrated in FIG. **6** beginning at **610**. Each week, a responsible person at the central pharmacy, such as the director of the pharmacy transfers inventory for the week's shipments to a segregated warehouse location for production inventory. At **620**, a purchase order is generated for the inventory transferred to the production location and is sent, such as by fax, to a controller, such as the controller of the company that obtained approval for distribution and use of the sensitive drug. At **630**, the controller invoices the central pharmacy for the product moved to production. The process ends at **640**.

The central database described above is a relational database running on the system of FIG. **1**, or a server based system having a similar architecture coupled to workstations via a network, as represented by communications **160**. The database is likely stored in storage **140**, and contains multiple fields of information as indicated at **700** in FIG. **7**. The organization and groupings of the fields are shown in one format for convenience. It is recognized that many different organizations or schemas may be utilized. In one embodiment, the groups of fields comprise prescriber fields **710**, patient fields **720**, prescription fields **730** and insurance fields **740**. For purposes of illustration, all the entries described with respect to the above processes are included in the fields. In further embodiments, no such groupings are made, and the data is organized in a different manner.

Several queries are illustrated at **800** in FIG. **8**. There may be many other queries as required by individual state reporting requirements. A first query at **810** is used to identify prescriptions written by physician. The queries may be written in structured query language, natural query languages or in any other manner compatible with the database. A second query **820** is used to pull information from the database related to prescriptions by patient name. A third query **830** is used to determine prescriptions by frequency, and a n^{th} query finds prescriptions by dose at **840**. Using query languages combined with the depth of data in the central database allows many other methods of investigating for potential abuse of the drugs. The central database ensures that all prescriptions, prescribers and patients are tracked and subject to such investigations. In further embodiments, the central database may be distributed among multiple computers provided a query operates over all data relating to such prescriptions, prescribers and patients for the drug.

An example of one prescription and enrollment form is shown at **900** in FIG. **9**. As previously indicated, several fields are included for prescriber information, prescription information and patient information.

FIG. **10** is a copy of one example NORD application request form **1000** used to request that an application be sent to a patient for financial assistance.

FIG. **11** is a copy of one example application **1100** for financial assistance as requested by form **1000**. The form requires both patient and physician information. Social security number information is also requested. The form provides information for approving the financial assistance and for tracking assistance provided.

FIG. **12** is a copy of one example voucher request for medication for use with the NORD application request form of FIG. **10**. In addition to patient and physician information, prescription information and diagnosis information is also provided.

FIGS. **13**A, **13**B and **13**C are descriptions of sample reports obtained by querying a central database having fields represented in FIG. **7**. The activities grouped by sales, regulatory, quality assurance, call center, pharmacy, inventory, reimbursement, patient care and drug information. Each report has an associated frequency or frequencies. The reports are obtained by running queries against the database, with the queries written in one of many query languages.

While the invention has been described with respect to a Schedule III drug, it is useful for other sensitive drugs that are DEA or Federally scheduled drugs in Schedule II-V, as well as still other sensitive drugs where multiple controls are desired for distribution and use.

The invention claimed is:

1. A computerized method to control abuse of a prescription drug comprising:

controlling with a computer processor the distribution of said prescription drug via an exclusive central pharmacy that maintains a central database that tracks all prescriptions of said prescription drug and analyzes for potential abuse situations;

receiving in the computer processor all prescription requests, for any and all patients being prescribed the prescription drug, only at the exclusive central pharmacy, from any and all medical doctors allowed to prescribe the prescription drug;

processing with the computer processor all prescriptions for the prescription drug only by the exclusive central pharmacy using only the central database;

determining with the computer processor current and anticipated patterns of potential prescription abuse of said prescription drug from periodic reports generated only by the central database based on prescription request data from a particular medical doctor and further based on filling of prescriptions by a particular patient, wherein said request data contain information identifying the patient, the drug prescribed, and credentials of the medical doctor; and

selecting with the computer processor multiple controls for distribution by said exclusive central pharmacy, the controls comprising communicating prescriptions from a physician to the central pharmacy; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying the physician is eligible to prescribe the prescription drug by

consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has reviewed the educational materials; verifying the home address of the patient; shipping via US postal service or a commercial shipping service; receiving the name of an at least 18 year old designee to receive the drug; confirming receipt of an initial shipment of the drug to the patient returning the drug to the pharmacy after two attempts to deliver; launching an investigation when a shipment is lost; shipping to another pharmacy for delivery; requiring manufacture at a single location; releasing inventory in a controlled manner to the central pharmacy; questioning early refills; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; limiting the prescription to a one month supply; requiring rewriting of the prescription periodically; and making the database available to the DEA for checking for abuse patterns in the data, for cash payments, and for inappropriate questions.

2. The method of claim **1** wherein initially selected controls comprise communicating prescriptions from a physician to the central pharmacy; identifying the physician's name, license, and DEA registration information; verifying the prescription; obtaining patient information; verifying the physician is eligible to prescribe the prescription drug by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has reviewed the educational materials; verifying the home address of the patient; shipping via US postal service; confirming receipt of an initial shipment of the drug to the patient; releasing inventory in a controlled manner to the central pharmacy; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; and making the database available to the DEA for checking for abuse patterns in the data.

3. The method of claim **1** which further comprises consulting a separate database to verify that the medical doctor is eligible to prescribe the drug.

4. A computerized method to control abuse of gamma hydroxy butyrate (GHB) comprising:

controlling with a computer processor the distribution of GHB via an exclusive central pharmacy that maintains a central database that tracks all prescriptions of GHB and analyzes for potential abuse situations;

receiving in the computer processor all prescription requests, for any and all patients being prescribed GHB, only at the exclusive central pharmacy, from any and all medical doctors allowed to prescribe GHB;

processing in the computer processor all prescriptions for GHB only by the exclusive central pharmacy using only the central database;

determining with the computer processor current and anticipated patterns of potential prescription abuse of GHB from periodic reports generated only by the central database based on prescription request data from a particular medical doctor and based on filling of prescriptions by a particular patient, wherein said request data contain information identifying the patient, GHB as the drug prescribed, and credentials of the medical doctor; and

selecting with the computer processor multiple controls for distribution by said exclusive central pharmacy, the controls comprising communicating prescriptions from a physician to the central pharmacy; identifying the physician's name, license, and DEA (Drug Enforcement Agency) registration information; verifying the prescription; obtaining patient information; verifying the physician is eligible to prescribe the GHB by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; providing comprehensive printed materials to the physician; contacting the patient's insurance company if any; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has reviewed the educational materials; verifying the home address of the patient; shipping via US postal service or a commercial shipping service; receiving the name of an at least 18 year old designee to receive the drug; confirming receipt of an initial shipment of the drug to the patient returning the drug to the pharmacy after two attempts to deliver; launching an investigation when a shipment is lost; shipping to another pharmacy for delivery; requiring manufacture at a single location; releasing inventory in a controlled manner to the central pharmacy; questioning early refills; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; limiting the prescription to a one month supply; requiring rewriting of the prescription periodically; and making the database available to the DEA for checking for abuse patterns in the data, for cash payments, and for inappropriate questions.

5. The method of claim **4** wherein initially selected controls comprise

communicating prescriptions from a physician to the central pharmacy; identifying the physician's name, license, and DEA registration information; verifying the prescription; obtaining patient information; verifying the physician is eligible to prescribe the GHB by consulting the National Technical Information Services to determine whether the physician has an active DEA number and to check on whether any actions are pending against the physician; verifying patient registry information; providing comprehensive education information to the patient; verifying the patient has reviewed the educational materials; verifying the home address of the patient; shipping via US postal service; confirming receipt of an initial shipment of the drug to the patient; releasing inventory in a controlled manner to the central pharmacy; flagging repeat instances of lost, stolen, destroyed, or spilled prescriptions; and making the database available to the DEA for checking for abuse patterns in the data.

6. The method of claim **4** which further comprises consulting a separate database to verify that the medical doctor is eligible to prescribe the drug.

* * * * *

EXHIBIT D

US007895059B2

(12) **United States Patent**
Reardan et al.

(10) **Patent No.: US 7,895,059 B2**
(45) **Date of Patent: *Feb. 22, 2011**

(54) **SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **12/704,097**

(22) Filed: **Feb. 11, 2010**

(65) **Prior Publication Data**

US 2010/0138237 A1 Jun. 3, 2010

Related U.S. Application Data

(63) Continuation of application No. 10/322,348, filed on Dec. 17, 2002, now Pat. No. 7,668,730.

(51) **Int. Cl.**
G06Q 10/00 (2006.01)

(52) **U.S. Cl.** **705/2**; 705/3; 600/300

(58) **Field of Classification Search** 705/2, 705/3; 600/300

See application file for complete search history.

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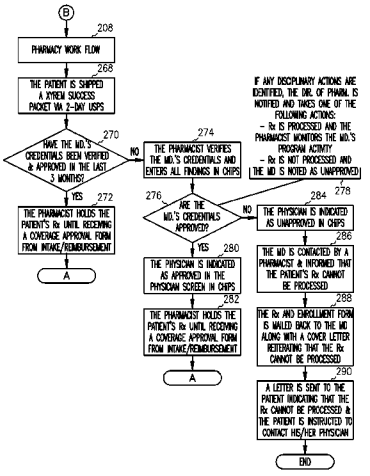
(57) **ABSTRACT**

A drug distribution system and method utilizes a central pharmacy and database to track all prescriptions for a sensitive drug. Information is kept in the database regarding all physicians allowed to prescribe the sensitive drug, and all patients receiving the drug. Abuses are identified by monitoring data in the database for prescription patterns by physicians and prescriptions obtained by patients. Further verification is made that the physician is eligible to prescribe the drug by consulting a separate database, and optionally whether any actions are taken against the physician. Multiple controls beyond those for normal drugs are imposed on the distribution depending on the sensitivity of the drug.

16 Claims, 16 Drawing Sheets



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Ukens, C., "Specialty Pharmacy", Drug Topics, 144, (Jun. 5, 2000), 40-47.

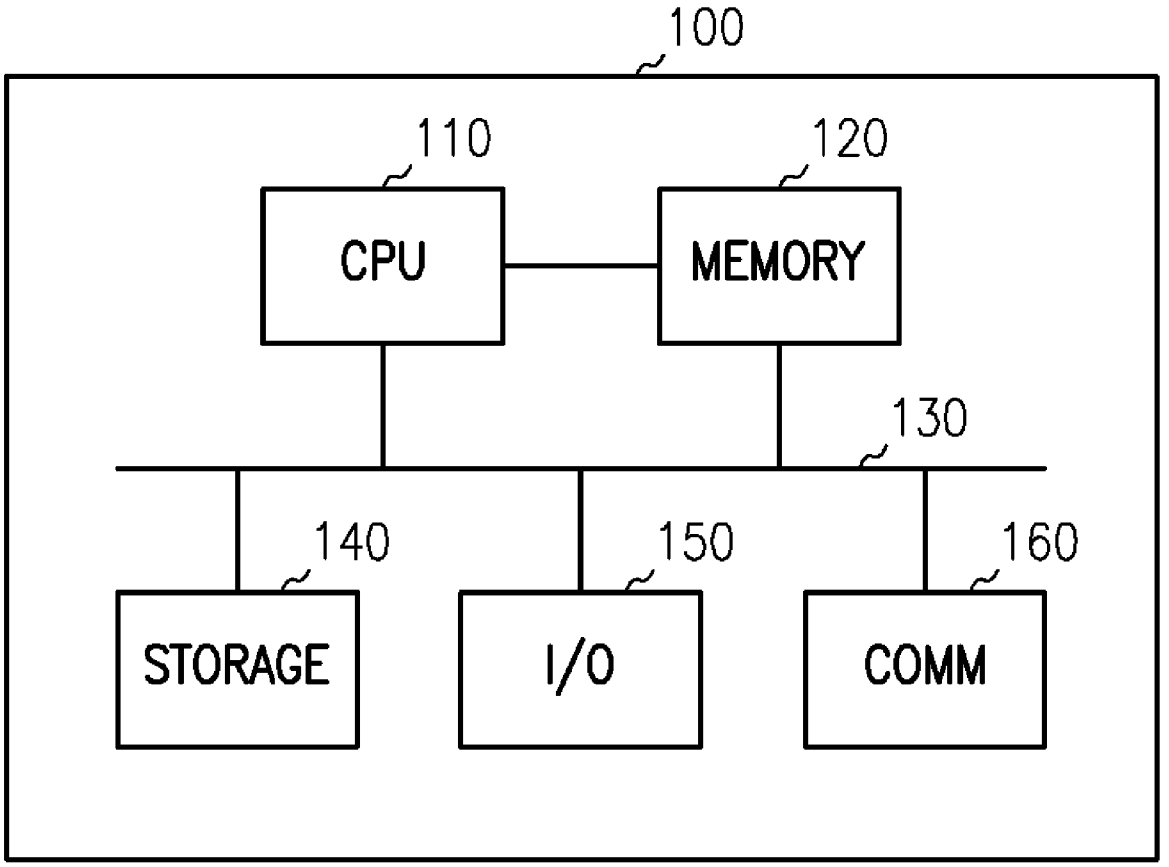

FIG. 1

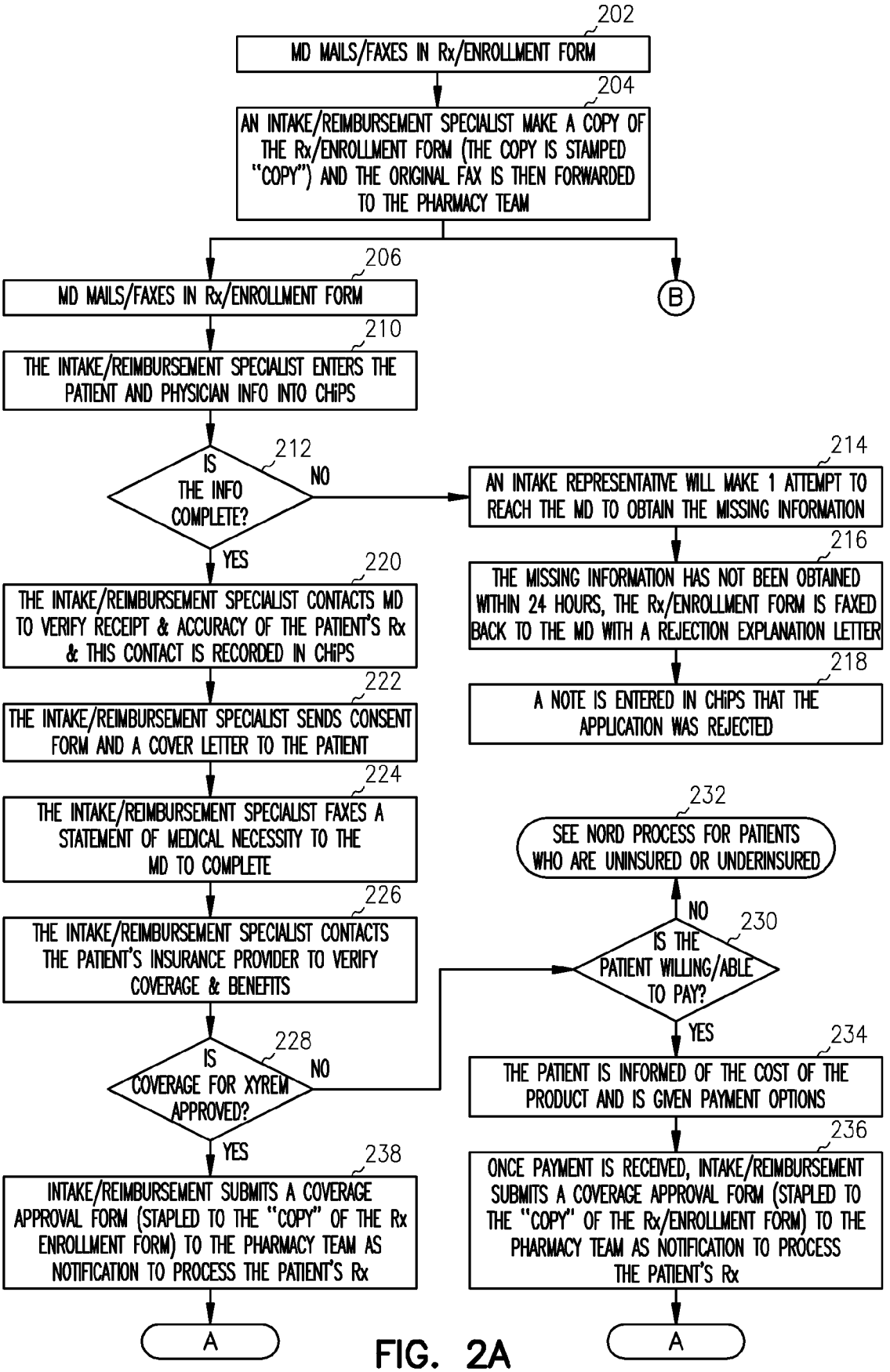
202
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
204
AN INTAKE/REIMBURSEMENT SPECIALIST MAKE A COPY OF THE Rx/ENROLLMENT FORM (THE COPY IS STAMPED "COPY") AND THE ORIGINAL FAX IS THEN FORWARDED TO THE PHARMACY TEAM
206
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
B
210
THE INTAKE/REIMBURSEMENT SPECIALIST ENTERS THE PATIENT AND PHYSICIAN INFO INTO CHiPS
212
IS THE INFO COMPLETE?
NO
214
AN INTAKE REPRESENTATIVE WILL MAKE 1 ATTEMPT TO REACH THE MD TO OBTAIN THE MISSING INFORMATION
YES
220
THE INTAKE/REIMBURSEMENT SPECIALIST CONTACTS MD TO VERIFY RECEIPT & ACCURACY OF THE PATIENT'S Rx & THIS CONTACT IS RECORDED IN CHiPS
216
THE MISSING INFORMATION HAS NOT BEEN OBTAINED WITHIN 24 HOURS, THE Rx/ENROLLMENT FORM IS FAXED BACK TO THE MD WITH A REJECTION EXPLANATION LETTER
218
A NOTE IS ENTERED IN CHiPS THAT THE APPLICATION WAS REJECTED
222
THE INTAKE/REIMBURSEMENT SPECIALIST SENDS CONSENT FORM AND A COVER LETTER TO THE PATIENT
224
THE INTAKE/REIMBURSEMENT SPECIALIST FAXES A STATEMENT OF MEDICAL NECESSITY TO THE MD TO COMPLETE
226
THE INTAKE/REIMBURSEMENT SPECIALIST CONTACTS THE PATIENT'S INSURANCE PROVIDER TO VERIFY COVERAGE & BENEFITS
228
IS COVERAGE FOR XYREM APPROVED?
NO
232
SEE NORD PROCESS FOR PATIENTS WHO ARE UNINSURED OR UNDERINSURED
230
IS THE PATIENT WILLING/ABLE TO PAY?
NO
YES
234
THE PATIENT IS INFORMED OF THE COST OF THE PRODUCT AND IS GIVEN PAYMENT OPTIONS
YES
238
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM (STAPLED TO THE "COPY" OF THE Rx ENROLLMENT FORM) TO THE PHARMACY TEAM AS NOTIFICATION TO PROCESS THE PATIENT'S Rx
236
ONCE PAYMENT IS RECEIVED, INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM (STAPLED TO THE "COPY" OF THE Rx/ENROLLMENT FORM) TO THE PHARMACY TEAM AS NOTIFICATION TO PROCESS THE PATIENT'S Rx
A
A

FIG. 2A

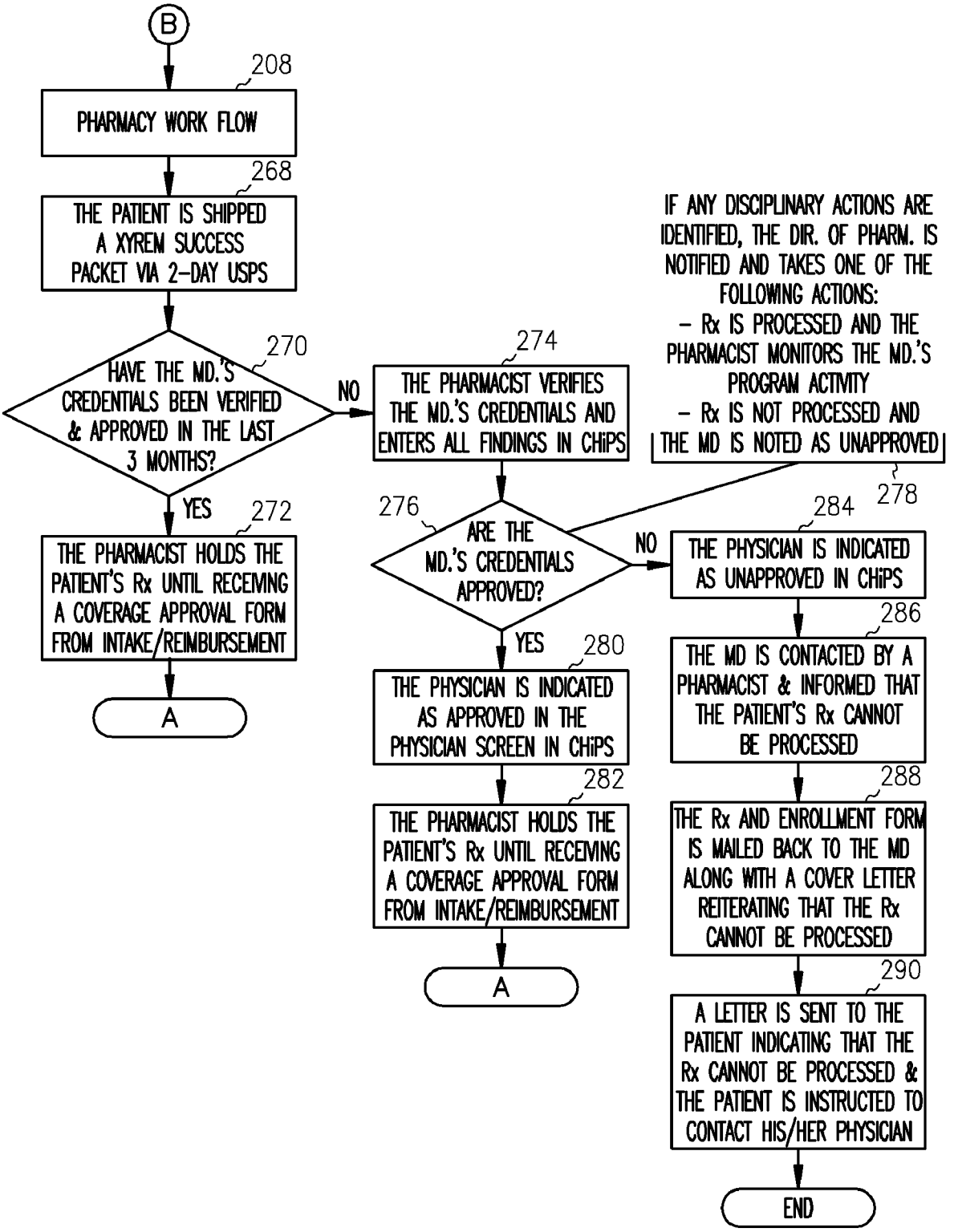
B
208
PHARMACY WORK FLOW
268
THE PATIENT IS SHIPPED A XYREM SUCCESS PACKET VIA 2-DAY USPS
270
HAVE THE MD.'S CREDENTIALS BEEN VERIFIED & APPROVED IN THE LAST 3 MONTHS?
NO
YES
272
THE PHARMACIST HOLDS THE PATIENT'S Rx UNTIL RECEIVING A COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT
A
274
THE PHARMACIST VERIFIES THE MD.'S CREDENTIALS AND ENTERS ALL FINDINGS IN CHiPS
276
ARE THE MD.'S CREDENTIALS APPROVED?
NO
YES
280
THE PHYSICIAN IS INDICATED AS APPROVED IN THE PHYSICIAN SCREEN IN CHiPS
282
THE PHARMACIST HOLDS THE PATIENT'S Rx UNTIL RECEIVING A COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT
A
IF ANY DISCIPLINARY ACTIONS ARE IDENTIFIED, THE DIR. OF PHARM. IS NOTIFIED AND TAKES ONE OF THE FOLLOWING ACTIONS:
- Rx IS PROCESSED AND THE PHARMACIST MONITORS THE MD.'S PROGRAM ACTIVITY
- Rx IS NOT PROCESSED AND THE MD IS NOTED AS UNAPPROVED
278
284
THE PHYSICIAN IS INDICATED AS UNAPPROVED IN CHiPS
286
THE MD IS CONTACTED BY A PHARMACIST & INFORMED THAT THE PATIENT'S Rx CANNOT BE PROCESSED
288
THE Rx AND ENROLLMENT FORM IS MAILED BACK TO THE MD ALONG WITH A COVER LETTER REITERATING THAT THE Rx CANNOT BE PROCESSED
290
A LETTER IS SENT TO THE PATIENT INDICATING THAT THE Rx CANNOT BE PROCESSED & THE PATIENT IS INSTRUCTED TO CONTACT HIS/HER PHYSICIAN
END

FIG. 2B

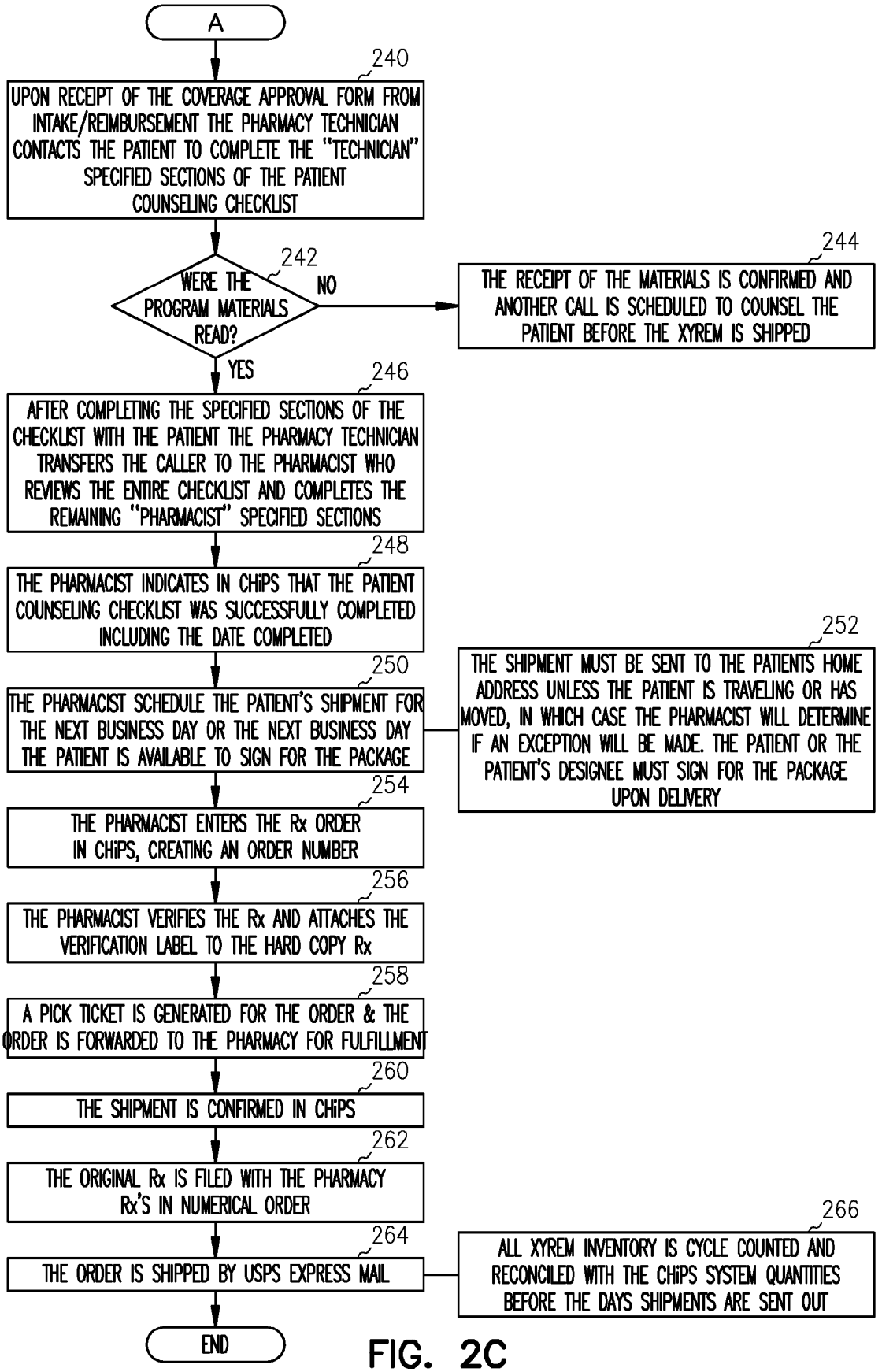
A
240
UPON RECEIPT OF THE COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE THE "TECHNICIAN" SPECIFIED SECTIONS OF THE PATIENT COUNSELING CHECKLIST
242
WERE THE PROGRAM MATERIALS READ?
NO
244
THE RECEIPT OF THE MATERIALS IS CONFIRMED AND ANOTHER CALL IS SCHEDULED TO COUNSEL THE PATIENT BEFORE THE XYREM IS SHIPPED
YES
246
AFTER COMPLETING THE SPECIFIED SECTIONS OF THE CHECKLIST WITH THE PATIENT THE PHARMACY TECHNICIAN TRANSFERS THE CALLER TO THE PHARMACIST WHO REVIEWS THE ENTIRE CHECKLIST AND COMPLETES THE REMAINING "PHARMACIST" SPECIFIED SECTIONS
248
THE PHARMACIST INDICATES IN CHIPS THAT THE PATIENT COUNSELING CHECKLIST WAS SUCCESSFULLY COMPLETED INCLUDING THE DATE COMPLETED
250
THE PHARMACIST SCHEDULE THE PATIENT'S SHIPMENT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
252
THE SHIPMENT MUST BE SENT TO THE PATIENTS HOME ADDRESS UNLESS THE PATIENT IS TRAVELING OR HAS MOVED, IN WHICH CASE THE PHARMACIST WILL DETERMINE IF AN EXCEPTION WILL BE MADE. THE PATIENT OR THE PATIENT'S DESIGNEE MUST SIGN FOR THE PACKAGE UPON DELIVERY
254
THE PHARMACIST ENTERS THE Rx ORDER IN CHIPS, CREATING AN ORDER NUMBER
256
THE PHARMACIST VERIFIES THE Rx AND ATTACHES THE VERIFICATION LABEL TO THE HARD COPY Rx
258
A PICK TICKET IS GENERATED FOR THE ORDER & THE ORDER IS FORWARDED TO THE PHARMACY FOR FULFILLMENT
260
THE SHIPMENT IS CONFIRMED IN CHIPS
262
THE ORIGINAL Rx IS FILED WITH THE PHARMACY Rx'S IN NUMERICAL ORDER
264
THE ORDER IS SHIPPED BY USPS EXPRESS MAIL
266
ALL XYREM INVENTORY IS CYCLE COUNTED AND RECONCILED WITH THE CHIPS SYSTEM QUANTITIES BEFORE THE DAYS SHIPMENTS ARE SENT OUT
END

FIG. 2C

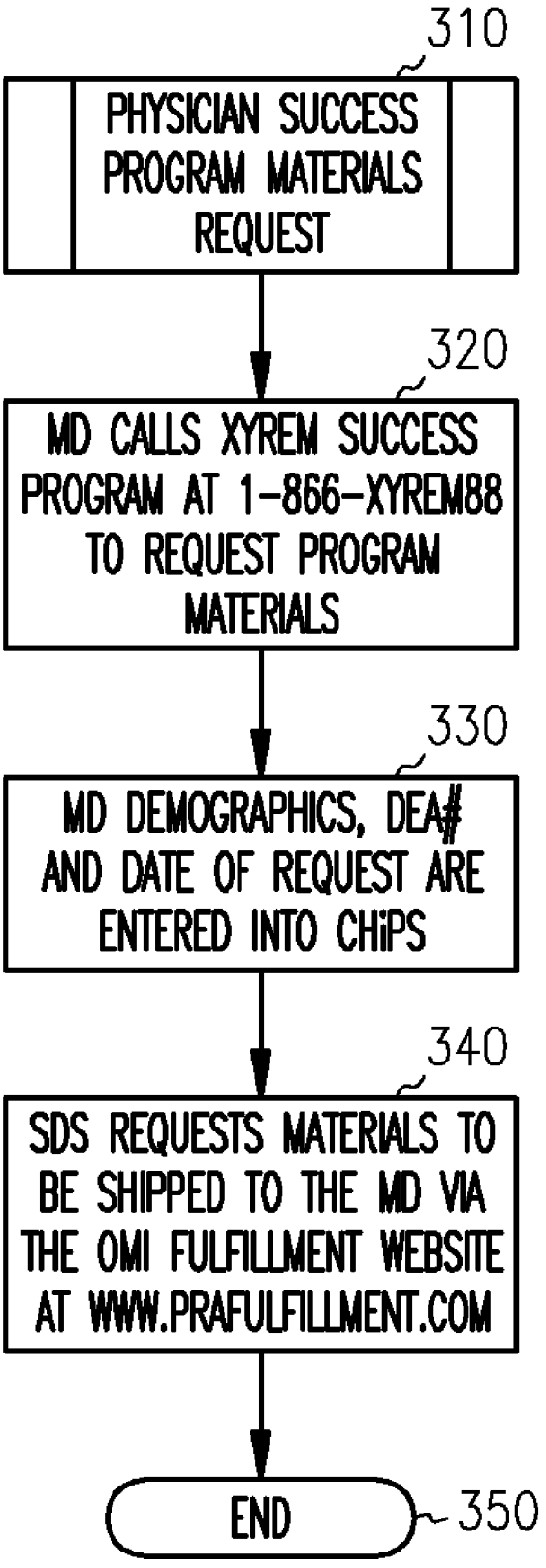
310
PHYSICIAN SUCCESS PROGRAM MATERIALS REQUEST
320
MD CALLS XYREM SUCCESS PROGRAM AT 1-866-XYREM88 TO REQUEST PROGRAM MATERIALS
330
MD DEMOGRAPHICS, DEA# AND DATE OF REQUEST ARE ENTERED INTO CHiPS
340
SDS REQUESTS MATERIALS TO BE SHIPPED TO THE MD VIA THE OMI FULFILLMENT WEBSITE AT WWW.PRAFULFILLMENT.COM
END
350

FIG. 3

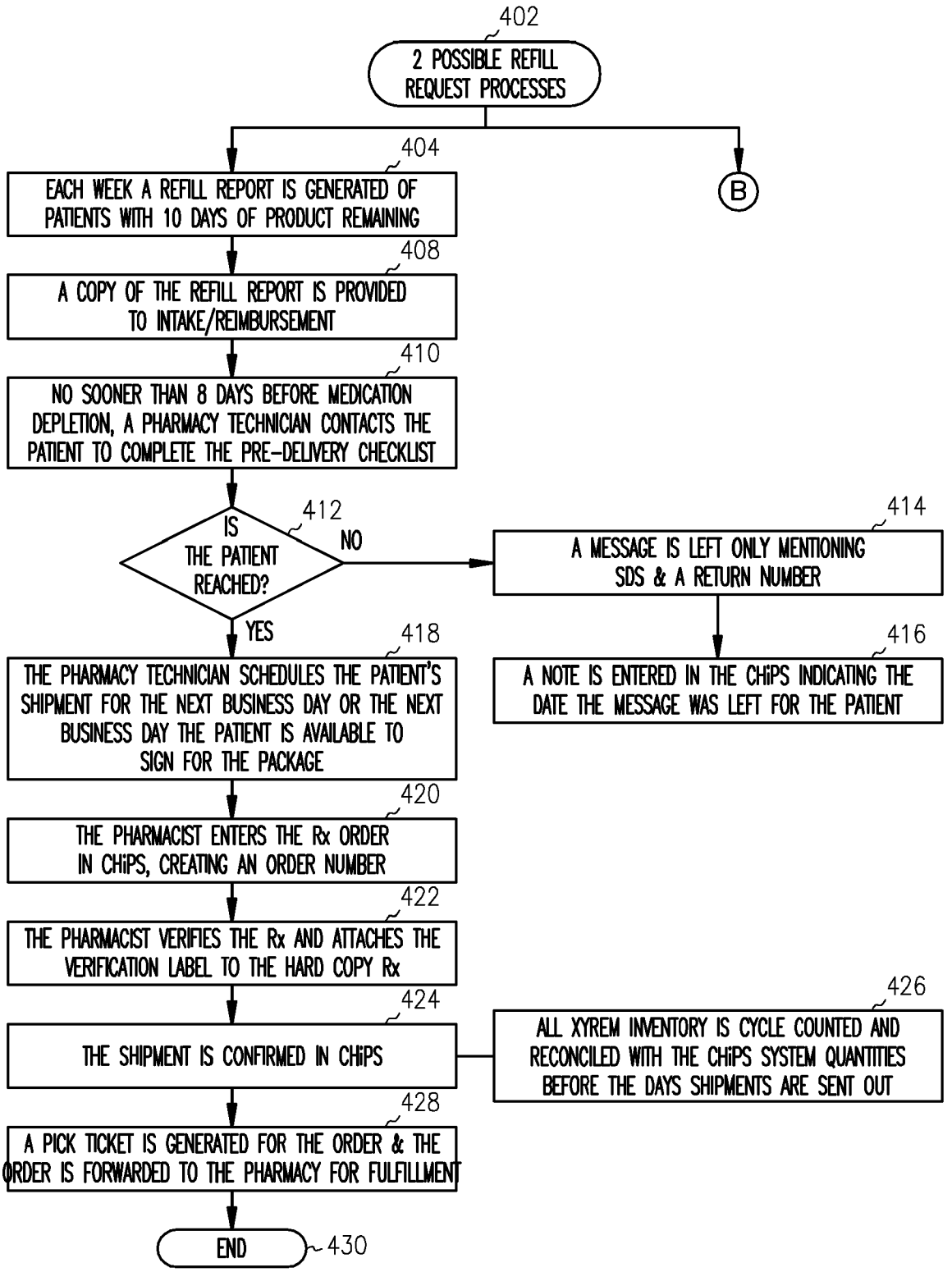
402
2 POSSIBLE REFILL REQUEST PROCESSES
404
EACH WEEK A REFILL REPORT IS GENERATED OF PATIENTS WITH 10 DAYS OF PRODUCT REMAINING
B
408
A COPY OF THE REFILL REPORT IS PROVIDED TO INTAKE/REIMBURSEMENT
410
NO SOONER THAN 8 DAYS BEFORE MEDICATION DEPLETION, A PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE THE PRE-DELIVERY CHECKLIST
412
IS THE PATIENT REACHED?
NO
414
A MESSAGE IS LEFT ONLY MENTIONING SDS & A RETURN NUMBER
YES
418
THE PHARMACY TECHNICIAN SCHEDULES THE PATIENT'S SHIPMENT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
416
A NOTE IS ENTERED IN THE CHIPS INDICATING THE DATE THE MESSAGE WAS LEFT FOR THE PATIENT
420
THE PHARMACIST ENTERS THE Rx ORDER IN CHIPS, CREATING AN ORDER NUMBER
422
THE PHARMACIST VERIFIES THE Rx AND ATTACHES THE VERIFICATION LABEL TO THE HARD COPY Rx
424
THE SHIPMENT IS CONFIRMED IN CHIPS
426
ALL XYREM INVENTORY IS CYCLE COUNTED AND RECONCILED WITH THE CHIPS SYSTEM QUANTITIES BEFORE THE DAYS SHIPMENTS ARE SENT OUT
428
A PICK TICKET IS GENERATED FOR THE ORDER & THE ORDER IS FORWARDED TO THE PHARMACY FOR FULFILLMENT
END
430

FIG. 4A

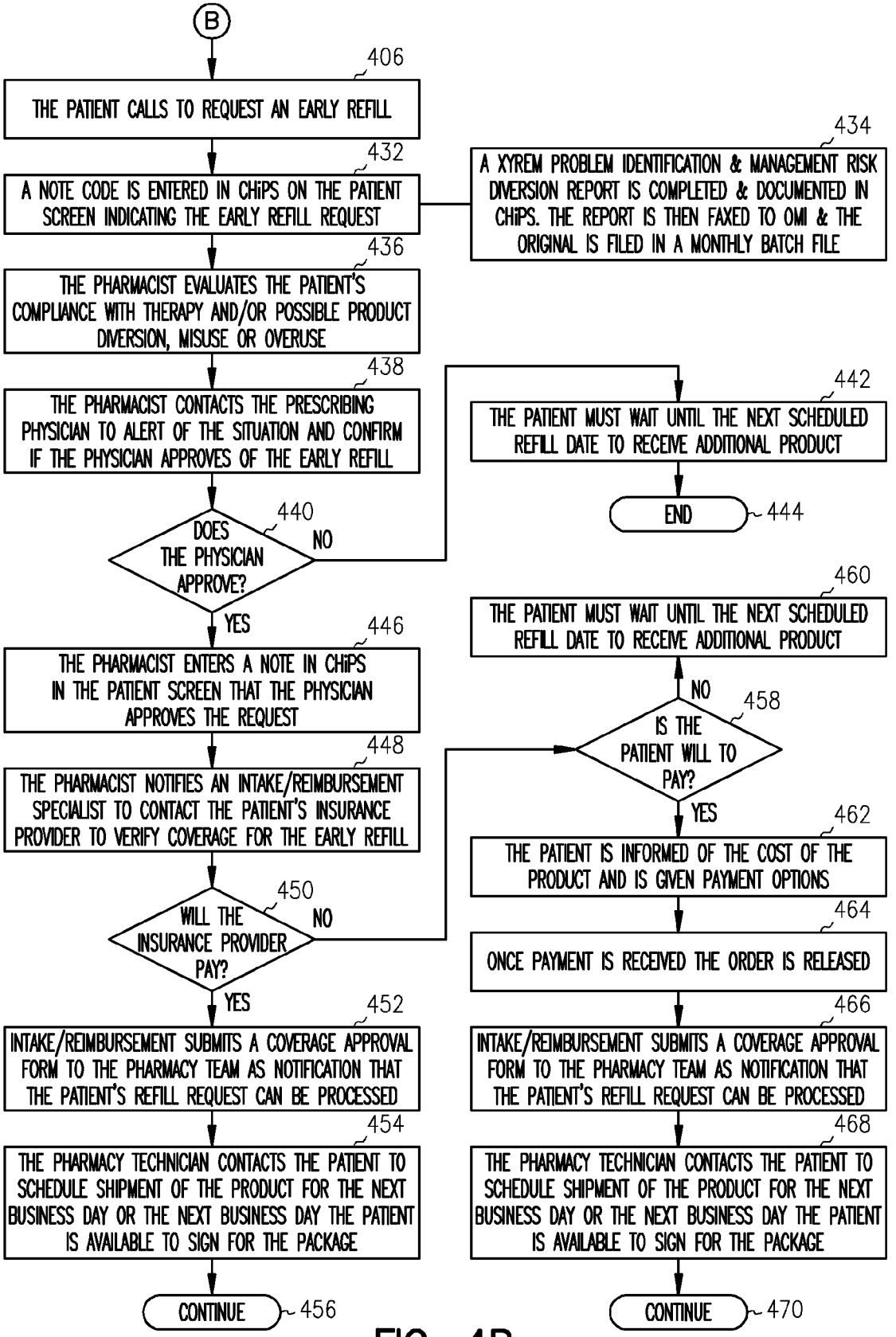
B
406
THE PATIENT CALLS TO REQUEST AN EARLY REFILL
432
A NOTE CODE IS ENTERED IN CHiPS ON THE PATIENT SCREEN INDICATING THE EARLY REFILL REQUEST
434
A XYREM PROBLEM IDENTIFICATION & MANAGEMENT RISK DIVERSION REPORT IS COMPLETED & DOCUMENTED IN CHiPS. THE REPORT IS THEN FAXED TO OMI & THE ORIGINAL IS FILED IN A MONTHLY BATCH FILE
436
THE PHARMACIST EVALUATES THE PATIENT'S COMPLIANCE WITH THERAPY AND/OR POSSIBLE PRODUCT DIVERSION, MISUSE OR OVERUSE
438
THE PHARMACIST CONTACTS THE PRESCRIBING PHYSICIAN TO ALERT OF THE SITUATION AND CONFIRM IF THE PHYSICIAN APPROVES OF THE EARLY REFILL
440
DOES THE PHYSICIAN APPROVE?
NO
442
THE PATIENT MUST WAIT UNTIL THE NEXT SCHEDULED REFILL DATE TO RECEIVE ADDITIONAL PRODUCT
END
444
YES
446
THE PHARMACIST ENTERS A NOTE IN CHiPS IN THE PATIENT SCREEN THAT THE PHYSICIAN APPROVES THE REQUEST
448
THE PHARMACIST NOTIFIES AN INTAKE/REIMBURSEMENT SPECIALIST TO CONTACT THE PATIENT'S INSURANCE PROVIDER TO VERIFY COVERAGE FOR THE EARLY REFILL
450
WILL THE INSURANCE PROVIDER PAY?
NO
460
THE PATIENT MUST WAIT UNTIL THE NEXT SCHEDULED REFILL DATE TO RECEIVE ADDITIONAL PRODUCT
458
IS THE PATIENT WILL TO PAY?
NO
YES
462
THE PATIENT IS INFORMED OF THE COST OF THE PRODUCT AND IS GIVEN PAYMENT OPTIONS
464
ONCE PAYMENT IS RECEIVED THE ORDER IS RELEASED
YES
452
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT'S REFILL REQUEST CAN BE PROCESSED
466
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT'S REFILL REQUEST CAN BE PROCESSED
454
THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO SCHEDULE SHIPMENT OF THE PRODUCT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
468
THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO SCHEDULE SHIPMENT OF THE PRODUCT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
CONTINUE
456
CONTINUE
470

FIG. 4B

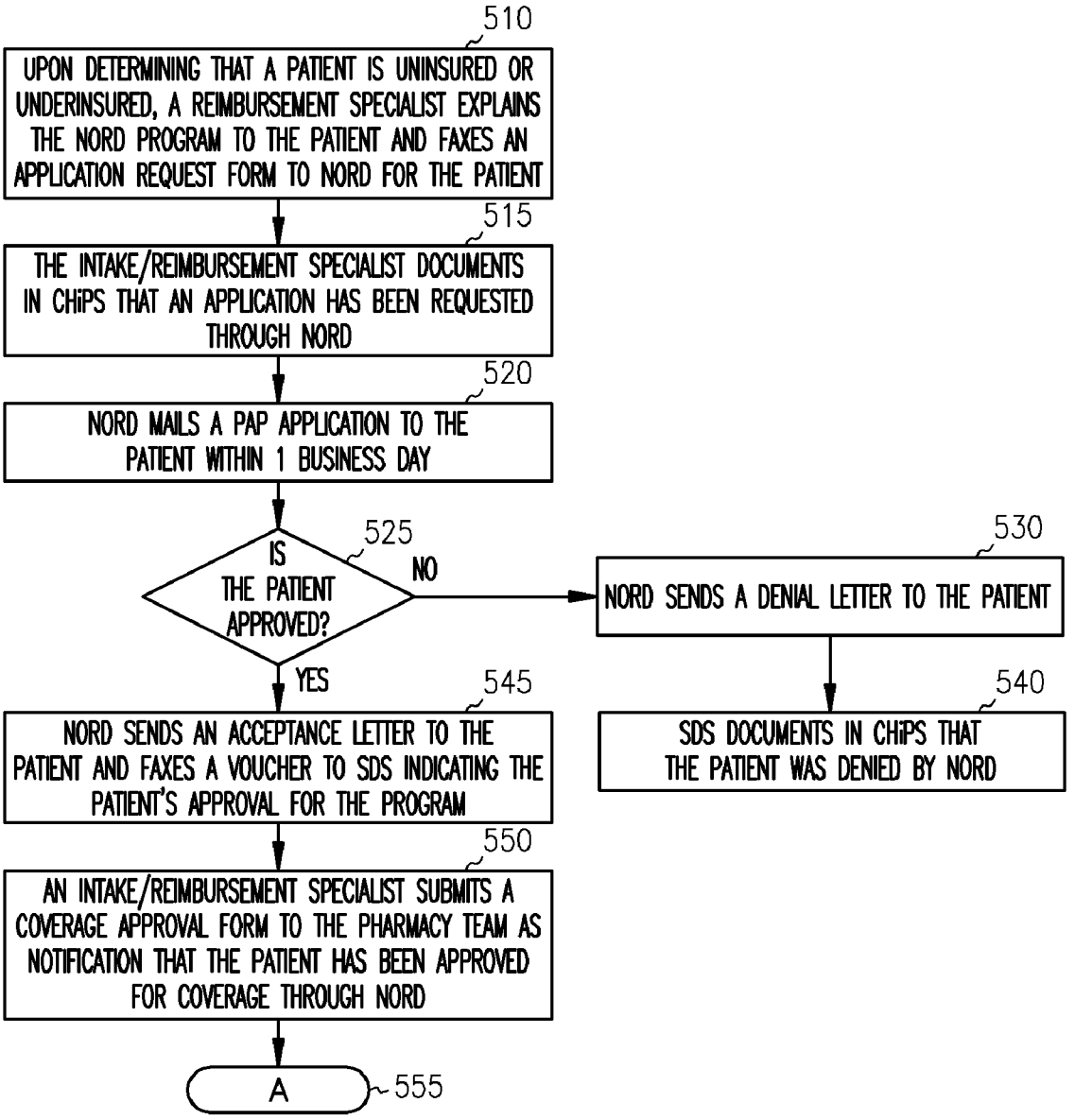
510
UPON DETERMINING THAT A PATIENT IS UNINSURED OR UNDERINSURED, A REIMBURSEMENT SPECIALIST EXPLAINS THE NORD PROGRAM TO THE PATIENT AND FAXES AN APPLICATION REQUEST FORM TO NORD FOR THE PATIENT
515
THE INTAKE/REIMBURSEMENT SPECIALIST DOCUMENTS IN CHiPS THAT AN APPLICATION HAS BEEN REQUESTED THROUGH NORD
520
NORD MAILS A PAP APPLICATION TO THE PATIENT WITHIN 1 BUSINESS DAY
525
IS THE PATIENT APPROVED?
NO
530
NORD SENDS A DENIAL LETTER TO THE PATIENT
YES
545
NORD SENDS AN ACCEPTANCE LETTER TO THE PATIENT AND FAXES A VOUCHER TO SDS INDICATING THE PATIENT'S APPROVAL FOR THE PROGRAM
540
SDS DOCUMENTS IN CHiPS THAT THE PATIENT WAS DENIED BY NORD
550
AN INTAKE/REIMBURSEMENT SPECIALIST SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT HAS BEEN APPROVED FOR COVERAGE THROUGH NORD
A
555

FIG. 5

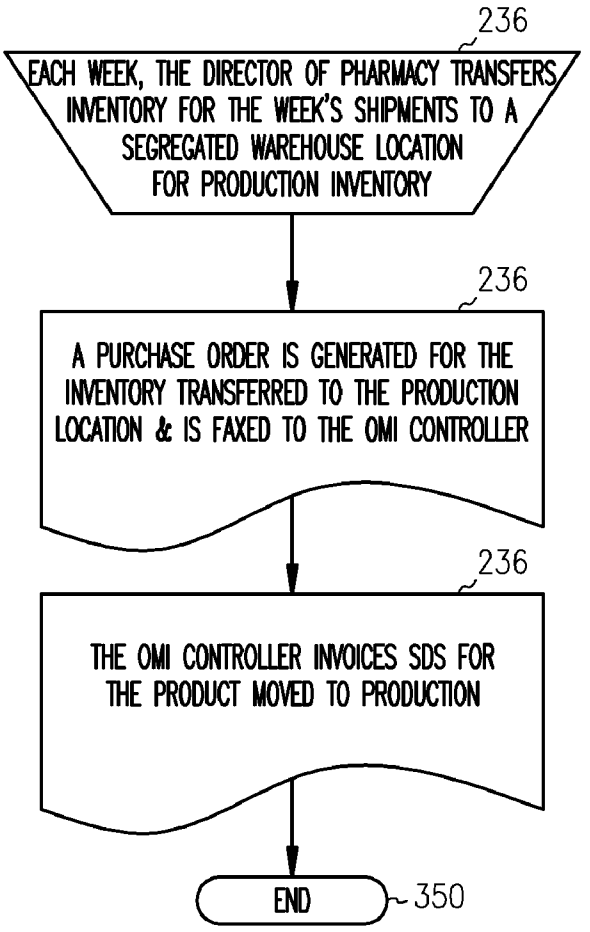

FIG. 6

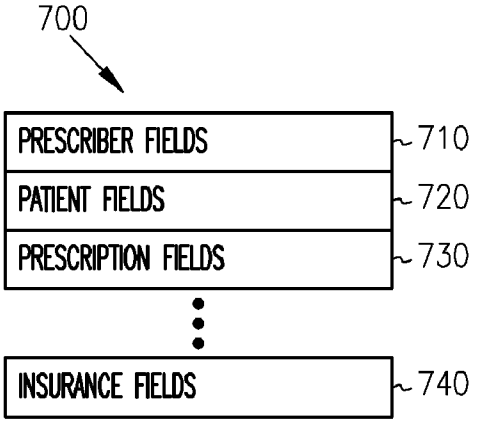

FIG. 7

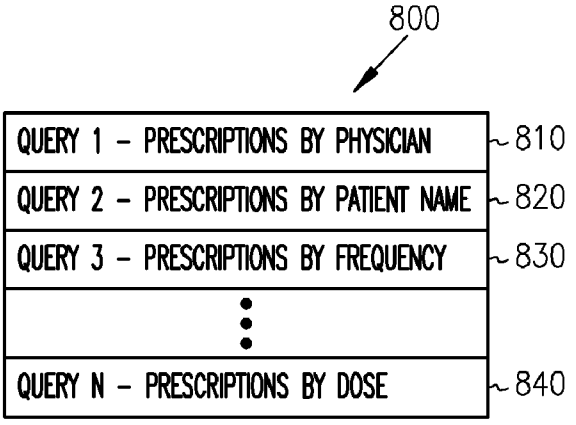

FIG. 8

900

PRESCRIPTION AND ENROLLMENT FORM

PRESCRIBER INFORMATION

PRESCRIBER'S NAME: _____ OFFICE CONTACT: _____
STREET ADDRESS: _____
CITY: _____ STATE: _____ ZIP: _____
PHONE: _____ FAX: _____
LICENSE NUMBER: _____ DEA NUMBER: _____
MD SPECIALTY: _____

PRESCRIPTION FORM

PATIENT NAME: _____ SS#: _____ DOB: _____ SEX M / F
ADDRESS: _____
CITY: STATE: ZIP:
Rx: XYREM ORAL SOLUTION (500 mg/mL) 180 Ml. BOTTLE QUANTITY: _____ MONTHS SUPPLY
SIG: TAKE ____ GMS P.O. DILUTED IN 60 mL WATER AT H.S. AND THEN AGAIN 2 1/2 TO 4 HOURS LATER
REFILLS (CIRCLE ONE): 0 1 2 (MAXIMUM OF 3 MONTH SUPPLY)
_____ DATE: ____/____/____
PRESCRIBER'S SIGNATURE

PHYSICIAN DECLARATION–PLEASE CHECK EACH BOX | TO BE COMPLETED AT INITIAL PRESCRIPTION ONLY

- ☐ I HAVE READ THE MATERIALS IN THE XYREM PHYSICIAN SUCCESS PROGRAM
- ☐ I VERIFY THAT THE PATIENT HAS BEEN EDUCATED WITH RESPECT TO XYREM PREPARATION, DOSING AND SCHEDULING.
- ☐ I UNDERSTAND THAT XYREM IS APPROVED FOR THE TREATMENT OF CATAPLEXY IN PATIENTS WITH NARCOLEPSY, AND THAT SAFETY OR EFFICACY HAS NOT BEEN ESTABLISHED FOR ANY OTHER INDICATION.
- ☐ I UNDERSTAND THAT THE SAFETY OF DOSES GREATER THAN 9gm/DAY HAS NOT BEEN ESTABLISHED

PATIENT INFORMATION

BEST TIME TO CONTACT PATIENT: ☐ DAY ☐ NIGHT
DAY #: _____ EVENING #: _____
INSURANCE COMPANY NAME: _____ PHONE #: _____
INSURED'S NAME: _____ RELATIONSHIP TO PATIENT: _____
IDENTIFICATION NUMBER: _____ POLICY/GROUP NUMBER: _____
PRESCRIPTION CARD: ☐ NO ☐ YES IF YES, CARRIER: _____ POLICY #: _____ GROUP: _____

PLEASE ATTACH COPIES OF PATIENT'S INSURANCE CARDS

FAX COMPLETED FORM TO XYREM SUCCESS PROGRAM (TOLL-FREE) 1-866-470-1744
FOR INFORMATION, CALL THE XYREM TEAM (TOLL FREE) AT 1-866-XYREM88 (1-866-997-3688)

FIG. 9

PATIENT ASSISTANCE APPLICATION REQUEST FORM

DATE:

TO: PATIENT ASSISTANCE ORGANIZATION
FROM: SDS

FAX #: 203-798-2291

PLEASE SEND A XYREM PATIENT ASSISTANCE PROGRAM APPLICATION TO:

PATIENT NAME _____

ADDRESS _____

_____

_____

TELEPHONE: ( ) _____

PATIENT DOSAGE: _____ (GRAMS) TWICE NIGHTLY FOR A TOTAL DOSAGE OF _____ (GRAMS)

_____ BOTTLES (THREE MONTHS SUPPLY)

BACKGROUND INFORMATION:

_____

_____

_____

_____

_____

_____

FIG. 10

1100

SENSITIVE DRUG PATIENT ASSISTANCE PROGRAM

VOUCHER REQUEST FOR MEDICATION

PATIENT INFORMATION
<FIRST NAME><LAST NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890
DOB: 01/01/1900
SSN: 123-45-6789
DRUG ALLOTMENT: 100%
LRD: 03/01/2001

PHYSICIAN INFORMATION
<PHYSICIAN NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890

CASE CODE: ********

FIRST SHIPMENT THIS YEAR

DRUG	QUANTITY
XYREEM 180ml btl	1

VALIDATION DATE: 03/01/2001
EXPIRATION DATE: 05/31/2001
ISSUE DATE: 03/15/2001

APPROVED _____

PHARMACY USE

NORD COPY

****

(DETACH HERE)

PATIENT INFORMATION
<FIRST NAME><LAST NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890
DOB: 01/01/1900
SSN: 123-45-6789
DRUG ALLOTMENT: 100%
LRD: 03/01/2001

PHYSICIAN INFORMATION
<PHYSICIAN NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890

CASE CODE: ********

FIRST SHIPMENT THIS YEAR

DRUG	QUANTITY
XYREM 180ml btl	1

VALIDATION DATE: 03/01/2001
EXPIRATION DATE: 05/31/2001
ISSUE DATE: 03/15/2001

APPROVED _____

PHARMACY USE

FIG. 11

1200

SENSITIVE DRUG PHYSICIAN'S CERTIFICATE OF MEDICAL NEED

PATIENT INFORMATION

DATE: _____

NAME: _____
LAST FIRST M

DATE OF BIRTH: _____

DRUG BEING PRESCRIBED: XYREM

DIAGNOSIS/CONDITION FOR WHICH DRUG IS BEING PRESCRIBED: _____

ICD-9: _____

PHYSICIAN INFORMATION

PHYSICIAN'S NAME (PLEASE PRINT): _____

PHYSICIAN'S SIGNATURE: _____ DATE: _____

PLEASE FAX BACK TO SENSITIVE DRUG SUCCESS PROGRAM: (1-800-TOLL FREE NUMBER)

FIG. 12

ACTIVITY REPORTS

	REPORT FREQUENCY		
	WEEKLY	MONTHLY	QUARTERLY
SALES			
Rx BY ZIP (NEW AND TOTAL)	X	X	X
Rx BY PHYSICIAN BY ZIP	X	X	
$ BY ZIP	X	X	X
REGULATORY			
# OF PHYSICIAN REGISTRIES		X	
# OF DENIED PHYSICIAN REGISTRIES AND REASON		X	
# OF COMPLETED PATIENT REGISTRIES		X	
# OF PROBLEM IDENTIFICATION & MANAGEMENT RISK DIVERSION REPORTS COMPLETED	X		
# OF CYCLE COUNTS PERFORMED & ACCURACY OF EACH		X	
QUALITY ASSURANCE			
# OF PRODUCT DEFECTS/COMPLAINTS REPORTED, TYPE AND LOT #		X	
CALL CENTER			
# OF CALLS RECEIVED		X	
# OF CALLS INITIATED		X	
# OF CALLS ANSWERED IN 30 SECONDS, ETC.		X	
PERCENTAGE OF CALLS ANSWERED IN 30 SECONDS		X	
# OF ABANDONED CALLS		X	
% OF ABANDONED CALLS		X	
AVERAGE CALL LENGTH		X	
PHARMACY			
# OF FAXED Rx/ENROLLMENT FORMS		X	
# OF MAILED Rx/ENROLLEMENT FORMS		X	
# OF RxS SHIPPED W/IN 1, 2, 3, 4 ETC. DAYS (FROM THE TIME INITIAL RECEIPT TO SHIPMENT OF Rx)		X	
# OF PATIENT SUCCESS PACKETS SHIPPED		X	

FIG. 13A

ACTIVITY REPORTS

PHARMACY			
# OF PHYSICIAN SUCCESS PACKETS SHIPPED			X
# OF COMPLETED SHIPMENTS			X
# OF INCOMPLETE SHIPMENTS AND REASON			X
# OF SHIPPING ERRORS			X
# OF PAP SHIPMENTS			X
# OF PAP APPLICATIONS			X
# OF PAP APPROVALS			X
# OF CANCELED ORDERS			X
# OF USPS ERRORS			X
INVENTORY			X
# OF RETURNED PRODUCTS AND REASON			X
# OF OUTDATED BOTTLES OF PRODUCT			X
INVENTORY COUNTS OF CONSIGNMENT & PRODUCTION INVENTORY			X
# OF UNITS RECEIVED			X
LOTS RECEIVED			X
REIMBURSEMENT			X
# OF PENDED AND WHY			X
# OF APPROVALS			X
# OF DENIALS			X
# OF REJECTIONS			X
PAYOR TYPES			X

FIG. 13B

ACTIVITY REPORTS

PATIENT CARE			
# OF ADVERSE EVENTS REPORTED AND TYPE		X	
# OF ADVERSE EVENTS SENT TO OMI		X	
# OF DOSING PROBLEMS AND TYPE		X	
# OF NONCOMPLIANCE EPISODES AND REASON		X	
# OF PATIENT COUNSELED AND REASON		X	
# OF PATIENTS DISCONTINUED AND REASON		X	
PATIENT CARE		X	
# OF PATIENTS REFERRED TO PHYSICIAN AND REASON		X	
# OF ACTIVE PATIENTS		X	
# OF NEW PATIENTS		X	
# OF RESTART PATIENTS		X	
# OF DISCONTINUED PATIENTS AND REASON		X	
DRUG INFORMATION		X	
# OF DRUG INFORMATION REQUESTS AND TYPE		X	
# OF CALLS TRIAGED TO OMI		X	

FIG. 13C

SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

RELATED APPLICATION

This application is a continuation of U.S. Serial application Ser. No. 10/322,348, filed on Dec. 17, 2002, which is incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

The present invention relates to distribution of drugs, and in particular to the distribution of sensitive drugs.

BACKGROUND OF THE INVENTION

Sensitive drugs are controlled to minimize risk and ensure that they are not abused, or cause adverse reactions. Such sensitive drugs are approved for specific uses by the Food and Drug Administration, and must be prescribed by a licensed physician in order to be purchased by consumers. Some drugs, such as cocaine and other common street drugs are the object of abuse and illegal schemes to distribute for profit. Some schemes include Dr. shopping, diversion, and pharmacy thefts. A locked cabinet or safe is a requirement for distribution of some drugs.

Certain agents, such as gamma hydroxy buterate (GHB) are also abused, yet also are effective for therapeutic purposes such as treatment of daytime cataplexy in patients with narcolepsy. Some patients however, will obtain prescriptions from multiple doctors, and have them filled at different pharmacies. Still further, an unscrupulous physician may actually write multiple prescriptions for a patient, or multiple patients, who use cash to pay for the drugs. These patients will then sell the drug to dealers or others for profit.

There is a need for a distribution system and method that directly addresses these abuses. There is a further need for such a system and method that provides education and limits the potential for such abuse.

SUMMARY OF THE INVENTION

A drug distribution system and method utilizes a central pharmacy and database to track all prescriptions for a sensitive drug. Information is kept in a central database regarding all physicians allowed to prescribe the sensitive drug, and all patients receiving the drug. Abuses are identified by monitoring data in the database for prescription patterns by physicians and prescriptions obtained by patients. Further verification is made that the physician is eligible to prescribe the drug by consulting a separate database for a valid DEA license, and optionally state medical boards to determine whether any corrective or approved disciplinary actions relating to controlled substances have been brought against the physician. Multiple controls beyond those for traditional drugs are imposed on the distribution depending on the sensitivity of the drug.

Education is provided to both physician and patient. Prior to shipping the drug for the first time, the patient is contacted to ensure that product and abuse related educational materials have been received and/or read. The patient may provide the name of a designee to the central pharmacy who is authorized to accept shipment of the drug. Receipt of the initial drug shipment is confirmed by contacting the patient. Either a phone call or other communication to the patient within a set time after delivery may be made to ensure receipt. Further, a courier service's tracking system is used to confirm delivery in further embodiments. If a shipment is lost, an investigation is launched to find it.

In one embodiment, the drug may be shipped by the central pharmacy to another pharmacy for patient pick-up. The second pharmacy's ability to protect against diversion before shipping the drug must be confirmed. This ability may be checked through NTIS and State Boards of Pharmacy.

Prescription refills are permitted in the number specified in the original prescription. In addition, if a prescription refill is requested by the patient prior to the anticipated due date, such refills will be questioned. A lost, stolen, destroyed or spilled prescription/supply is documented and replaced to the extent necessary to honor the prescription, and will also cause a review or full investigation.

The exclusive central database contains all relevant data related to distribution of the drug and process of distributing it, including patient, physician and prescription information. Several queries and reports are run against the database to provide information which might reveal potential abuse of the sensitive drug, such as early refills.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a block diagram of a computer system for use in implementing the system and method of the present invention.

FIGS. **2**A, **2**B and **2**C are a flowchart describing a method for sensitive drug distribution at least partially utilizing a computer system such as that shown in FIG. **1**.

FIG. **3** is a flowchart of a physician success program at least partially implemented on a computer system such as that shown in FIG. **1**.

FIGS. **4**A and **4**B are a flowchart describing a method for handling refill requests at least partially utilizing a computer system such as that shown in FIG. **1**.

FIG. **5** is a flowchart of a process for requesting special reimbursement when a patient is uninsured or underinsured at least partially utilizing a computer system as that shown in FIG. **1**.

FIG. **6** is a flowchart of a process for inventory control at least partially utilizing a computer system such as that shown in FIG. **1**.

FIG. **7** is a block diagram of database fields.

FIG. **8** is a block diagram showing a list of queries against the database fields.

FIG. **9** is a copy of one example prescription and enrollment form.

FIG. **10** is a copy of one example of a NORD application request form for patient financial assistance.

FIG. **11** is a copy of one example voucher request for medication for use with the NORD application request form of FIG. **10**.

FIG. **12** is a copy of certificate of medical need.

FIGS. **13**A, **13**B and **13**C are descriptions of sample reports obtained by querying a central database having fields represented in FIG. **7**.

DETAILED DESCRIPTION OF THE INVENTION

In the following description, reference is made to the accompanying drawings that form a part hereof, and in which is shown by way of illustration specific embodiments in which the invention may be practiced. These embodiments are described in sufficient detail to enable those skilled in the art to practice the invention, and it is to be understood that other embodiments may be utilized and that structural, logical

and electrical changes may be made without departing from the scope of the present invention. The following description is, therefore, not to be taken in a limited sense, and the scope of the present invention is defined by the appended claims.

The functions or algorithms described herein are implemented in software or a combination of software and human implemented procedures in one embodiment. The software comprises computer executable instructions stored on computer readable media such as memory or other type of storage devices. The term "computer readable media" is also used to represent carrier waves on which the software is transmitted. Further, such functions correspond to modules, which are software, hardware, firmware of any combination thereof. Multiple functions are performed in one or more modules as desired, and the embodiments described are merely examples. The software is executed on a digital signal processor, ASIC, microprocessor, or other type of processor operating on a computer system, such as a personal computer, server or other computer system.

A sensitive drug is one which can be abused, or has addiction properties or other properties that render the drug sensitive. One example of such a drug is sodium oxybate, also known as gamma hydroxy butyrate (GHB $C_4H_7NaO_3$) which is useful for treatment of cataplexy in patients with narcolepsy. GHB is marketed under the trademark of Xyrem® (sodium oxybate oral solution), which trademark can be used interchangeably with GHB herein. Sensitive drugs also include narcotics or other drugs which require controls on their distribution and use to monitor behaviors to prevent abuse and adverse side effects.

In one embodiment, Xyrem® is subject to a restricted distribution program. One aspect of the program is to educate physicians and patients about the risks and benefits of Xyrem, including support via ongoing contact with patients and a toll free helpline. Initial prescriptions are filled only after a prescriber and patient have received and read the educational materials. Further, patient and prescribing physician registries are maintained and monitored to ensure proper distribution.

In a further embodiment, bulk sodium oxybate is manufactured at a single site, as is the finished drug product. Following manufacture of the drug product, it is stored at a facility compliant with FDA Schedule III regulations, where a consignment inventory is maintained. The inventory is owned by a company, and is managed by a central pharmacy, which maintains the consignment inventory. Xyrem® is distributed and dispensed through a primary and exclusive central pharmacy, and is not stocked in retail pharmacy outlets. It is distributed by overnight carriers, or by US mail in one embodiment to potentially invoke mail fraud laws if attempts of abuse occur.

FIG. **1** is a simplified block diagram of a computer system **100**, such as a personal computer for implementing at least a portion of the methods described herein. A central processing unit (CPU) **110** executes computer programs stored on a memory **120**. Memory **120** in one embodiment comprises one or more levels of cache as desired to speed execution of the program and access to data on which the programs operate. The CPU is directly coupled to memory **120** in one embodiment. Both CPU **110** and memory **120** are coupled to a bus **130**. A storage **140**, I/O **150** and communications **160** are also coupled to the bus **130**. Storage **140** is usually a long term storage device, such as a disk drive, tape drive, DVD, CD or other type of storage device. In one embodiment, storage **140** is used to house a database for use with the present invention. I/O **150** comprises keyboards, sound devices, displays and other mechanisms by which a user interacts with the computer system **100**. Communications **160** comprises a network, phone connection, local area network, wide area network or other mechanism for communicating with external devices. Such external devices comprise servers, other peer computers and other devices. In one embodiment, such external device comprises a database server that is used in place of the database on storage **140**. Other computer system architectures capable of executing software and interacting with a database and users may also be used. Appropriate security measures such as encryption are used to ensure confidentiality. Further, data integrity and backup measures are also used to prevent data loss.

FIGS. **2**A, **2**B and **2**C represent an initial prescription order entry process for a sensitive drug, such as Xyrem. At **202**, a medical doctor (MD) sends a Rx/enrollment form via mail, fax, email or other means to an intake/reimbursement specialist at **204**, who makes a copy of the RX/enrollment form that is stamped "copy". The original fax is forwarded to a pharmacy team. The enrollment form contains prescriber information, prescription information, checkboxes for the prescriber indicating they have read materials, educated the patient, understand the use in treatment, and understand certain safety information, and also contains patient information.

The prescriber information contains standard contact information as well as license number, DEA number and physician specialty. Patient and prescription information includes name, social security number, date of birth, gender, contact information, drug identification, patient's appropriate dosage, and number of refills allowed, along with a line for the prescriber's signature. Patient insurance information is also provided.

There are two workflows involved at the pharmacy team, intake reimbursement **206** and pharmacy workflow **208**, which may proceed in parallel or serially. The intake work flow **206** starts with an intake reimbursement specialist entering the patient and physician information into an application/database referred to as CHIPS, which is used to maintain a record of a client home infusion program (CHIP) for Xyrem®. A check is made to ensure the information is complete at **212**. If not, at **214**, an intake representative attempts to reach the MD or prescriber to obtain the missing information. If the missing information has not been obtained within a predetermined period of time, such as 24 hours at **216**, the Rx/Enrollment form is sent back to the MD with a rejection explanation. A note is entered in CHIPS that the application was rejected.

If the information is complete at **212**, the MD is contacted at **220** to verify receipt and accuracy of the patient's Rx. This contact is recorded in CHIPS. The intake and reimbursement specialist then sends a consent form and a cover letter to the patient at **224**. The insurance provider is contacted at **226** to verify coverage and benefits. At **228**, a determination is made regarding coverage for the drug. If it is not available, it is determined at **230** whether the patient is willing and able to pay. If not, a process is performed for handling patients who are uninsured or underinsured. In one embodiment, the process is referred to as a NORD process.

If the patient is willing and able to pay at **230**, the patient is informed of the cost of the product and is given payment options at **234**. At **236**, once payment is received, the intake reimbursement specialist submits a coverage approval form with the enrollment form to the pharmacy team as notification to process the patient's prescription. If coverage is approved at **228**, the intake reimbursement specialist also submits the coverage approval form with the enrollment form to the pharmacy team as notification to process the patient's prescription. Processing of the prescription is described below.

Upon receipt and initial processing of the prescription enrollment form and sending an original to the pharmacy work flow block **208**, the patient is shipped a Xyrem® success packet via mail. In one embodiment, the Xyrem® success packet contains educational material for a patient that advises of the proper use, care and handling of the drug and consequences of diversion at **268**. The medical doctor's credentials are checked to determine if the physician has a current DEA license to prescribe controlled substances and if he or she has had any actions related to misuse/misprescribing of controlled drugs against him or her, within a predetermined time, such as three months at **270**. If they have, a pharmacist holds the prescription until receiving a coverage approval form from the intake reimbursement specialist at **272**.

If the credentials have not been recently checked, the pharmacist verifies the credentials and enters all findings in the database at **274**. If the credentials are approved at **276**, the physician is indicated as approved in a physician screen populated by information from the database at **280**. The prescription is then held pending coverage approval at **282**.

If any disciplinary actions are identified, as referenced at block **278**, management of the pharmacy is notified and either approves processing of the prescription with continued monitoring of the physician, or processing of the prescription is not performed, and the physician is noted in the database as unapproved at **284**. The enrollment form is then mailed back to the physician with a cover letter reiterating that the prescription cannot be processed at **288**. The patient is also sent a letter at **290** indicating that the prescription cannot be processed and the patient is instructed to contact their physician.

Actual filling of the approved prescription begins with receipt of the coverage approval form as indicated at **240**. The patient is contacted by the pharmacy, such as by a technician to complete a technician section of a patient counseling checklist. If a pharmacist verifies that the program materials were not read at **242**, the receipt of the material is confirmed at **244** and another call is scheduled to counsel the patient before the drug is shipped.

If the program materials, were read at **242**, the checklist is completed at **246** and the technician transfers the patient to the pharmacist who reviews the entire checklist and completes remaining pharmacist specified sections. At **248**, the pharmacists indicates in the database that the patient counseling and checklist was successfully completed, indicating the date completed.

At **250**, the pharmacist schedules the patient's shipment for the next business day or the next business day that the patient or designee is able to sign for the package. Further, as indicated at **252**, the shipment must be sent to the patient's home address unless the patient is traveling or has moved. In that event, the pharmacist may determine that an exception may be made. The patient or the patient's designee who is at least 18 years old, must sign for the package upon delivery.

At **254**, the pharmacist enters the prescription order in the database, creating an order number. The pharmacist then verifies at **256** the prescription and attaches a verification label to the hard copy prescription. At **258**, a pick ticket is generated for the order and the order is forwarded to the pharmacy for fulfillment. The shipment is confirmed in the database at **260**, and the order is shipped by USPS Express Mail. Use of the US mail invokes certain criminal penalties for unauthorized diversion. Optionally, other mail services may be used. Potential changes in the law may also bring criminal penalties into play. Following shipment, the patient is called by the central pharmacy to confirm that the prescription was received.

As noted at **266**, for the sensitive drug, Xyrem, all inventory is cycle counted and reconciled with the database system quantities before shipments for the day are sent. This provides a very precise control of the inventory.

A physician success program materials request process begins at **310** in FIG. **3**. At **320**, the MD calls to the central pharmacy to request program materials. A special phone number is provided. MD demographics, DEA number, and data or request are entered into the database at **330**. At **340**, a request is made to ship the materials to the MD via a fulfillment website, or other mechanism. The request process ends at **350**.

A refill request process begins at **302** in FIGS. **4**A and **4**B. There are two different paths for refills. A first path beginning at **404** involves generating a report from the central database of patients with a predetermined number of days or product remaining. A second path beginning at **406** is followed when a patient calls to request an early refill.

In the first path, a copy of the report is provided to an intake reimbursement specialist at **408**. No sooner than 8 days before the medication depletion, a pharmacy technician contacts the patient at **410** to complete the pre-delivery checklist. At **412**, if the patient is not reached, a message is left mentioning the depletion, and a return number at **414**. A note is also entered into the database indicating the date the message was left at **416**.

If the patient is reached at **412**, the next shipment is scheduled at **418**, the prescription is entered into the database creating an order at **420**, the pharmacist verifies the prescription and attaches a verification label at **422** and the shipment is confirmed in the database at **424**. Note at **426** that the inventory is cycle counted and reconciled with the database quantities before the shipments for a day or other time period are sent. A pick ticket is generated for the order and the order is forwarded for fulfillment at **428**, with the first path ending at **430**.

The second path, beginning at **406** results in a note code being entered into the database on a patient screen indicating an early refill request at **432**. The pharmacist evaluates the patient's compliance with therapy or possible product diversion, misuse or over-use at **436**. In one embodiment, cash payers are also identified. The pharmacist then contacts the prescribing physician to alert them of the situation and confirm if the physician approves of the early refill at **438**. If the physician does not approve as indicated at **440**, the patient must wait until the next scheduled refill date to receive additional product as indicated at **442**, and the process ends at **444**.

If the physician approves at **440**, the pharmacist enters a note in the database on a patient screen that the physician approves the request at **446**. The pharmacist notifies an intake reimbursement specialist to contact the patient's insurance provider to verify coverage for the early refill at **448**. If the insurance provider will pay as determined at **450**, the specialist submits the coverage approval form as notification that the refill may be processed at **452**. At **454**, the pharmacy technician contacts the patient to schedule shipment of the product for the next business day, and the process of filling the order is continued at **456** by following the process beginning at **240**.

If the insurance provider will not pay at **450**, it is determined whether the patient is willing and/or able to pay at **458**. If not, the patient must wait until the next scheduled refill date to receive additional product at **460**. If it was determined at **458** that the patient was willing and able to pay, the patient is informed of the cost of the product and is given payment options at **462**. Once payment is received as indicated at **464**, the specialist submits a coverage approval form to the pharmacy team as notification that the refill request can be pro-

cessed at **466**. At **468**, the pharmacy technician contacts the patient to schedule shipment. The process of filling the order is continued at **470** by following the process beginning at **240**.

A process, referred to as a NORD process in one embodiment is used to determine whether donated, third party funds are available for paying for prescriptions where neither insurance will, nor the patient can pay. The process begins at **510** upon determining that a patient is uninsured or underinsured. A reimbursement specialist explains the NORD program to the patient and faxes an application request form to NORD for the patient. At **515**, the intake reimbursement specialist documents in the database that an application has been received through NORD. At **520**, NORD mails an application to the patient within one business day.

A determination is made at **525** by NORD whether the patient is approved. If not, at **530**, NORD sends a denial letter to the patient, and it is documented in the database at **540** that the patient was denied by NORD. If the patient is approved, NORD sends an acceptance letter to the patient and faxes a voucher to the central pharmacy (SDS in one embodiment) to indicate the approval at **545**. At **550**, an intake reimbursement specialist submits a coverage approval form to the pharmacy team as notification that the patient has been approved for coverage. The process of filling the order is continued at **555** by following the process beginning at **240**.

An inventory control process is illustrated in FIG. **6** beginning at **610**. Each week, a responsible person at the central pharmacy, such as the director of the pharmacy transfers inventory for the week's shipments to a segregated warehouse location for production inventory. At **620**, a purchase order is generated for the inventory transferred to the production location and is sent, such as by fax, to a controller, such as the controller of the company that obtained approval for distribution and use of the sensitive drug. At **630**, the controller invoices the central pharmacy for the product moved to production. The process ends at **640**.

The central database described above is a relational database running on the system of FIG. **1**, or a server based system having a similar architecture coupled to workstations via a network, as represented by communications **160**. The database is likely stored in storage **140**, and contains multiple fields of information as indicated at **700** in FIG. **7**. The organization and groupings of the fields are shown in one format for convenience. It is recognized that many different organizations or schemas may be utilized. In one embodiment, the groups of fields comprise prescriber fields **710**, patient fields **720**, prescription fields **730** and insurance fields **740**. For purposes of illustration, all the entries described with respect to the above processes are included in the fields. In further embodiments, no such groupings are made, and the data is organized in a different manner.

Several queries are illustrated at **800** in FIG. **8**. There may be many other queries as required by individual state reporting requirements. A first query at **810** is used to identify prescriptions written by physician. The queries may be written in structured query language, natural query languages or in any other manner compatible with the database. A second query **820** is used to pull information from the database related to prescriptions by patient name. A third query **830** is used to determine prescriptions by frequency, and a n^{th} query finds prescriptions by dose at **840**. Using query languages combined with the depth of data in the central database allows many other methods of investigating for potential abuse of the drugs. The central database ensures that all prescriptions, prescribers and patients are tracked and subject to such investigations. In further embodiments, the central database may be distributed among multiple computers provided a query operates over all data relating to such prescriptions, prescribers and patients for the drug.

An example of one prescription and enrollment form is shown at **900** in FIG. **9**. As previously indicated, several fields are included for prescriber information, prescription information and patient information.

FIG. **10** is a copy of one example NORD application request form **1000** used to request that an application be sent to a patient for financial assistance.

FIG. **11** is a copy of one example application **1100** for financial assistance as requested by form **1000**. The form requires both patient and physician information. Social security number information is also requested. The form provides information for approving the financial assistance and for tracking assistance provided.

FIG. **12** is a copy of one example voucher request for medication for use with the NORD application request form of FIG. **10**. In addition to patient and physician information, prescription information and diagnosis information is also provided.

FIGS. **13**A, **13**B and **13**C are descriptions of sample reports obtained by querying a central database having fields represented in FIG. **7**. The activities grouped by sales, regulatory, quality assurance, call center, pharmacy, inventory, reimbursement, patient care and drug information. Each report has an associated frequency or frequencies. The reports are obtained by running queries against the database, with the queries written in one of many query languages.

While the invention has been described with respect to a Schedule III drug, it is useful for other sensitive drugs that are DEA or Federally scheduled drugs in Schedule II-V, as well as still other sensitive drugs where multiple controls are desired for distribution and use.

The invention claimed is:

1. A computerized method of distributing a prescription drug under exclusive control of an exclusive central pharmacy, the method comprising:

receiving in a computer processor all prescription requests, for any and all patients being prescribed the prescription drug, only at the exclusive central pharmacy from any and all medical doctors allowed to prescribe the prescription drug, the prescription requests containing information identifying patients, the prescription drug, and various credentials of the any and all medical doctors;

requiring entering of the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations, such that all prescriptions for the prescription drug are processed only by the exclusive central pharmacy using only the exclusive computer database;

checking with the computer processor the credentials of the any and all doctors to determine the eligibility of the doctors to prescribe the prescription drug;

confirming with a patient that educational material has been received and/or read prior to shipping the prescription drug;

checking the exclusive computer database for potential abuse of the prescription drug;

mailing or sending by courier the prescription drug to the patient only if no potential abuse is found by the patient to whom the prescription drug is prescribed and the doctor prescribing the prescription drug;

confirming receipt by the patient of the prescription drug; and

generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.

2. The method of claim **1**, wherein the exclusive central pharmacy controls the exclusive computer database.

3. The method of claim **1**, comprising selectively blocking shipment of the prescription drug to a patient.

4. The method of claim **1**, wherein an abuse pattern is associated with a patient, and shipment is blocked upon such association.

5. The method of claim **1**, wherein the prescription drug comprises gamma hydroxy butyrate (GHB).

6. A computerized method of distributing a prescription drug under control of an exclusive central pharmacy, the method comprising:

receiving in a computer processor prescription requests, for any and all patients being prescribed the prescription drug, only at the central pharmacy from any and all authorized prescribers allowed to prescribed the prescription drug, the prescription requests containing information identifying patients, the prescription drug, and various credentials of the any and all authorized prescribers;

entering the information into an exclusive computer database under exclusive control of the central pharmacy for analysis of potential abuse situations, wherein the use of the exclusive computer database is required for distribution of the prescription drug, such that all prescriptions for the prescription drug are processed only by the exclusive central pharmacy using only the exclusive computer database;

checking with the computer processor the credentials of the any and all authorized prescribers to determine the eligibility of the prescribers to prescribe the prescription drug;

confirming with a patient that educational material has been received and/or read prior to providing the prescription drug to the patient;

requiring checking of the exclusive computer database for potential abuse associated with the patient and the authorized prescriber;

providing the prescription drug to the patient only provided information in the exclusive computer database is not indicative of potential abuse by the patient to whom the prescription drug is prescribed and the authorized prescriber of the prescription drug;

confirming receipt by the patient of the prescription drug; and

generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.

7. The computerized method of claim **6**, wherein providing the prescription drug to the patient comprises the central pharmacy authorizing the prescription drug to be dispensed to the patient by another pharmacy.

8. The computerized method of claim **7**, wherein the another pharmacy places controls on the distribution of the prescription drug, the controls selected from the group consisting of confirming with the patient that the educational material has been received and/or read by the patient, confirming receipt of the prescription drug by the patient, contacting the patient's insurance company, questioning early refill requests by the patient, flagging repeat instances of lost, stolen, destroyed or spilled prescriptions, flagging that the patient paid cash for the prescription drug, flagging early requests to refill the prescription drug, and limiting the prescription to a supply of limited duration.

9. A computerized method of distributing gamma hydroxy butyrate (GHB) under control of an exclusive central pharmacy, the method comprising:

receiving in a computer processor prescription requests for GHB, for any and all patients being prescribed GHB, only at the central pharmacy from any and all authorized prescribers allowed to prescribe GHB, the prescription requests for GHB containing information identifying patients and various credentials of the any and all authorized prescribers;

entering the information into an exclusive computer database under exclusive control of the central pharmacy for analysis of potential abuse situations, wherein the use of the exclusive computer database is required for distribution of GHB, such that all prescriptions for GHB are processed only by the exclusive central pharmacy using only the exclusive computer database;

checking with the computer processor the credentials of the any and all authorized prescribers to determine the eligibility of the prescribers to prescribe GHB;

confirming with the patient that GHB educational material has been received and/or read prior to providing GHB to the patient a first time;

requiring checking of the exclusive computer database for potential GHB abuse associated with the patient;

providing GHB to the patient only provided information in the exclusive computer database is not indicative of potential abuse by the patient to whom GHB is prescribed and the authorized prescriber of the GHB;

confirming receipt by the patient of the GHB; and

generating with the computer processor periodic reports via the exclusive computer database to evaluate potential GHB diversion patterns.

10. The computerized method of claim **9**, wherein providing GHB to the patient comprises the central pharmacy authorizing the prescription drug to be dispensed to the patient by another pharmacy.

11. The computerized method of claim **10**, wherein the another pharmacy places controls on the distribution of GHB, the controls selected from the group consisting of confirming with the patient that the educational material has been received and/or read by the patient, confirming receipt of GHB by the patient, contacting the patient's insurance company, questioning early refill requests by the patient, flagging repeat instances of lost, stolen, destroyed or spilled prescriptions, flagging that the patient paid cash for GHB, flagging early requests to refill the GHB, and limiting the prescription to a supply of limited duration.

12. A computerized method of distributing gamma hydroxy butyrate (GHB) under control of an exclusive central pharmacy, the method comprising:

receiving in a computer processor prescription requests for GHB, for any and all patients being prescribed GHB, only at the central pharmacy from any and all authorized prescribers allowed to prescribe GHB, the prescription requests containing information identifying patients and various credentials of the any and all authorized prescribers;

entering the information into an exclusive computer database under exclusive control of the central pharmacy for analysis of potential abuse situations, wherein the use of the exclusive computer database is required for distribution of GHB, such that all prescriptions for GHB are processed only by the exclusive central pharmacy using only the exclusive computer database;

checking with the computer processor the credentials of the any and all authorized prescribers to determine the eligibility of the prescribers to prescribe GHB;

confirming with the patient that GHB educational material has been received and/or read prior to providing GHB to the patient a first time;

requiring checking of the exclusive computer database for potential GHB abuse associated with the patient;

mailing or sending by courier GHB to the patient only provided information in the exclusive computer database is not indicative of potential abuse by the patient to whom GHB is prescribed and the authorized prescriber of the GHB;

confirming receipt by the patient of the GHB; and

generating with the computer processor periodic reports via the exclusive computer database to evaluate potential GHB diversion patterns.

13. A computerized method of distributing gamma hydroxy butyrate (GHB) under control of an exclusive central pharmacy, the method comprising:

manufacturing GHB;

providing manufactured GHB only to the exclusive central pharmacy;

receiving in a computer processor all prescription requests for GHB, for any and all patients being prescribed GHB, only at the central pharmacy from any and all authorized prescribers allowed to prescribe GHB, the prescription requests containing information identifying patients and various credentials of the any and all authorized prescribers;

entering the information into an exclusive computer database under exclusive control of the central pharmacy for analysis of potential abuse situations, wherein the use of the exclusive computer database is required for distribution of GHB, such that all prescriptions for GHB are processed only by the exclusive central pharmacy using only the exclusive computer database;

checking with the computer processor the credentials of the any and all authorized prescribers to determine the eligibility of the prescribers to prescribe GHB;

confirming with the patient that GHB educational material has been received and/or read prior to providing GHB to the patient a first time;

requiring checking of the exclusive computer database for potential GHB abuse associated with the patient;

mailing or sending by courier GHB to the patient only provided information in the exclusive computer database is not indicative of potential abuse by the patient to whom GHB is prescribed and the doctor prescribing the GHB;

confirming receipt by the patient of the GHB; and

generating with the computer processor periodic reports via the exclusive computer database to evaluate potential GHB diversion patterns.

14. A computerized method of distributing a prescription drug under control of an exclusive central pharmacy, the method comprising:

receiving in a computer processor all prescription requests, for any and all patients being prescribed the prescription drug, only at the central pharmacy from any and all authorized prescribers allowed to prescribed the prescription drug, the prescription requests containing information identifying patients, the prescription drug, and various credentials of the any and all authorized prescribers;

entering the information into an exclusive computer database under exclusive control of the central pharmacy for analysis of potential abuse situations, wherein the use of the exclusive computer database is required for distribution of the prescription drug, such that all prescriptions for the prescription drug are processed only by the exclusive central pharmacy using only the exclusive computer database;

checking with the computer processor the credentials of the any and all authorized prescribers to determine the eligibility of the prescribers to prescribe the prescription drug;

confirming with the patient that educational material has been received and/or read prior to providing the prescription drug to the patient;

requiring checking of the exclusive computer database for potential abuse by the patient to whom the prescription drug is prescribed and the authorized prescriber allowed to prescribe the prescription drug;

providing the prescription drug to the patient only provided information in the exclusive computer database is not indicative of potential abuse by the patient to whom the prescription drug is prescribed and the authorized prescriber allowed to prescribe the prescription drug; and

confirming receipt by the patient of the prescription drug.

15. The computerized method of claim **14**, wherein providing the prescription drug to the patient comprises the central pharmacy authorizing the prescription drug to be dispensed to the patient by another pharmacy.

16. The computerized method of claim **15**, wherein the another pharmacy places controls on the distribution of the prescription drug, the controls selected from the group consisting of confirming with the patient that the educational material has been received and/or read by the patient, confirming receipt of the prescription drug by the patient, contacting the patient's insurance company, questioning early refill requests by the patient, flagging repeat instances of lost, stolen, destroyed or spilled prescriptions, flagging that the patient paid cash for the prescription drug, flagging early requests to refill the prescription drug, and limiting the prescription to a supply of limited duration.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,895,059 B2
APPLICATION NO. : 12/704097
DATED : February 22, 2011
INVENTOR(S) : Dayton T. Reardan et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On page 2, under "US Patent Documents", in column 1, line 1, delete "Reardon" and insert -- Reardan --, therefor.

On Sheet 9 of 16, above Box 1, Figure 6, delete reference numeral "236" and insert -- 610 --, therefor. (Drawing sheet attached.)

On Sheet 9 of 16, above Box 2, Figure 6, delete reference numeral "236" and insert -- 620 --, therefor. (Drawing sheet attached.)

On Sheet 9 of 16, above Box 3, Figure 6, delete reference numeral "236" and insert -- 630 --, therefor. (Drawing sheet attached.)

On Sheet 9 of 16, above Box 4, Figure 6, delete reference numeral "350" and insert -- 640 --, therefor. (Drawing sheet attached.)

On Sheet 12 of 16, Figure 11, line 14, delete "XYREEM" and insert -- XYREM® --, therefor.

On Sheet 14 of 16, Figure 13A, line 26, delete "Rx/ENROLLEMENT" and insert --Rx/ENROLLMENT --, therefor.

ln column 1, line 28, delete "buterate" and insert -- butyrate --, therefor.

ln column 3, line 33, delete "Xyrem," and insert -- Xyrem®, --, therefor.

ln column 4, line 14, delete "Xyrem." and insert -- Xyrem®. --, therefor.

ln column 6, line 1, delete "Xyrem," and insert -- Xyrem®, --, therefor.

Signed and Sealed this
Thirty-first Day of May, 2011

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

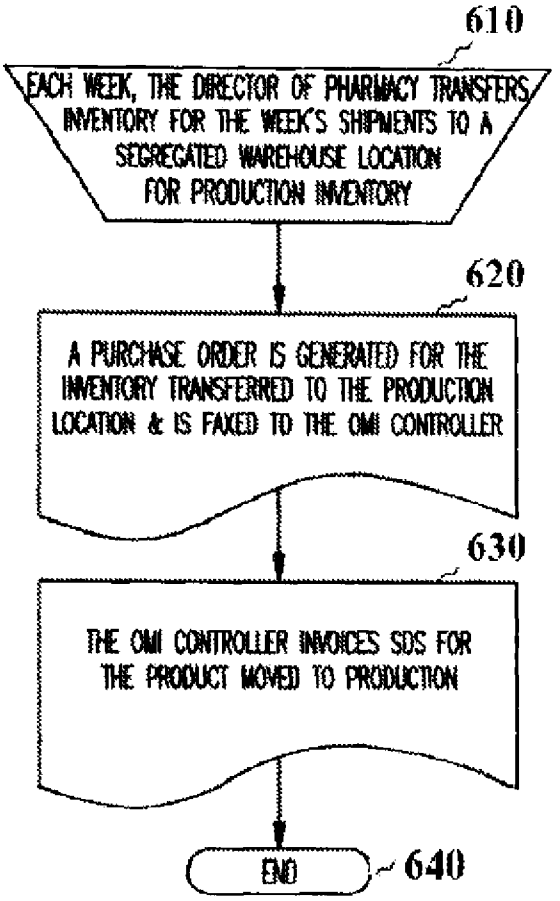

FIG. 6

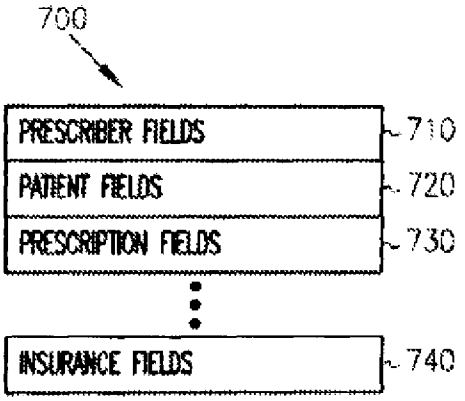

FIG. 7

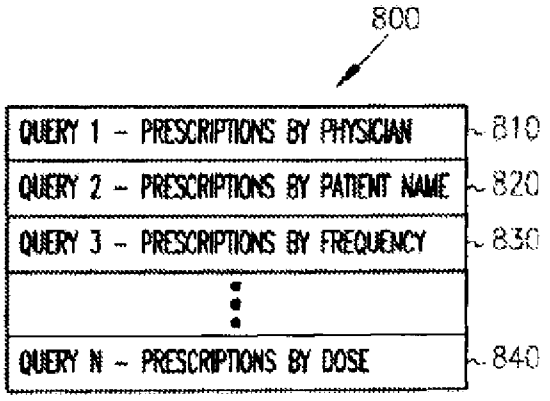

FIG. 8

EXHIBIT E

US008457988B1

(12) **United States Patent**
Reardan et al.

(10) **Patent No.: US 8,457,988 B1**
(45) **Date of Patent: *Jun. 4, 2013**

(54) **SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD**

(75) Inventors: **Dayton T. Reardan**, Shorewood, MN (US); **Patti A. Engel**, Eagan, MN (US); **Bob Gagne**, St. Paul, MN (US)

(73) Assignee: **Jazz Pharmaceuticals, Inc.**, Palo Alto, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/595,757**

(22) Filed: **Aug. 27, 2012**

Related U.S. Application Data

(60) Division of application No. 13/013,680, filed on Jan. 25, 2011, now abandoned, which is a continuation of application No. 12/704,097, filed on Feb. 11, 2010, now Pat. No. 7,895,059, which is a continuation of application No. 10/322,348, filed on Dec. 17, 2002, now Pat. No. 7,668,730.

(51) **Int. Cl.**
G06Q 10/00 (2012.01)

(52) **U.S. Cl.**
USPC **705/2**; 705/3; 600/300

(58) **Field of Classification Search**
USPC 705/2, 3; 600/300
See application file for complete search history.

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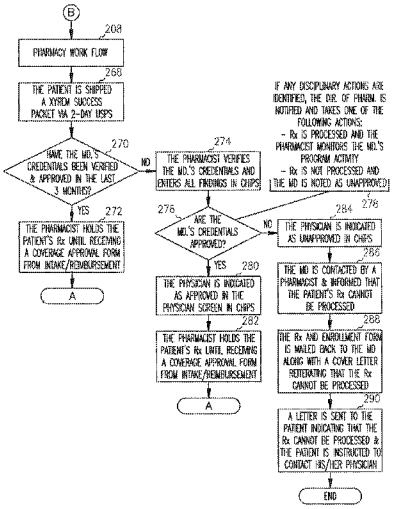
Primary Examiner — Lena Najarian
(74) *Attorney, Agent, or Firm* — Schwegman Lundberg & Woessner, P.A.

(57) **ABSTRACT**

A drug distribution system and method utilizes a central pharmacy and database to track all prescriptions for a sensitive drug. Information is kept in the database regarding all physicians allowed to prescribe the sensitive drug, and all patients receiving the drug. Abuses are identified by monitoring data in the database for prescription patterns by physicians and prescriptions obtained by patients. Further verification is made that the physician is eligible to prescribe the drug by consulting a separate database, and optionally whether any actions are taken against the physician. Multiple controls beyond those for normal drugs are imposed on the distribution depending on the sensitivity of the drug.

15 Claims, 16 Drawing Sheets



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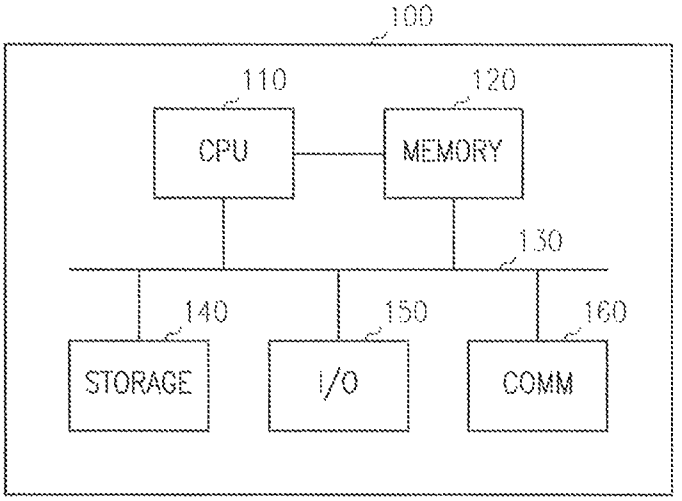

FIG. 1

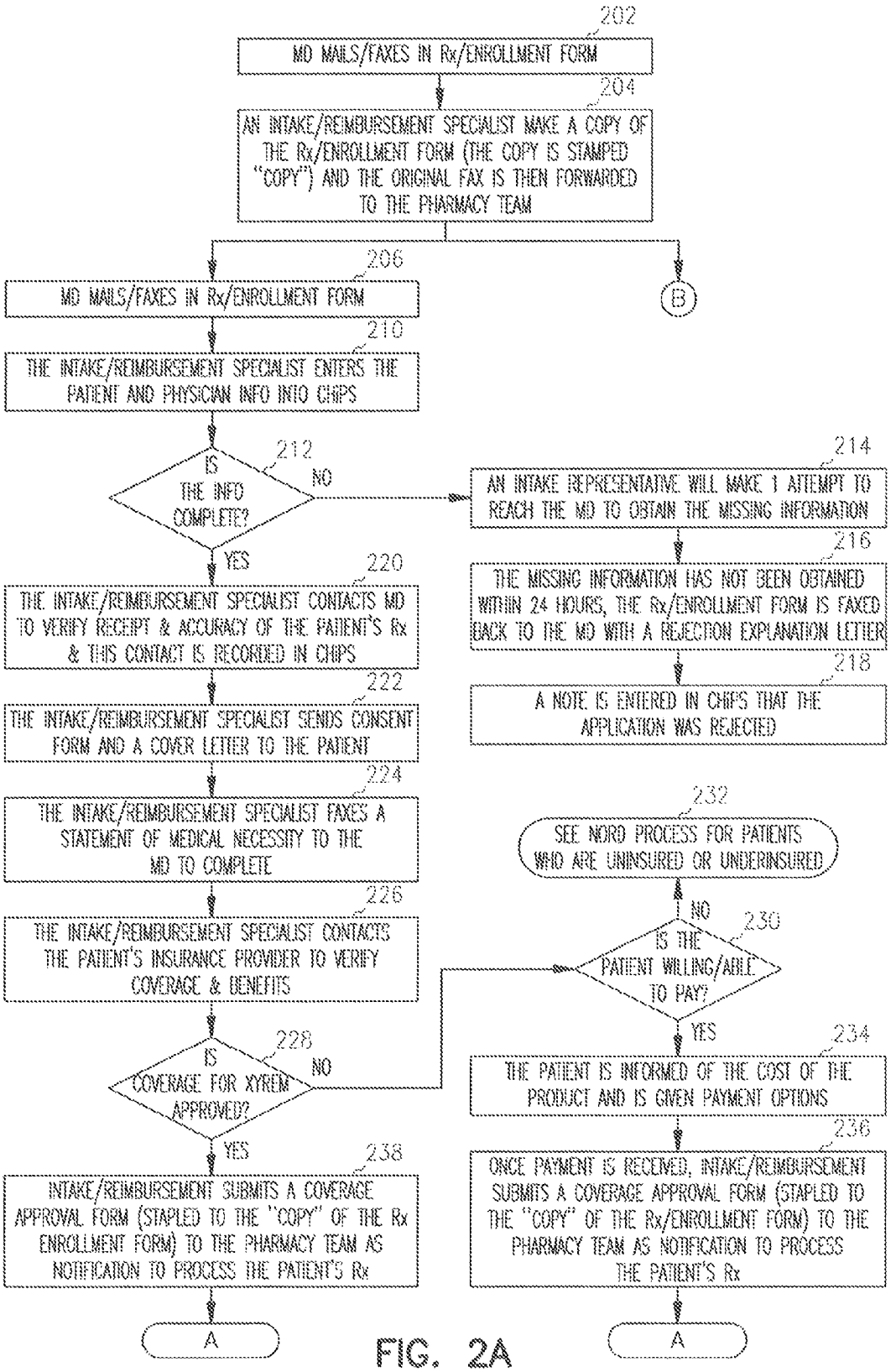
202
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
204
AN INTAKE/REIMBURSEMENT SPECIALIST MAKE A COPY OF THE Rx/ENROLLMENT FORM (THE COPY IS STAMPED "COPY") AND THE ORIGINAL FAX IS THEN FORWARDED TO THE PHARMACY TEAM
206
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
B
210
THE INTAKE/REIMBURSEMENT SPECIALIST ENTERS THE PATIENT AND PHYSICIAN INFO INTO CHIPS
212
IS THE INFO COMPLETE?
NO
YES
214
AN INTAKE REPRESENTATIVE WILL MAKE 1 ATTEMPT TO REACH THE MD TO OBTAIN THE MISSING INFORMATION
216
THE MISSING INFORMATION HAS NOT BEEN OBTAINED WITHIN 24 HOURS, THE Rx/ENROLLMENT FORM IS FAXED BACK TO THE MD WITH A REJECTION EXPLANATION LETTER
218
A NOTE IS ENTERED IN CHIPS THAT THE APPLICATION WAS REJECTED
220
THE INTAKE/REIMBURSEMENT SPECIALIST CONTACTS MD TO VERIFY RECEIPT & ACCURACY OF THE PATIENT'S Rx & THIS CONTACT IS RECORDED IN CHIPS
222
THE INTAKE/REIMBURSEMENT SPECIALIST SENDS CONSENT FORM AND A COVER LETTER TO THE PATIENT
224
THE INTAKE/REIMBURSEMENT SPECIALIST FAXES A STATEMENT OF MEDICAL NECESSITY TO THE MD TO COMPLETE
226
THE INTAKE/REIMBURSEMENT SPECIALIST CONTACTS THE PATIENT'S INSURANCE PROVIDER TO VERIFY COVERAGE & BENEFITS
228
IS COVERAGE FOR XYREM APPROVED?
NO
YES
232
SEE NORD PROCESS FOR PATIENTS WHO ARE UNINSURED OR UNDERINSURED
230
IS THE PATIENT WILLING/ABLE TO PAY?
NO
YES
234
THE PATIENT IS INFORMED OF THE COST OF THE PRODUCT AND IS GIVEN PAYMENT OPTIONS
236
ONCE PAYMENT IS RECEIVED, INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM (STAPLED TO THE "COPY" OF THE Rx/ENROLLMENT FORM) TO THE PHARMACY TEAM AS NOTIFICATION TO PROCESS THE PATIENT'S Rx
238
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM (STAPLED TO THE "COPY" OF THE Rx ENROLLMENT FORM) TO THE PHARMACY TEAM AS NOTIFICATION TO PROCESS THE PATIENT'S Rx
A
A

FIG. 2A

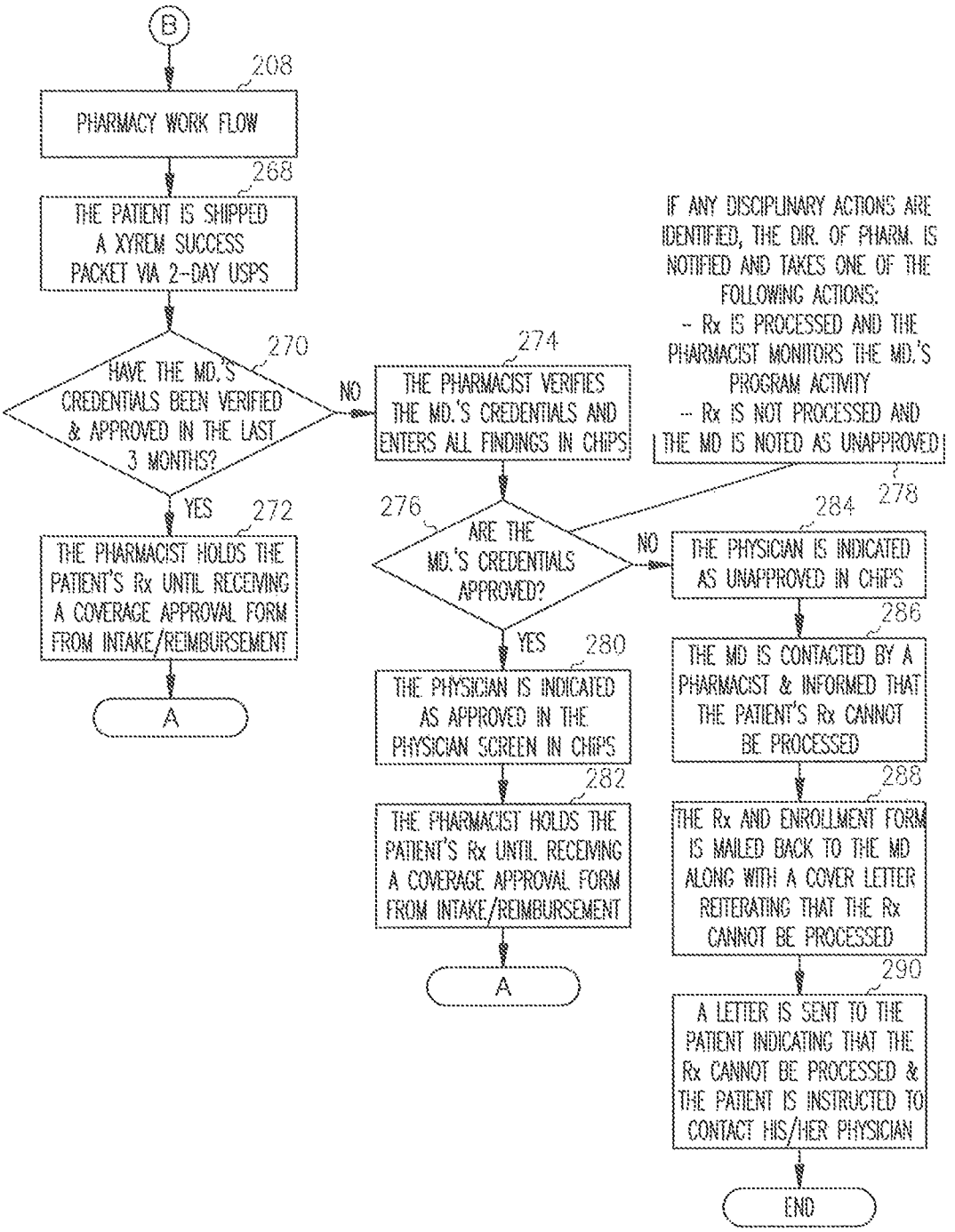
B
208
PHARMACY WORK FLOW
268
THE PATIENT IS SHIPPED A XYREM SUCCESS PACKET VIA 2-DAY USPS
270
HAVE THE MD.'S CREDENTIALS BEEN VERIFIED & APPROVED IN THE LAST 3 MONTHS?
NO
274
THE PHARMACIST VERIFIES THE MD.'S CREDENTIALS AND ENTERS ALL FINDINGS IN CHIPS
IF ANY DISCIPLINARY ACTIONS ARE IDENTIFIED, THE DIR. OF PHARM. IS NOTIFIED AND TAKES ONE OF THE FOLLOWING ACTIONS:
- Rx IS PROCESSED AND THE PHARMACIST MONITORS THE MD.'S PROGRAM ACTIVITY
-- Rx IS NOT PROCESSED AND THE MD IS NOTED AS UNAPPROVED
278
YES
272
THE PHARMACIST HOLDS THE PATIENT'S Rx UNTIL RECEIVING A COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT
A
276
ARE THE MD.'S CREDENTIALS APPROVED?
NO
284
THE PHYSICIAN IS INDICATED AS UNAPPROVED IN CHIPS
286
THE MD IS CONTACTED BY A PHARMACIST & INFORMED THAT THE PATIENT'S Rx CANNOT BE PROCESSED
YES
280
THE PHYSICIAN IS INDICATED AS APPROVED IN THE PHYSICIAN SCREEN IN CHIPS
282
THE PHARMACIST HOLDS THE PATIENT'S Rx UNTIL RECEIVING A COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT
A
288
THE Rx AND ENROLLMENT FORM IS MAILED BACK TO THE MD ALONG WITH A COVER LETTER REITERATING THAT THE Rx CANNOT BE PROCESSED
290
A LETTER IS SENT TO THE PATIENT INDICATING THAT THE Rx CANNOT BE PROCESSED & THE PATIENT IS INSTRUCTED TO CONTACT HIS/HER PHYSICIAN
END

FIG. 2B

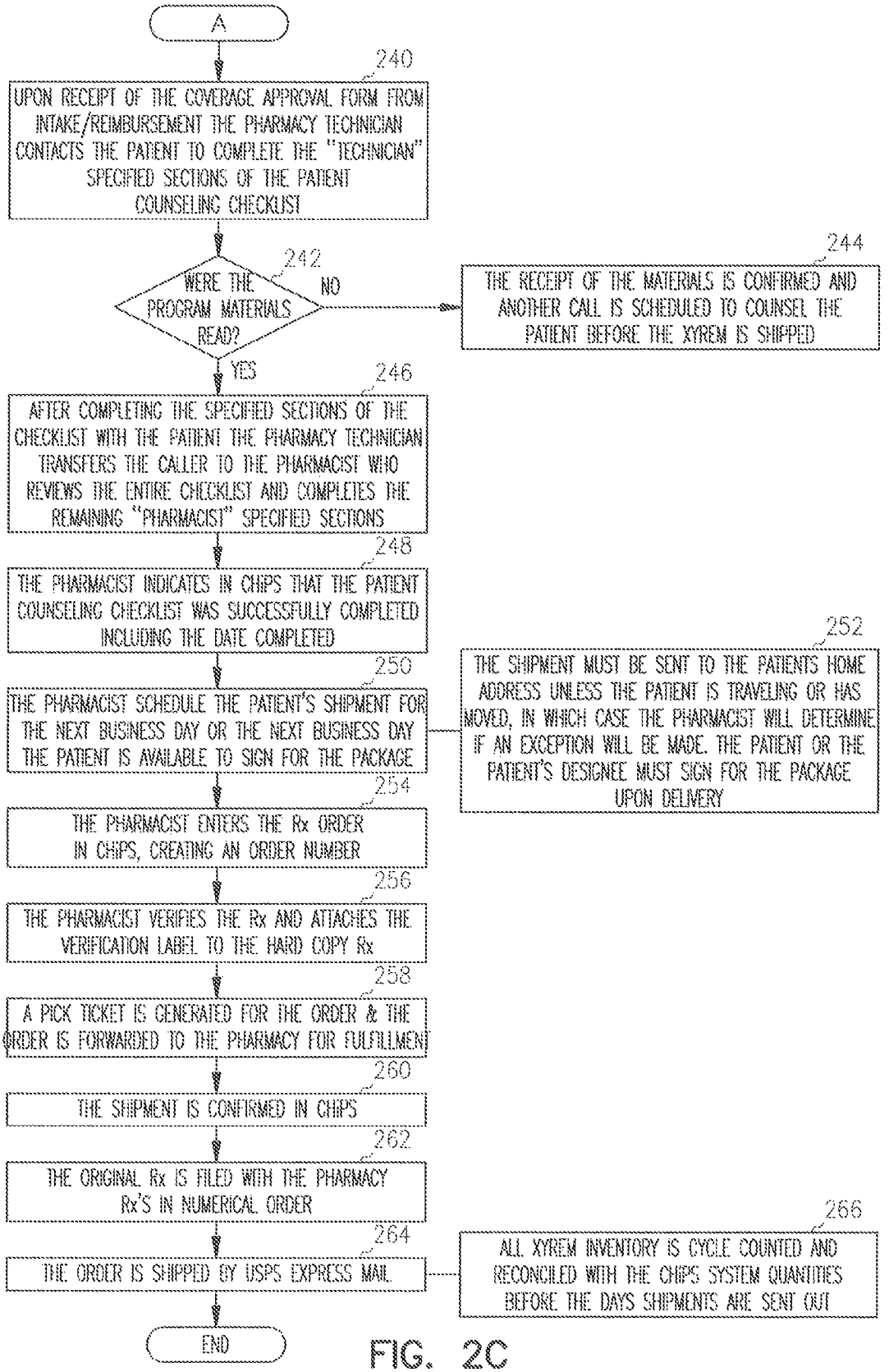
A
240
UPON RECEIPT OF THE COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE THE "TECHNICIAN" SPECIFIED SECTIONS OF THE PATIENT COUNSELING CHECKLIST
242
WERE THE PROGRAM MATERIALS READ?
NO
244
THE RECEIPT OF THE MATERIALS IS CONFIRMED AND ANOTHER CALL IS SCHEDULED TO COUNSEL THE PATIENT BEFORE THE XYREM IS SHIPPED
YES
246
AFTER COMPLETING THE SPECIFIED SECTIONS OF THE CHECKLIST WITH THE PATIENT THE PHARMACY TECHNICIAN TRANSFERS THE CALLER TO THE PHARMACIST WHO REVIEWS THE ENTIRE CHECKLIST AND COMPLETES THE REMAINING "PHARMACIST" SPECIFIED SECTIONS
248
THE PHARMACIST INDICATES IN CHIPS THAT THE PATIENT COUNSELING CHECKLIST WAS SUCCESSFULLY COMPLETED INCLUDING THE DATE COMPLETED
252
THE SHIPMENT MUST BE SENT TO THE PATIENTS HOME ADDRESS UNLESS THE PATIENT IS TRAVELING OR HAS MOVED, IN WHICH CASE THE PHARMACIST WILL DETERMINE IF AN EXCEPTION WILL BE MADE. THE PATIENT OR THE PATIENT'S DESIGNEE MUST SIGN FOR THE PACKAGE UPON DELIVERY
250
THE PHARMACIST SCHEDULE THE PATIENT'S SHIPMENT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
254
THE PHARMACIST ENTERS THE Rx ORDER IN CHIPS, CREATING AN ORDER NUMBER
256
THE PHARMACIST VERIFIES THE Rx AND ATTACHES THE VERIFICATION LABEL TO THE HARD COPY Rx
258
A PICK TICKET IS GENERATED FOR THE ORDER & THE ORDER IS FORWARDED TO THE PHARMACY FOR FULFILLMENT
260
THE SHIPMENT IS CONFIRMED IN CHIPS
262
THE ORIGINAL Rx IS FILED WITH THE PHARMACY Rx'S IN NUMERICAL ORDER
266
ALL XYREM INVENTORY IS CYCLE COUNTED AND RECONCILED WITH THE CHIPS SYSTEM QUANTITIES BEFORE THE DAYS SHIPMENTS ARE SENT OUT
264
THE ORDER IS SHIPPED BY USPS EXPRESS MAIL
END

FIG. 2C

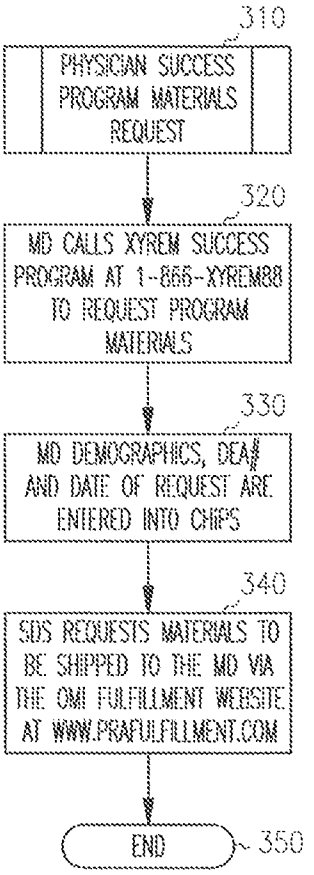
310
PHYSICIAN SUCCESS PROGRAM MATERIALS REQUEST
320
MD CALLS XYREM SUCCESS PROGRAM AT 1-866-XYREM88 TO REQUEST PROGRAM MATERIALS
330
MD DEMOGRAPHICS, DEA# AND DATE OF REQUEST ARE ENTERED INTO CHP'S
340
SDS REQUESTS MATERIALS TO BE SHIPPED TO THE MD VIA THE OMI FULFILLMENT WEBSITE AT WWW.PRAFULFILLMENT.COM
END
350

FIG. 3

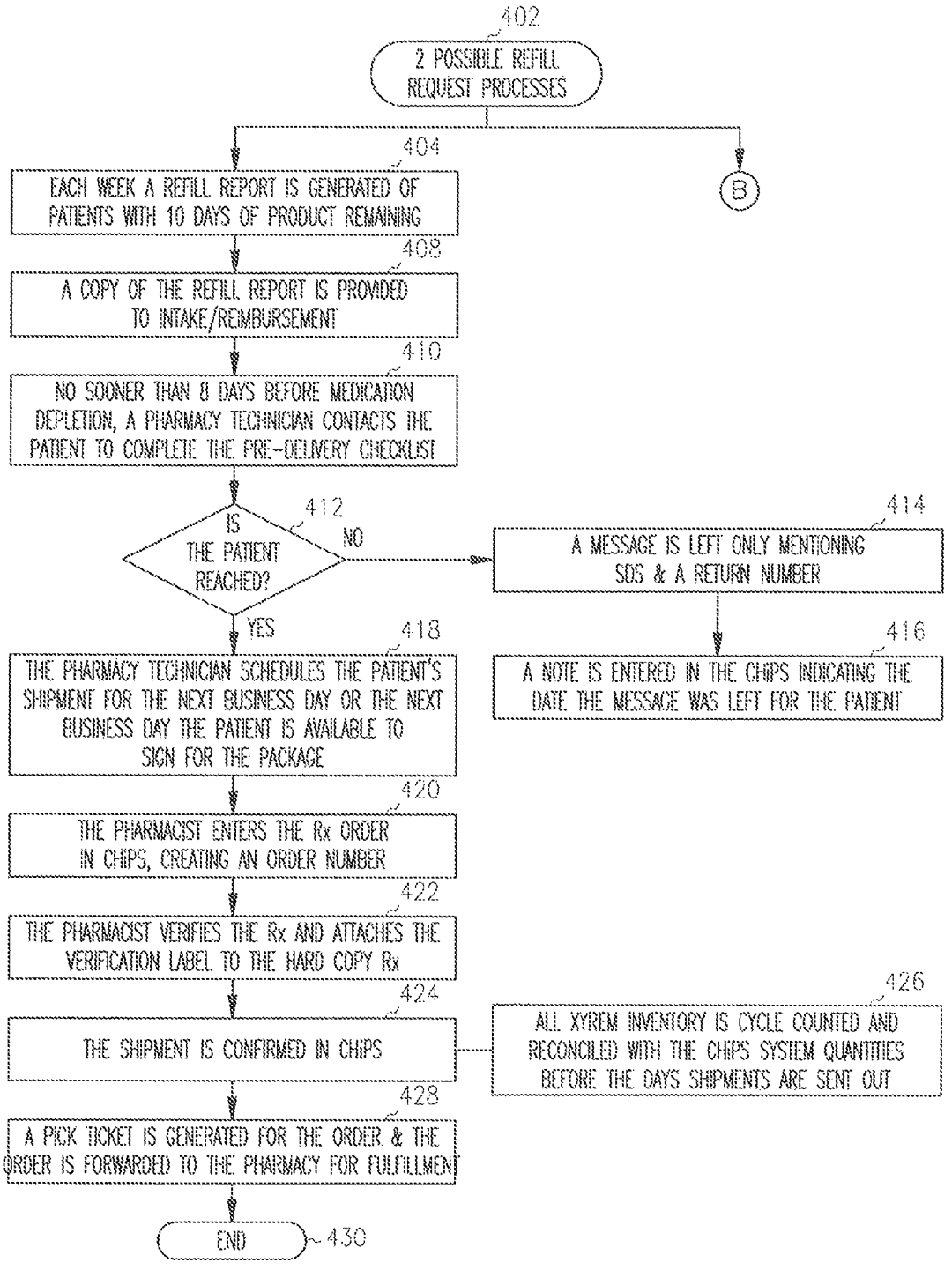
402
2 POSSIBLE REFILL REQUEST PROCESSES
404
EACH WEEK A REFILL REPORT IS GENERATED OF PATIENTS WITH 10 DAYS OF PRODUCT REMAINING
B
408
A COPY OF THE REFILL REPORT IS PROVIDED TO INTAKE/REIMBURSEMENT
410
NO SOONER THAN 8 DAYS BEFORE MEDICATION DEPLETION, A PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE THE PRE-DELIVERY CHECKLIST
412
IS THE PATIENT REACHED?
NO
414
A MESSAGE IS LEFT ONLY MENTIONING SOS & A RETURN NUMBER
YES
418
THE PHARMACY TECHNICIAN SCHEDULES THE PATIENT'S SHIPMENT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
416
A NOTE IS ENTERED IN THE CHIPS INDICATING THE DATE THE MESSAGE WAS LEFT FOR THE PATIENT
420
THE PHARMACIST ENTERS THE Rx ORDER IN CHIPS, CREATING AN ORDER NUMBER
422
THE PHARMACIST VERIFIES THE Rx AND ATTACHES THE VERIFICATION LABEL TO THE HARD COPY Rx
424
THE SHIPMENT IS CONFIRMED IN CHIPS
426
ALL XYREM INVENTORY IS CYCLE COUNTED AND RECONCILED WITH THE CHIPS SYSTEM QUANTITIES BEFORE THE DAYS SHIPMENTS ARE SENT OUT
428
A PICK TICKET IS GENERATED FOR THE ORDER & THE ORDER IS FORWARDED TO THE PHARMACY FOR FULFILLMENT
END
430

FIG. 4A

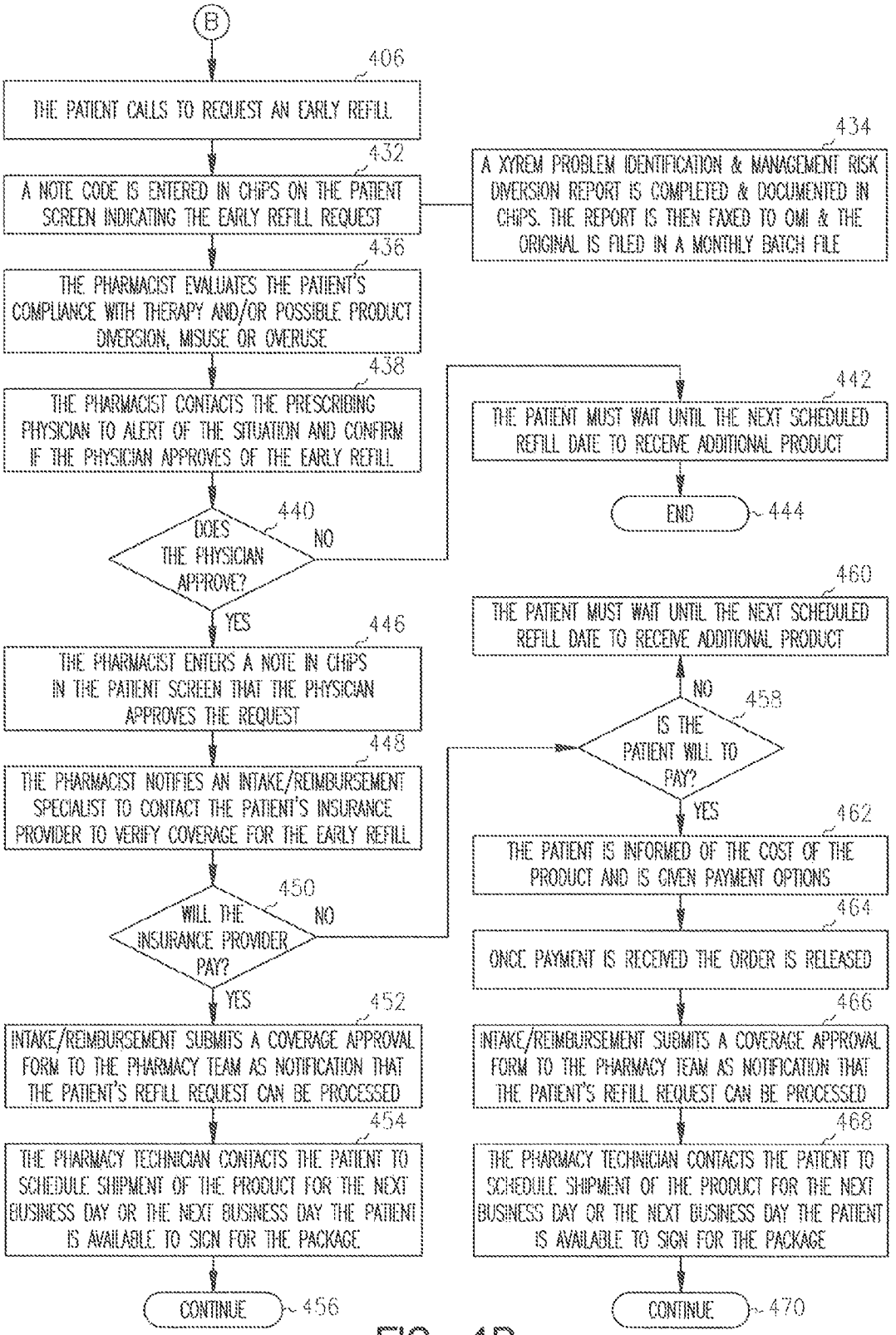
B
406
THE PATIENT CALLS TO REQUEST AN EARLY REFILL
432
A NOTE CODE IS ENTERED IN CHIPS ON THE PATIENT SCREEN INDICATING THE EARLY REFILL REQUEST
434
A XYREM PROBLEM IDENTIFICATION & MANAGEMENT RISK DIVERSION REPORT IS COMPLETED & DOCUMENTED IN CHIPS. THE REPORT IS THEN FAXED TO OMI & THE ORIGINAL IS FILED IN A MONTHLY BATCH FILE
436
THE PHARMACIST EVALUATES THE PATIENT'S COMPLIANCE WITH THERAPY AND/OR POSSIBLE PRODUCT DIVERSION, MISUSE OR OVERUSE
438
THE PHARMACIST CONTACTS THE PRESCRIBING PHYSICIAN TO ALERT OF THE SITUATION AND CONFIRM IF THE PHYSICIAN APPROVES OF THE EARLY REFILL
440
DOES THE PHYSICIAN APPROVE?
NO
442
THE PATIENT MUST WAIT UNTIL THE NEXT SCHEDULED REFILL DATE TO RECEIVE ADDITIONAL PRODUCT
END
444
YES
446
THE PHARMACIST ENTERS A NOTE IN CHIPS IN THE PATIENT SCREEN THAT THE PHYSICIAN APPROVES THE REQUEST
448
THE PHARMACIST NOTIFIES AN INTAKE/REIMBURSEMENT SPECIALIST TO CONTACT THE PATIENT'S INSURANCE PROVIDER TO VERIFY COVERAGE FOR THE EARLY REFILL
450
WILL THE INSURANCE PROVIDER PAY?
NO
YES
452
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT'S REFILL REQUEST CAN BE PROCESSED
454
THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO SCHEDULE SHIPMENT OF THE PRODUCT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
CONTINUE
456
460
THE PATIENT MUST WAIT UNTIL THE NEXT SCHEDULED REFILL DATE TO RECEIVE ADDITIONAL PRODUCT
NO
458
IS THE PATIENT WILL TO PAY?
YES
462
THE PATIENT IS INFORMED OF THE COST OF THE PRODUCT AND IS GIVEN PAYMENT OPTIONS
464
ONCE PAYMENT IS RECEIVED THE ORDER IS RELEASED
466
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT'S REFILL REQUEST CAN BE PROCESSED
468
THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO SCHEDULE SHIPMENT OF THE PRODUCT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
CONTINUE
470

FIG. 4B

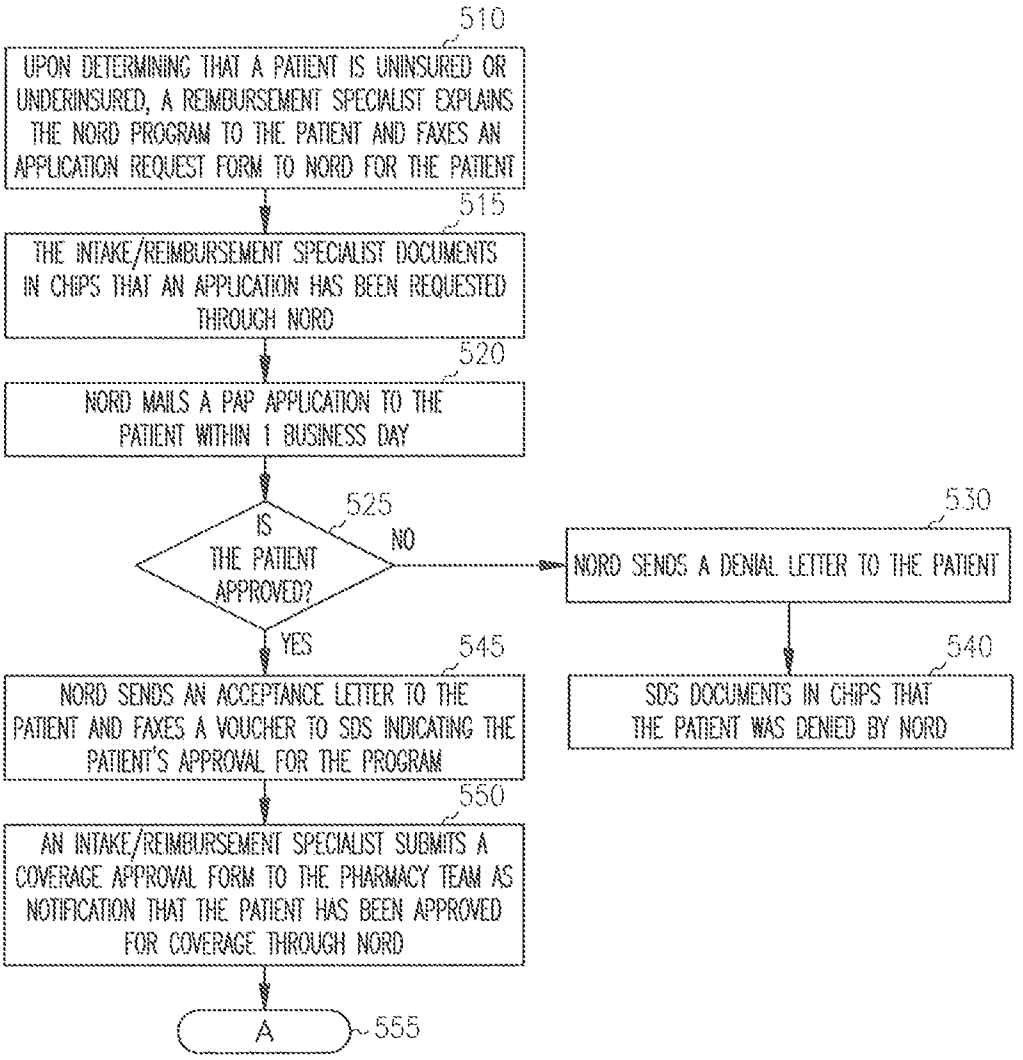
510
UPON DETERMINING THAT A PATIENT IS UNINSURED OR UNDERINSURED, A REIMBURSEMENT SPECIALIST EXPLAINS THE NORD PROGRAM TO THE PATIENT AND FAXES AN APPLICATION REQUEST FORM TO NORD FOR THE PATIENT
515
THE INTAKE/REIMBURSEMENT SPECIALIST DOCUMENTS IN CHIPS THAT AN APPLICATION HAS BEEN REQUESTED THROUGH NORD
520
NORD MAILS A PAP APPLICATION TO THE PATIENT WITHIN 1 BUSINESS DAY
525
IS THE PATIENT APPROVED?
NO
530
NORD SENDS A DENIAL LETTER TO THE PATIENT
YES
545
NORD SENDS AN ACCEPTANCE LETTER TO THE PATIENT AND FAXES A VOUCHER TO SDS INDICATING THE PATIENT'S APPROVAL FOR THE PROGRAM
540
SDS DOCUMENTS IN CHIPS THAT THE PATIENT WAS DENIED BY NORD
550
AN INTAKE/REIMBURSEMENT SPECIALIST SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT HAS BEEN APPROVED FOR COVERAGE THROUGH NORD
A
555

FIG. 5

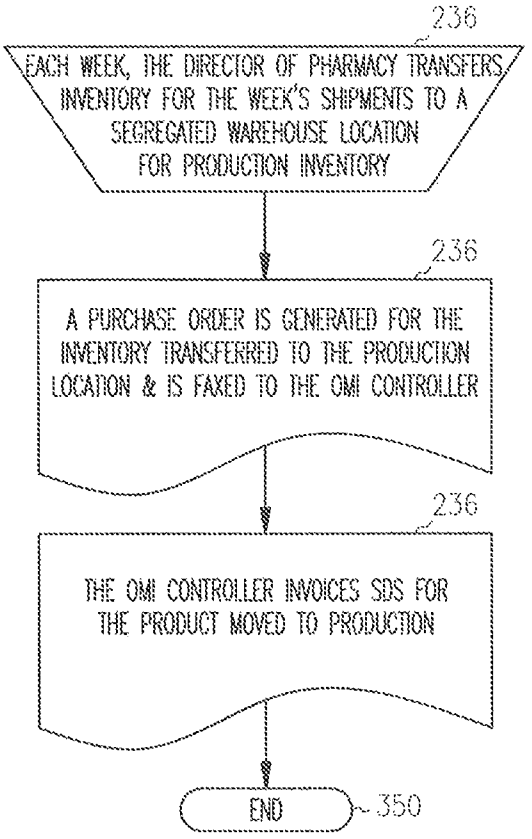

FIG. 6

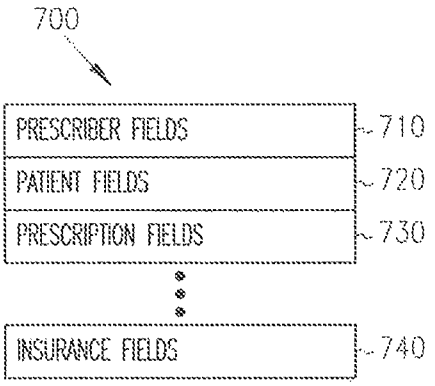

FIG. 7

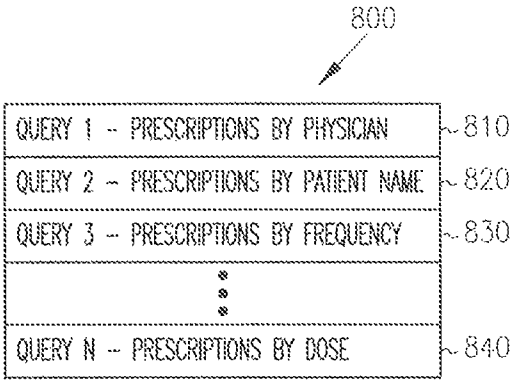

FIG. 8

900

PRESCRIPTION AND ENROLLMENT FORM

PRESCRIBER INFORMATION

PRESCRIBER'S NAME: ..... OFFICE CONTACT: .....
STREET ADDRESS: .....
CITY: ..... STATE: ..... ZIP: .....
PHONE: ..... FAX: .....
LICENSE NUMBER: ..... DEA NUMBER: .....
MD SPECIALTY: .....

PRESCRIPTION FORM

PATIENT NAME: ..... SS#: ..... DOB: ..... SEX M / F
ADDRESS: .....
CITY: ..... STATE: ..... ZIP: .....
Rx: XYREM ORAL SOLUTION (500 mg/mL) 180 ML BOTTLE QUANTITY: ..... MONTHS SUPPLY
SIG: TAKE ..... GMS P.O. DILUTED IN 60 mL WATER AT H.S. AND THEN AGAIN 2 1/2 TO 4 HOURS LATER
REFILLS (CIRCLE ONE): 0 1 2 (MAXIMUM OF 3 MONTH SUPPLY)
..... DATE: ...../...../.....
PRESCRIBER'S SIGNATURE

PHYSICIAN DECLARATION–PLEASE CHECK EACH BOX | TO BE COMPLETED AT INITIAL PRESCRIPTION ONLY

☐ I HAVE READ THE MATERIALS IN THE XYREM PHYSICIAN SUCCESS PROGRAM
☐ I VERIFY THAT THE PATIENT HAS BEEN EDUCATED WITH RESPECT TO XYREM PREPARATION, DOSING AND SCHEDULING.
☐ I UNDERSTAND THAT XYREM IS APPROVED FOR THE TREATMENT OF CATAPLEXY IN PATIENTS WITH NARCOLEPSY, AND THAT SAFETY OR EFFICACY HAS NOT BEEN ESTABLISHED FOR ANY OTHER INDICATION.
☐ I UNDERSTAND THAT THE SAFETY OF DOSES GREATER THAN 9gm/DAY HAS NOT BEEN ESTABLISHED

PATIENT INFORMATION

BEST TIME TO CONTACT PATIENT: ☐ DAY ☐ NIGHT
DAY #: ..... EVENING #: .....
INSURANCE COMPANY NAME: ..... PHONE #: .....
INSURED'S NAME: ..... RELATIONSHIP TO PATIENT: .....
IDENTIFICATION NUMBER: ..... POLICY/GROUP NUMBER: .....
PRESCRIPTION CARD: ☐ NO ☐ YES IF YES, CARRIER: ..... POLICY #: ..... GROUP: .....

PLEASE ATTACH COPIES OF PATIENT'S INSURANCE CARDS

FAX COMPLETED FORM TO XYREM SUCCESS PROGRAM (TOLL-FREE) 1-866-470-1744
FOR INFORMATION, CALL THE XYREM TEAM (TOLL FREE) AT 1-866-XYREM88 (1-866-997-3688)

FIG. 9


1000
PATIENT ASSISTANCE APPLICATION REQUEST FORM
DATE:
TO: PATIENT ASSISTANCE ORGANIZATION
FROM: SDS
FAX #: 203-798-2291
PLEASE SEND A XYREM PATIENT ASSISTANCE PROGRAM APPLICATION TO:
PATIENT NAME
ADDRESS
TELEPHONE: ( )
PATIENT DOSAGE: (GRAMS) TWICE NIGHTLY FOR A TOTAL DOSAGE OF (GRAMS)
BOTTLES (THREE MONTHS SUPPLY)
BACKGROUND INFORMATION:

FIG. 10

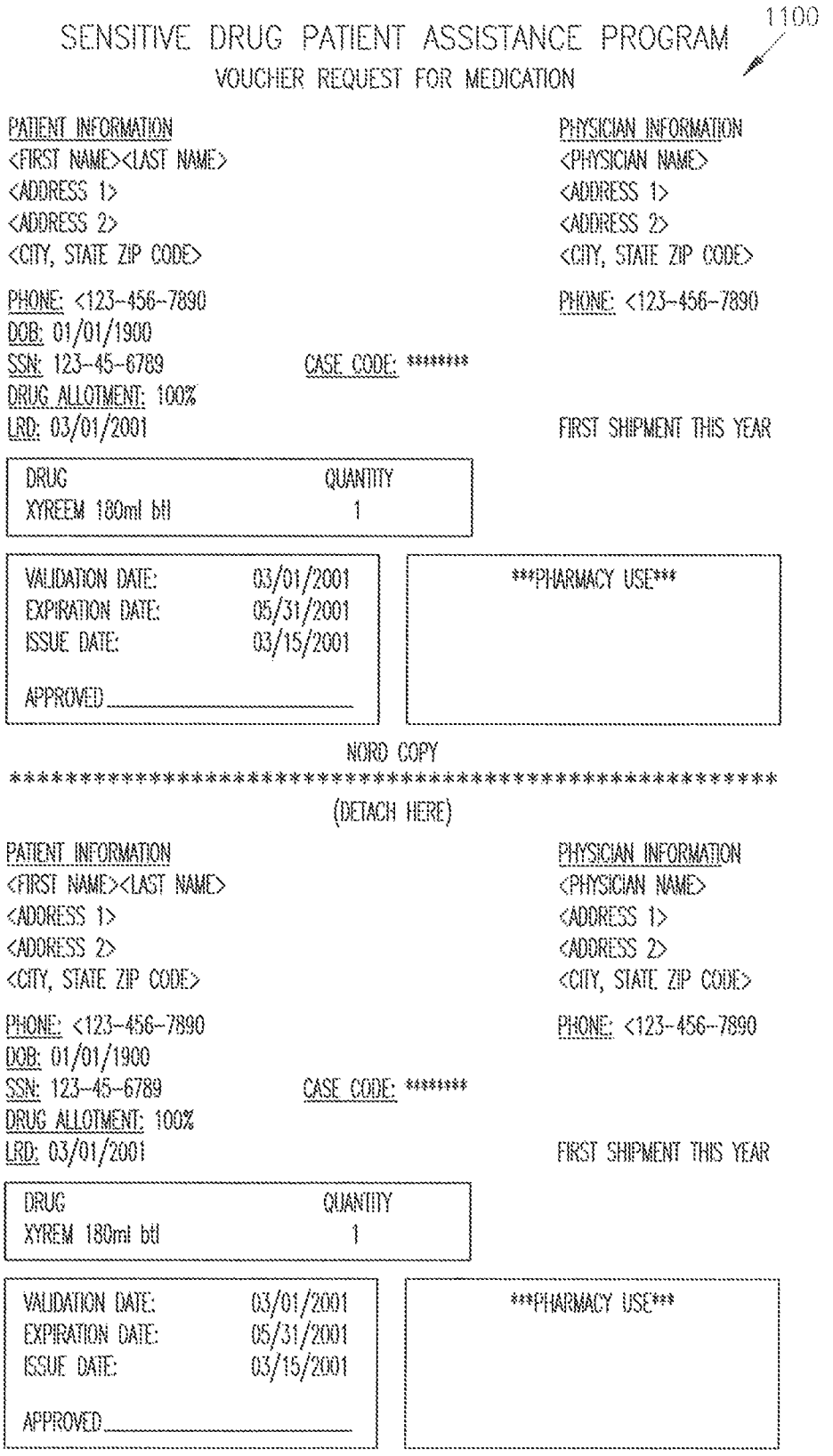
1100
SENSITIVE DRUG PATIENT ASSISTANCE PROGRAM
VOUCHER REQUEST FOR MEDICATION
PATIENT INFORMATION
<FIRST NAME><LAST NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>
PHONE: <123-456-7890
DOB: 01/01/1900
SSN: 123-45-6789
CASE CODE: ********
DRUG ALLOTMENT: 100%
LRD: 03/01/2001
PHYSICIAN INFORMATION
<PHYSICIAN NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>
PHONE: <123-456-7890
FIRST SHIPMENT THIS YEAR
DRUG
QUANTITY
XYREEM 180ml bll
1
VALIDATION DATE: 03/01/2001
EXPIRATION DATE: 05/31/2001
ISSUE DATE: 03/15/2001
APPROVED
PHARMACY USE
NORD COPY
(DETACH HERE)
PATIENT INFORMATION
<FIRST NAME><LAST NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>
PHONE: <123-456-7890
DOB: 01/01/1900
SSN: 123-45-6789
CASE CODE: ********
DRUG ALLOTMENT: 100%
LRD: 03/01/2001
PHYSICIAN INFORMATION
<PHYSICIAN NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>
PHONE: <123-456-7890
FIRST SHIPMENT THIS YEAR
DRUG
QUANTITY
XYREM 180ml bll
1
VALIDATION DATE: 03/01/2001
EXPIRATION DATE: 05/31/2001
ISSUE DATE: 03/15/2001
APPROVED
PHARMACY USE

FIG. 11

SENSITIVE DRUG PHYSICIAN'S CERTIFICATE
OF MEDICAL NEED

PATIENT INFORMATION

DATE: .....

NAME: .....
LAST FIRST M

DATE OF BIRTH: .....

DRUG BEING PRESCRIBED: XYREM

DIAGNOSIS/CONDITION FOR WHICH DRUG IS BEING PRESCRIBED: .....

ICD-9: .....

PHYSICIAN INFORMATION

PHYSICIAN'S NAME (PLEASE PRINT): .....

PHYSICIAN'S SIGNATURE: ..... DATE: .....

PLEASE FAX BACK TO SENSITIVE DRUG SUCCESS PROGRAM: (1-800-TOLL FREE NUMBER)

FIG. 12

ACTIVITY REPORTS

	REPORT FREQUENCY		
	WEEKLY	MONTHLY	QUARTERLY
SALES			
Rx BY ZIP (NEW AND TOTAL)	X	X	X
Rx BY PHYSICIAN BY ZIP	X	X	
$ BY ZIP	X	X	X
REGULATORY			
# OF PHYSICIAN REGISTRIES		X	
# OF DENIED PHYSICIAN REGISTRIES AND REASON		X	
# OF COMPLETED PATIENT REGISTRIES		X	
# OF PROBLEM IDENTIFICATION & MANAGEMENT RISK DIVERSION REPORTS COMPLETED	X		
# OF CYCLE COUNTS PERFORMED & ACCURACY OF EACH		X	
QUALITY ASSURANCE			
# OF PRODUCT DEFECTS/COMPLAINTS REPORTED, TYPE AND LOT #		X	
CALL CENTER			
# OF CALLS RECEIVED		X	
# OF CALLS INITIATED		X	
# OF CALLS ANSWERED IN 30 SECONDS, ETC.		X	
PERCENTAGE OF CALLS ANSWERED IN 30 SECONDS		X	
# OF ABANDONED CALLS		X	
% OF ABANDONED CALLS		X	
AVERAGE CALL LENGTH		X	
PHARMACY			
# OF FAXED Rx/ENROLLMENT FORMS		X	
# OF MAILED Rx/ENROLLMENT FORMS		X	
# OF Rx'S SHIPPED WITH 1, 2, 3, 4 ETC. DAYS (FROM THE TIME INITIAL RECEIPT TO SHIPMENT OF Rx)		X	
# OF PATIENT SUCCESS PACKETS SHIPPED		X	

FIG. 13A

ACTIVITY REPORTS

PHARMACY		X	
# OF PHYSICIAN SUCCESS PACKETS SHIPPED		X	
# OF COMPLETED SHIPMENTS		X	
# OF INCOMPLETE SHIPMENTS AND REASON		X	
# OF SHIPPING ERRORS		X	
# OF PAP SHIPMENTS		X	
# OF PAP APPLICATIONS		X	
# OF PAP APPROVALS		X	
# OF CANCELED ORDERS		X	
# OF USPS ERRORS		X	
INVENTORY		X	
# OF RETURNED PRODUCTS AND REASON		X	
# OF OUTDATED BOTTLES OF PRODUCT		X	
INVENTORY COUNTS OF CONSIGNMENT & PRODUCTION INVENTORY		X	
# OF UNITS RECEIVED		X	
LOTS RECEIVED		X	
REIMBURSEMENT		X	
# OF PENDED AND WHY		X	
# OF APPROVALS		X	
# OF DENIALS		X	
# OF REJECTIONS		X	
PAYOR TYPES		X	

FIG. 13B

ACTIVITY REPORTS

PATIENT CARE			
# OF ADVERSE EVENTS REPORTED AND TYPE		X	
# OF ADVERSE EVENTS SENT TO OMI		X	
# OF DOSING PROBLEMS AND TYPE		X	
# OF NONCOMPLIANCE EPISODES AND REASON		X	
# OF PATIENT COUNSELED AND REASON		X	
# OF PATIENTS DISCONTINUED AND REASON		X	
PATIENT CARE		X	
# OF PATIENTS REFERRED TO PHYSICIAN AND REASON		X	
# OF ACTIVE PATIENTS		X	
# OF NEW PATIENTS		X	
# OF RESTART PATIENTS		X	
# OF DISCONTINUED PATIENTS AND REASON		X	
DRUG INFORMATION		X	
# OF DRUG INFORMATION REQUESTS AND TYPE		X	
# OF CALLS TRIAGED TO OMI		X	

FIG. 13C

SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

RELATED APPLICATION

This application is a Division of U.S. application Ser. No. 13/013,680, filed on Jan. 25, 2011, which is a Continuation of U.S. application Ser. No. 12/704,097, filed on Feb. 11, 2010 and issued on Feb. 22, 2011 as U.S. Pat. No. 7,895,059, which is a Continuation of U.S. application Ser. No. 10/322,348, filed on Dec. 17, 2002 and issued on Feb. 23, 2010 as U.S. Pat. No. 7,668,730, which applications are incorporated by reference herein in their entirety.

FIELD OF THE INVENTION

The present invention relates to distribution of drugs, and in particular to the distribution of sensitive drugs.

BACKGROUND OF THE INVENTION

Sensitive drugs are controlled to minimize risk and ensure that they are not abused, or cause adverse reactions. Such sensitive drugs are approved for specific uses by the Food and Drug Administration, and must be prescribed by a licensed physician in order to be purchased by consumers. Some drugs, such as cocaine and other common street drugs are the object of abuse and illegal schemes to distribute for profit. Some schemes include Dr. shopping, diversion, and pharmacy thefts. A locked cabinet or safe is a requirement for distribution of some drugs.

Certain agents, such as gamma hydroxy buterate (GHB) are also abused, yet also are effective for therapeutic purposes such as treatment of daytime cataplexy in patients with narcolepsy. Some patients however, will obtain prescriptions from multiple doctors, and have them filled at different pharmacies. Still further, an unscrupulous physician may actually write multiple prescriptions for a patient, or multiple patients, who use cash to pay for the drugs. These patients will then sell the drug to dealers or others for profit.

There is a need for a distribution system and method that directly addresses these abuses. There is a further need for such a system and method that provides education and limits the potential for such abuse.

SUMMARY OF THE INVENTION

A drug distribution system and method utilizes a central pharmacy and database to track all prescriptions for a sensitive drug. Information is kept in a central database regarding all physicians allowed to prescribe the sensitive drug, and all patients receiving the drug. Abuses are identified by monitoring data in the database for prescription patterns by physicians and prescriptions obtained by patients. Further verification is made that the physician is eligible to prescribe the drug by consulting a separate database for a valid DEA license, and optionally state medical boards to determine whether any corrective or approved disciplinary actions relating to controlled substances have been brought against the physician. Multiple controls beyond those for traditional drugs are imposed on the distribution depending on the sensitivity of the drug.

Education is provided to both physician and patient. Prior to shipping the drug for the first time, the patient is contacted to ensure that product and abuse related educational materials have been received and/or read. The patient may provide the name of a designee to the central pharmacy who is authorized

to accept shipment of the drug. Receipt of the initial drug shipment is confirmed by contacting the patient. Either a phone call or other communication to the patient within a set time after delivery may be made to ensure receipt. Further, a courier service's tracking system is used to confirm delivery in further embodiments. If a shipment is lost, an investigation is launched to find it.

In one embodiment, the drug may be shipped by the central pharmacy to another pharmacy for patient pick-up. The second pharmacy's ability to protect against diversion before shipping the drug must be confirmed. This ability may be checked through NTIS and State Boards of Pharmacy.

Prescription refills are permitted in the number specified in the original prescription. In addition, if a prescription refill is requested by the patient prior to the anticipated due date, such refills will be questioned. A lost, stolen, destroyed or spilled prescription/supply is documented and replaced to the extent necessary to honor the prescription, and will also cause a review or full investigation.

The exclusive central database contains all relevant data related to distribution of the drug and process of distributing it, including patient, physician and prescription information. Several queries and reports are run against the database to provide information which might reveal potential abuse of the sensitive drug, such as early refills.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a block diagram of a computer system for use in implementing the system and method of the present invention.

FIGS. **2**A, **2**B and **2**C are a flowchart describing a method for sensitive drug distribution at least partially utilizing a computer system such as that shown in FIG. **1**.

FIG. **3** is a flowchart of a physician success program at least partially implemented on a computer system such as that shown in FIG. **1**.

FIGS. **4**A and **4**B are a flowchart describing a method for handling refill requests at least partially utilizing a computer system such as that shown in FIG. **1**.

FIG. **5** is a flowchart of a process for requesting special reimbursement when a patient is uninsured or underinsured at least partially utilizing a computer system as that shown in FIG. **1**.

FIG. **6** is a flowchart of a process for inventory control at least partially utilizing a computer system such as that shown in FIG. **1**.

FIG. **7** is a block diagram of database fields.

FIG. **8** is a block diagram showing a list of queries against the database fields.

FIG. **9** is a copy of one example prescription and enrollment form.

FIG. **10** is a copy of one example of a NORD application request form for patient financial assistance.

FIG. **11** is a copy of one example voucher request for medication for use with the NORD application request form of FIG. **10**.

FIG. **12** is a copy of certificate of medical need.

FIGS. **13**A, **13**B and **13**C are descriptions of sample reports obtained by querying a central database having fields represented in FIG. **7**.

DETAILED DESCRIPTION OF THE INVENTION

In the following description, reference is made to the accompanying drawings that form a part hereof, and in which is shown by way of illustration specific embodiments in

which the invention may be practiced. These embodiments are described in sufficient detail to enable those skilled in the art to practice the invention, and it is to be understood that other embodiments may be utilized and that structural, logical and electrical changes may be made without departing from the scope of the present invention. The following description is, therefore, not to be taken in a limited sense, and the scope of the present invention is defined by the appended claims.

The functions or algorithms described herein are implemented in software or a combination of software and human implemented procedures in one embodiment. The software comprises computer executable instructions stored on computer readable media such as memory or other type of storage devices. The term "computer readable media" is also used to represent carrier waves on which the software is transmitted. Further, such functions correspond to modules, which are software, hardware, firmware of any combination thereof. Multiple functions are performed in one or more modules as desired, and the embodiments described are merely examples. The software is executed on a digital signal processor, ASIC, microprocessor, or other type of processor operating on a computer system, such as a personal computer, server or other computer system.

A sensitive drug is one which can be abused, or has addiction properties or other properties that render the drug sensitive. One example of such a drug is sodium oxybate, also known as gamma hydroxy butyrate (GHB $C_4H_7NaO_3$) which is useful for treatment of cataplexy in patients with narcolepsy. GHB is marketed under the trademark of Xyrem® (sodium oxybate oral solution), which trademark can be used interchangeably with GHB herein. Sensitive drugs also include narcotics or other drugs which require controls on their distribution and use to monitor behaviors to prevent abuse and adverse side effects.

In one embodiment, Xyrem® is subject to a restricted distribution program. One aspect of the program is to educate physicians and patients about the risks and benefits of Xyrem, including support via ongoing contact with patients and a toll free helpline. Initial prescriptions are filled only after a prescriber and patient have received and read the educational materials. Further, patient and prescribing physician registries are maintained and monitored to ensure proper distribution.

In a further embodiment, bulk sodium oxybate is manufactured at a single site, as is the finished drug product. Following manufacture of the drug product, it is stored at a facility compliant with FDA Schedule III regulations, where a consignment inventory is maintained. The inventory is owned by a company, and is managed by a central pharmacy, which maintains the consignment inventory. Xyrem® is distributed and dispensed through a primary and exclusive central pharmacy, and is not stocked in retail pharmacy outlets. It is distributed by overnight carriers, or by US mail in one embodiment to potentially invoke mail fraud laws if attempts of abuse occur.

FIG. **1** is a simplified block diagram of a computer system **100**, such as a personal computer for implementing at least a portion of the methods described herein. A central processing unit (CPU) **110** executes computer programs stored on a memory **120**. Memory **120** in one embodiment comprises one or more levels of cache as desired to speed execution of the program and access to data on which the programs operate. The CPU is directly coupled to memory **120** in one embodiment. Both CPU **110** and memory **120** are coupled to a bus **130**. A storage **140**, I/O **150** and communications **160** are also coupled to the bus **130**. Storage **140** is usually a long term storage device, such as a disk drive, tape drive, DVD, CD or other type of storage device. In one embodiment, storage **140** is used to house a database for use with the present invention. I/O **150** comprises keyboards, sound devices, displays and other mechanisms by which a user interacts with the computer system **100**. Communications **160** comprises a network, phone connection, local area network, wide area network or other mechanism for communicating with external devices. Such external devices comprise servers, other peer computers and other devices. In one embodiment, such external device comprises a database server that is used in place of the database on storage **140**. Other computer system architectures capable of executing software and interacting with a database and users may also be used. Appropriate security measures such as encryption are used to ensure confidentiality. Further, data integrity and backup measures are also used to prevent data loss.

FIGS. **2**A, **2**B and **2**C represent an initial prescription order entry process for a sensitive drug, such as Xyrem. At **202**, a medical doctor (MD) sends a Rx/enrollment form via mail, fax, email or other means to an intake/reimbursement specialist at **204**, who makes a copy of the RX/enrollment form that is stamped "copy". The original fax is forwarded to a pharmacy team. The enrollment form contains prescriber information, prescription information, checkboxes for the prescriber indicating they have read materials, educated the patient, understand the use in treatment, and understand certain safety information, and also contains patient information.

The prescriber information contains standard contact information as well as license number, DEA number and physician specialty. Patient and prescription information includes name, social security number, date of birth, gender, contact information, drug identification, patient's appropriate dosage, and number of refills allowed, along with a line for the prescriber's signature. Patient insurance information is also provided.

There are two workflows involved at the pharmacy team, intake reimbursement **206** and pharmacy workflow **208**, which may proceed in parallel or serially. The intake work flow **206** starts with an intake reimbursement specialist entering the patient and physician information into an application/database referred to as CHIPS, which is used to maintain a record of a client home infusion program (CHIP) for Xyrem®. A check is made to ensure the information is complete at **212**. If not, at **214**, an intake representative attempts to reach the MD or prescriber to obtain the missing information. If the missing information has not been obtained within a predetermined period of time, such as 24 hours at **216**, the Rx/Enrollment form is sent back to the MD with a rejection explanation. A note is entered in CHIPS that the application was rejected.

If the information is complete at **212**, the MD is contacted at **220** to verify receipt and accuracy of the patient's Rx. This contact is recorded in CHIPS. The intake and reimbursement specialist then sends a consent form and a cover letter to the patient at **224**. The insurance provider is contacted at **226** to verify coverage and benefits. At **228**, a determination is made regarding coverage for the drug. If it is not available, it is determined at **230** whether the patient is willing and able to pay. If not, a process is performed for handling patients who are uninsured or underinsured. In one embodiment, the process is referred to as a NORD process.

If the patient is willing and able to pay at **230**, the patient is informed of the cost of the product and is given payment options at **234**. At **236**, once payment is received, the intake reimbursement specialist submits a coverage approval form with the enrollment form to the pharmacy team as notification to process the patient's prescription. If coverage is approved

at **228**, the intake reimbursement specialist also submits the coverage approval form with the enrollment form to the pharmacy team as notification to process the patient's prescription. Processing of the prescription is described below.

Upon receipt and initial processing of the prescription enrollment form and sending an original to the pharmacy work flow block **208**, the patient is shipped a Xyrem® success packet via mail. In one embodiment, the Xyrem® success packet contains educational material for a patient that advises of the proper use, care and handling of the drug and consequences of diversion at **268**. The medical doctor's credentials are checked to determine if the physician has a current DEA license to prescribe controlled substances and if he or she has had any actions related to misuse/misprescribing of controlled drugs against him or her, within a predetermined time, such as three months at **270**. If they have, a pharmacist holds the prescription until receiving a coverage approval form from the intake reimbursement specialist at **272**.

If the credentials have not been recently checked, the pharmacist verifies the credentials and enters all findings in the database at **274**. If the credentials are approved at **276**, the physician is indicated as approved in a physician screen populated by information from the database at **280**. The prescription is then held pending coverage approval at **282**.

If any disciplinary actions are identified, as referenced at block **278**, management of the pharmacy is notified and either approves processing of the prescription with continued monitoring of the physician, or processing of the prescription is not performed, and the physician is noted in the database as unapproved at **284**. The enrollment form is then mailed back to the physician with a cover letter reiterating that the prescription cannot be processed at **288**. The patient is also sent a letter at **290** indicating that the prescription cannot be processed and the patient is instructed to contact their physician.

Actual filling of the approved prescription begins with receipt of the coverage approval form as indicated at **240**. The patient is contacted by the pharmacy, such as by a technician to complete a technician section of a patient counseling checklist. If a pharmacist verifies that the program materials were not read at **242**, the receipt of the material is confirmed at **244** and another call is scheduled to counsel the patient before the drug is shipped.

If the program materials, were read at **242**, the checklist is completed at **246** and the technician transfers the patient to the pharmacist who reviews the entire checklist and completes remaining pharmacist specified sections. At **248**, the pharmacists indicates in the database that the patient counseling and checklist was successfully completed, indicating the date completed.

At **250**, the pharmacist schedules the patient's shipment for the next business day or the next business day that the patient or designee is able to sign for the package. Further, as indicated at **252**, the shipment must be sent to the patient's home address unless the patient is traveling or has moved. In that event, the pharmacist may determine that an exception may be made. The patient or the patient's designee who is at least 18 years old, must sign for the package upon delivery.

At **254**, the pharmacist enters the prescription order in the database, creating an order number. The pharmacist then verifies at **256** the prescription and attaches a verification label to the hard copy prescription. At **258**, a pick ticket is generated for the order and the order is forwarded to the pharmacy for fulfillment. The shipment is confirmed in the database at **260**, and the order is shipped by USPS Express Mail. Use of the US mail invokes certain criminal penalties for unauthorized diversion. Optionally, other mail services may be used. Potential changes in the law may also bring criminal penalties into play. Following shipment, the patient is called by the central pharmacy to confirm that the prescription was received.

As noted at **266**, for the sensitive drug, Xyrem, all inventory is cycle counted and reconciled with the database system quantities before shipments for the day are sent. This provides a very precise control of the inventory.

A physician success program materials request process begins at **310** in FIG. **3**. At **320**, the MD calls to the central pharmacy to request program materials. A special phone number is provided. MD demographics, DEA number, and data or request are entered into the database at **330**. At **340**, a request is made to ship the materials to the MD via a fulfillment website, or other mechanism. The request process ends at **350**.

A refill request process begins at **302** in FIGS. **4**A and **4**B. There are two different paths for refills. A first path beginning at **404** involves generating a report from the central database of patients with a predetermined number of days or product remaining. A second path beginning at **406** is followed when a patient calls to request an early refill.

In the first path, a copy of the report is provided to an intake reimbursement specialist at **408**. No sooner than 8 days before the medication depletion, a pharmacy technician contacts the patient at **410** to complete the pre-delivery checklist. At **412**, if the patient is not reached, a message is left mentioning the depletion, and a return number at **414**. A note is also entered into the database indicating the date the message was left at **416**.

If the patient is reached at **412**, the next shipment is scheduled at **418**, the prescription is entered into the database creating an order at **420**, the pharmacist verifies the prescription and attaches a verification label at **422** and the shipment is confirmed in the database at **424**. Note at **426** that the inventory is cycle counted and reconciled with the database quantities before the shipments for a day or other time period are sent. A pick ticket is generated for the order and the order is forwarded for fulfillment at **428**, with the first path ending at **430**.

The second path, beginning at **406** results in a note code being entered into the database on a patient screen indicating an early refill request at **432**. The pharmacist evaluates the patient's compliance with therapy or possible product diversion, misuse or over-use at **436**. In one embodiment, cash payers are also identified. The pharmacist then contacts the prescribing physician to alert them of the situation and confirm if the physician approves of the early refill at **438**. If the physician does not approve as indicated at **440**, the patient must wait until the next scheduled refill date to receive additional product as indicated at **442**, and the process ends at **444**.

If the physician approves at **440**, the pharmacist enters a note in the database on a patient screen that the physician approves the request at **446**. The pharmacist notifies an intake reimbursement specialist to contact the patient's insurance provider to verify coverage for the early refill at **448**. If the insurance provider will pay as determined at **450**, the specialist submits the coverage approval form as notification that the refill may be processed at **452**. At **454**, the pharmacy technician contacts the patient to schedule shipment of the product for the next business day, and the process of filling the order is continued at **456** by following the process beginning at **240**.

If the insurance provider will not pay at **450**, it is determined whether the patient is willing and/or able to pay at **458**. If not, the patient must wait until the next scheduled refill date to receive additional product at **460**. If it was determined at **458** that the patient was willing and able to pay, the patient is informed of the cost of the product and is given payment

options at **462**. Once payment is received as indicated at **464**, the specialist submits a coverage approval form to the pharmacy team as notification that the refill request can be processed at **466**. At **468**, the pharmacy technician contacts the patient to schedule shipment. The process of filling the order is continued at **470** by following the process beginning at **240**.

A process, referred to as a NORD process in one embodiment is used to determine whether donated, third party funds are available for paying for prescriptions where neither insurance will, nor the patient can pay. The process begins at **510** upon determining that a patient is uninsured or underinsured. A reimbursement specialist explains the NORD program to the patient and faxes an application request form to NORD for the patient. At **515**, the intake reimbursement specialist documents in the database that an application has been received through NORD. At **520**, NORD mails an application to the patient within one business day.

A determination is made at **525** by NORD whether the patient is approved. If not, at **530**, NORD sends a denial letter to the patient, and it is documented in the database at **540** that the patient was denied by NORD. If the patient is approved, NORD sends an acceptance letter to the patient and faxes a voucher to the central pharmacy (SDS in one embodiment) to indicate the approval at **545**. At **550**, an intake reimbursement specialist submits a coverage approval form to the pharmacy team as notification that the patient has been approved for coverage. The process of filling the order is continued at **555** by following the process beginning at **240**.

An inventory control process is illustrated in FIG. **6** beginning at **610**. Each week, a responsible person at the central pharmacy, such as the director of the pharmacy transfers inventory for the week's shipments to a segregated warehouse location for production inventory. At **620**, a purchase order is generated for the inventory transferred to the production location and is sent, such as by fax, to a controller, such as the controller of the company that obtained approval for distribution and use of the sensitive drug. At **630**, the controller invoices the central pharmacy for the product moved to production. The process ends at **640**.

The central database described above is a relational database running on the system of FIG. **1**, or a server based system having a similar architecture coupled to workstations via a network, as represented by communications **160**. The database is likely stored in storage **140**, and contains multiple fields of information as indicated at **700** in FIG. **7**. The organization and groupings of the fields are shown in one format for convenience. It is recognized that many different organizations or schemas may be utilized. In one embodiment, the groups of fields comprise prescriber fields **710**, patient fields **720**, prescription fields **730** and insurance fields **740**. For purposes of illustration, all the entries described with respect to the above processes are included in the fields. In further embodiments, no such groupings are made, and the data is organized in a different manner.

Several queries are illustrated at **800** in FIG. **8**. There may be many other queries as required by individual state reporting requirements. A first query at **810** is used to identify prescriptions written by physician. The queries may be written in structured query language, natural query languages or in any other manner compatible with the database. A second query **820** is used to pull information from the database related to prescriptions by patient name. A third query **830** is used to determine prescriptions by frequency, and a n^{th} query finds prescriptions by dose at **840**. Using query languages combined with the depth of data in the central database allows many other methods of investigating for potential abuse of the drugs. The central database ensures that all prescriptions, prescribers and patients are tracked and subject to such investigations. In further embodiments, the central database may be distributed among multiple computers provided a query operates over all data relating to such prescriptions, prescribers and patients for the drug.

An example of one prescription and enrollment form is shown at **900** in FIG. **9**. As previously indicated, several fields are included for prescriber information, prescription information and patient information.

FIG. **10** is a copy of one example NORD application request form **1000** used to request that an application be sent to a patient for financial assistance.

FIG. **11** is a copy of one example application **1100** for financial assistance as requested by form **1000**. The form requires both patient and physician information. Social security number information is also requested. The form provides information for approving the financial assistance and for tracking assistance provided.

FIG. **12** is a copy of one example voucher request for medication for use with the NORD application request form of FIG. **10**. In addition to patient and physician information, prescription information and diagnosis information is also provided.

FIGS. **13**A, **13**B and **13**C are descriptions of sample reports obtained by querying a central database having fields represented in FIG. **7**. The activities grouped by sales, regulatory, quality assurance, call center, pharmacy, inventory, reimbursement, patient care and drug information. Each report has an associated frequency or frequencies. The reports are obtained by running queries against the database, with the queries written in one of many query languages.

While the invention has been described with respect to a Schedule III drug, it is useful for other sensitive drugs that are DEA or Federally scheduled drugs in Schedule II-V, as well as still other sensitive drugs where multiple controls are desired for distribution and use.

The invention claimed is:

1. A method of treatment of a narcoleptic patient with a prescription drug while controlling potential misuse, abuse or diversion of said prescription drug, comprising:

receiving in a computer processor all prescription requests, for any and all narcoleptic patients being prescribed the prescription drug, wherein the prescription drug is distributed by a company that obtained approval for distribution of the prescription drug, only at an exclusive central pharmacy from any and all medical doctors allowed to prescribe the company's prescription drug, the prescription requests containing information identifying narcoleptic patients, the prescription drug, and various credentials of the any and all medical doctors;

requiring entering of the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations, wherein the exclusive central pharmacy and the exclusive central database are the only pharmacy and database in existence for the company's prescription drug, and such that all prescriptions for the company's prescription drug are processed only by the exclusive central pharmacy using only the exclusive computer database;

checking with the computer processor the credentials of the any and all doctors to determine the eligibility of the doctors to prescribe the company's prescription drug;

confirming with a narcoleptic patient that educational material has been read prior to shipping the company's prescription drug;

checking the exclusive computer database for potential abuse of the company's prescription drug, wherein the

exclusive central pharmacy and the exclusive central database facilitate a determination of the potential abuse of the company's prescription drug;

providing the company's prescription drug to the narcoleptic patient only if no potential abuse is found by the narcoleptic patient to whom the company's prescription drug is prescribed and the doctor prescribing the company's prescription drug;

confirming receipt by the narcoleptic patient of the company's prescription drug; and

generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.

2. The method of claim **1**, wherein one or more of the exclusive central pharmacy and the exclusive central database are distributed over multiple computers, and wherein a query operates over all data in all the distributed databases relating to the prescriptions, the doctors, and the narcoleptic patients.

3. The method of claim **1**, wherein the providing the company's prescription drug to the narcoleptic patient comprises the exclusive central pharmacy authorizing the company's prescription drug to be dispensed to the narcoleptic patient by another pharmacy.

4. The method of claim **1**, comprising delivering the company's prescription drug to the narcoleptic patient in order to treat the narcoleptic patient with the company's prescription drug.

5. The method of claim **1**, wherein the exclusive central pharmacy enters data into the exclusive computer database.

6. The method of claim **1**, comprising selectively blocking shipment of the company's prescription drug to the narcoleptic patient.

7. The method of claim **1**, wherein an abuse pattern is associated with the narcoleptic patient, and shipment of the company's prescription drug is blocked based upon such association.

8. The computerized method of claim **1**, wherein the company's prescription drug comprises a gamma hydroxy butyrate (GHB) drug product.

9. A method of treatment of a narcoleptic patient with a prescription drug while controlling potential misuse, abuse or diversion of said prescription drug, comprising:

receiving in a computer processor all prescription requests, for any and all narcoleptic patients being prescribed the prescription drug, wherein the prescription drug inventory is owned by a company, only at an exclusive central pharmacy from any and all medical doctors allowed to prescribe the company's prescription drug, the prescription requests containing information identifying narcoleptic patients, the prescription drug, and various credentials of the any and all medical doctors;

requiring entering of the information into an exclusive computer database associated with the exclusive central pharmacy for analysis of potential abuse situations, wherein the exclusive central pharmacy and the exclusive central database are the only pharmacy and database in existence for the company's prescription drug, and such that all prescriptions for the company's prescription drug are processed only by the exclusive central pharmacy using only the exclusive computer database;

checking with the computer processor the credentials of the any and all doctors to determine the eligibility of the doctors to prescribe the company's prescription drug;

confirming with a narcoleptic patient that educational material has been read prior to shipping the company's prescription drug;

checking the exclusive computer database for potential abuse of the company's prescription drug, wherein the exclusive central pharmacy and the exclusive central database facilitate a determination of the potential abuse of the company's prescription drug;

providing the company's prescription drug to the narcoleptic patient only if no potential abuse is found by the narcoleptic patient to whom the company's prescription drug is prescribed and the doctor prescribing the company's prescription drug;

confirming receipt by the narcoleptic patient of the company's prescription drug; and

generating with the computer processor periodic reports via the exclusive computer database to evaluate potential diversion patterns.

10. The method of claim **9**, wherein one or more of the exclusive central pharmacy and the exclusive central database are distributed over multiple computers, and wherein a query operates over all data in all the distributed databases relating to the prescriptions, the doctors, and the narcoleptic patients.

11. The method of claim **9**, wherein the providing the company's prescription drug to the narcoleptic patient comprises the exclusive central pharmacy authorizing the company's prescription drug to be dispensed to the narcoleptic patient by another pharmacy.

12. The method of claim **9**, comprising delivering the company's prescription drug to the narcoleptic patient in order to treat the narcoleptic patient with the company's prescription drug.

13. The method of claim **9**, wherein the exclusive central pharmacy enters data into the exclusive computer database.

14. The method of claim **9**, wherein an abuse pattern is associated with the narcoleptic patient, and shipment of the company's prescription drug is blocked based upon such association.

15. The method of claim **9**, wherein the company's prescription drug comprises a gamma hydroxy butyrate (GHB) drug product.

* * * * *

EXHIBIT F

US008589182B1

(12) **United States Patent**
Reardan et al.

(10) **Patent No.: US 8,589,182 B1**
(45) **Date of Patent: Nov. 19, 2013**

(54) **SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **13/595,676**

(22) Filed: **Aug. 27, 2012**

Related U.S. Application Data

(63) Continuation of application No. 13/013,680, filed on Jan. 25, 2011, now abandoned, which is a continuation of application No. 12/704,097, filed on Feb. 11, 2010, now Pat. No. 7,895,059, which is a continuation of application No. 10/322,348, filed on Dec. 17, 2002, now Pat. No. 7,668,730.

(51) **Int. Cl.**
G06Q 10/00 (2012.01)

(52) **U.S. Cl.**
USPC **705/2**; 705/3

(58) **Field of Classification Search**
USPC 705/2, 3
See application file for complete search history.

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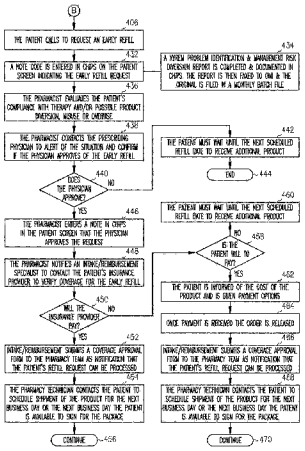
(57) **ABSTRACT**

A drug distribution system and method utilizes a central pharmacy and database to track all prescriptions for a sensitive drug. Information is kept in the database regarding all physicians allowed to prescribe the sensitive drug, and all patients receiving the drug. Abuses are identified by monitoring data in the database for prescription patterns by physicians and prescriptions obtained by patients. Further verification is made that the physician is eligible to prescribe the drug by consulting a separate database, and optionally whether any actions are taken against the physician. Multiple controls beyond those for normal drugs are imposed on the distribution depending on the sensitivity of the drug.

26 Claims, 16 Drawing Sheets



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"U.S. Appl. No. 10/979,665, Restriction Requirement mailed Jun. 25, 2009", 7 pgs.
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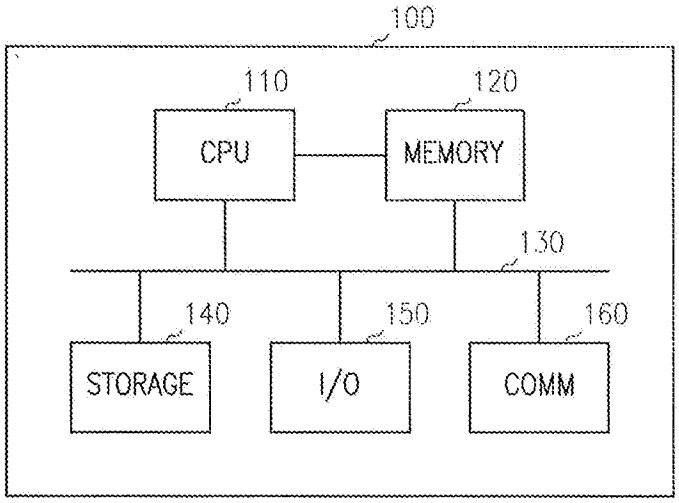

FIG. 1

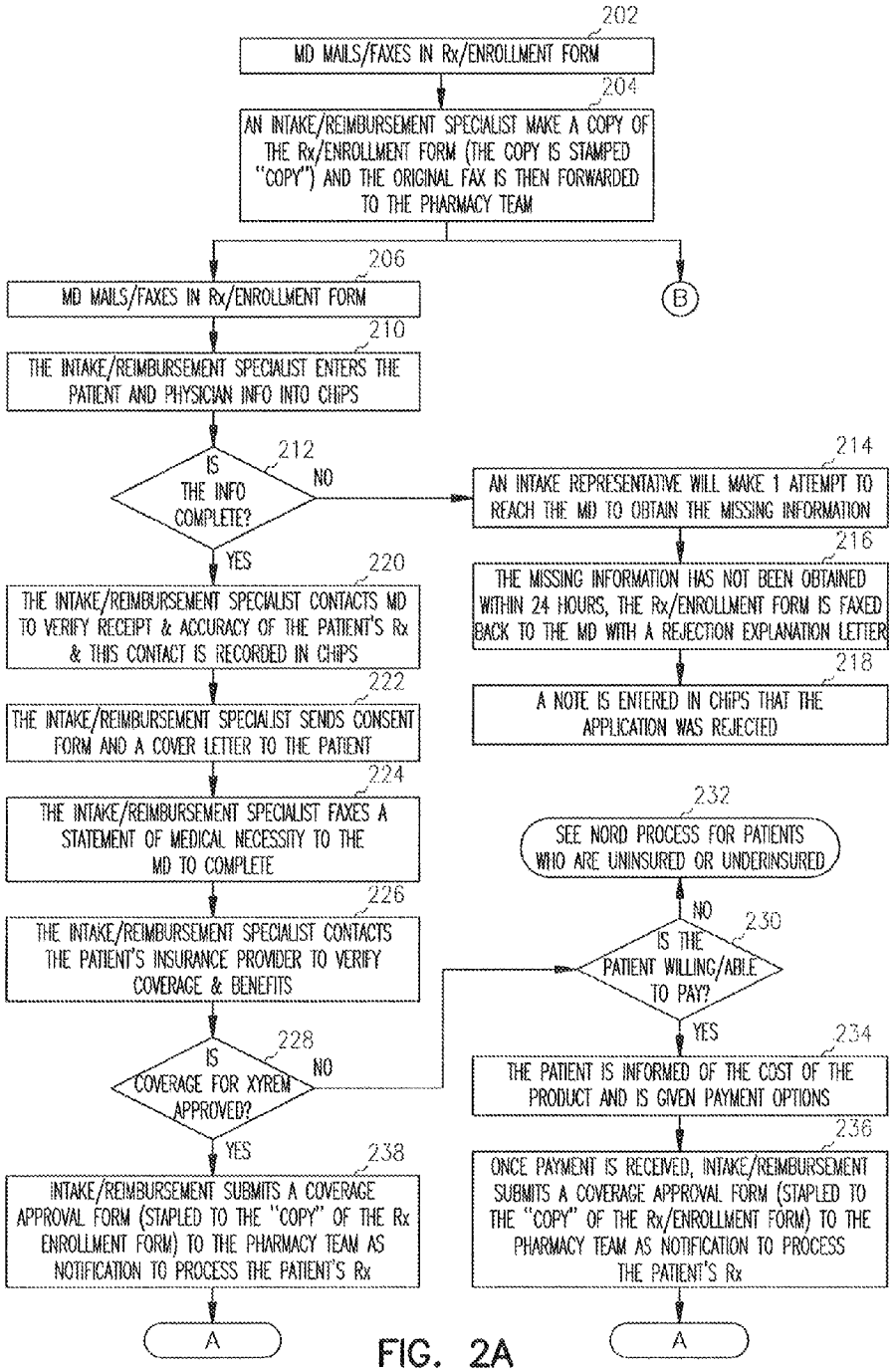
202
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
204
AN INTAKE/REIMBURSEMENT SPECIALIST MAKE A COPY OF THE Rx/ENROLLMENT FORM (THE COPY IS STAMPED "COPY") AND THE ORIGINAL FAX IS THEN FORWARDED TO THE PHARMACY TEAM
206
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
B
210
THE INTAKE/REIMBURSEMENT SPECIALIST ENTERS THE PATIENT AND PHYSICIAN INFO INTO CHIPS
212
IS THE INFO COMPLETE?
NO
214
AN INTAKE REPRESENTATIVE WILL MAKE 1 ATTEMPT TO REACH THE MD TO OBTAIN THE MISSING INFORMATION
216
THE MISSING INFORMATION HAS NOT BEEN OBTAINED WITHIN 24 HOURS, THE Rx/ENROLLMENT FORM IS FAXED BACK TO THE MD WITH A REJECTION EXPLANATION LETTER
218
A NOTE IS ENTERED IN CHIPS THAT THE APPLICATION WAS REJECTED
YES
220
THE INTAKE/REIMBURSEMENT SPECIALIST CONTACTS MD TO VERIFY RECEIPT & ACCURACY OF THE PATIENT'S Rx & THIS CONTACT IS RECORDED IN CHIPS
222
THE INTAKE/REIMBURSEMENT SPECIALIST SENDS CONSENT FORM AND A COVER LETTER TO THE PATIENT
224
THE INTAKE/REIMBURSEMENT SPECIALIST FAXES A STATEMENT OF MEDICAL NECESSITY TO THE MD TO COMPLETE
226
THE INTAKE/REIMBURSEMENT SPECIALIST CONTACTS THE PATIENT'S INSURANCE PROVIDER TO VERIFY COVERAGE & BENEFITS
228
IS COVERAGE FOR XYREM APPROVED?
NO
YES
232
SEE NORD PROCESS FOR PATIENTS WHO ARE UNINSURED OR UNDERINSURED
NO
230
IS THE PATIENT WILLING/ABLE TO PAY?
YES
234
THE PATIENT IS INFORMED OF THE COST OF THE PRODUCT AND IS GIVEN PAYMENT OPTIONS
236
ONCE PAYMENT IS RECEIVED, INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM (STAPLED TO THE "COPY" OF THE Rx/ENROLLMENT FORM) TO THE PHARMACY TEAM AS NOTIFICATION TO PROCESS THE PATIENT'S Rx
238
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM (STAPLED TO THE "COPY" OF THE Rx ENROLLMENT FORM) TO THE PHARMACY TEAM AS NOTIFICATION TO PROCESS THE PATIENT'S Rx
A
A

FIG. 2A

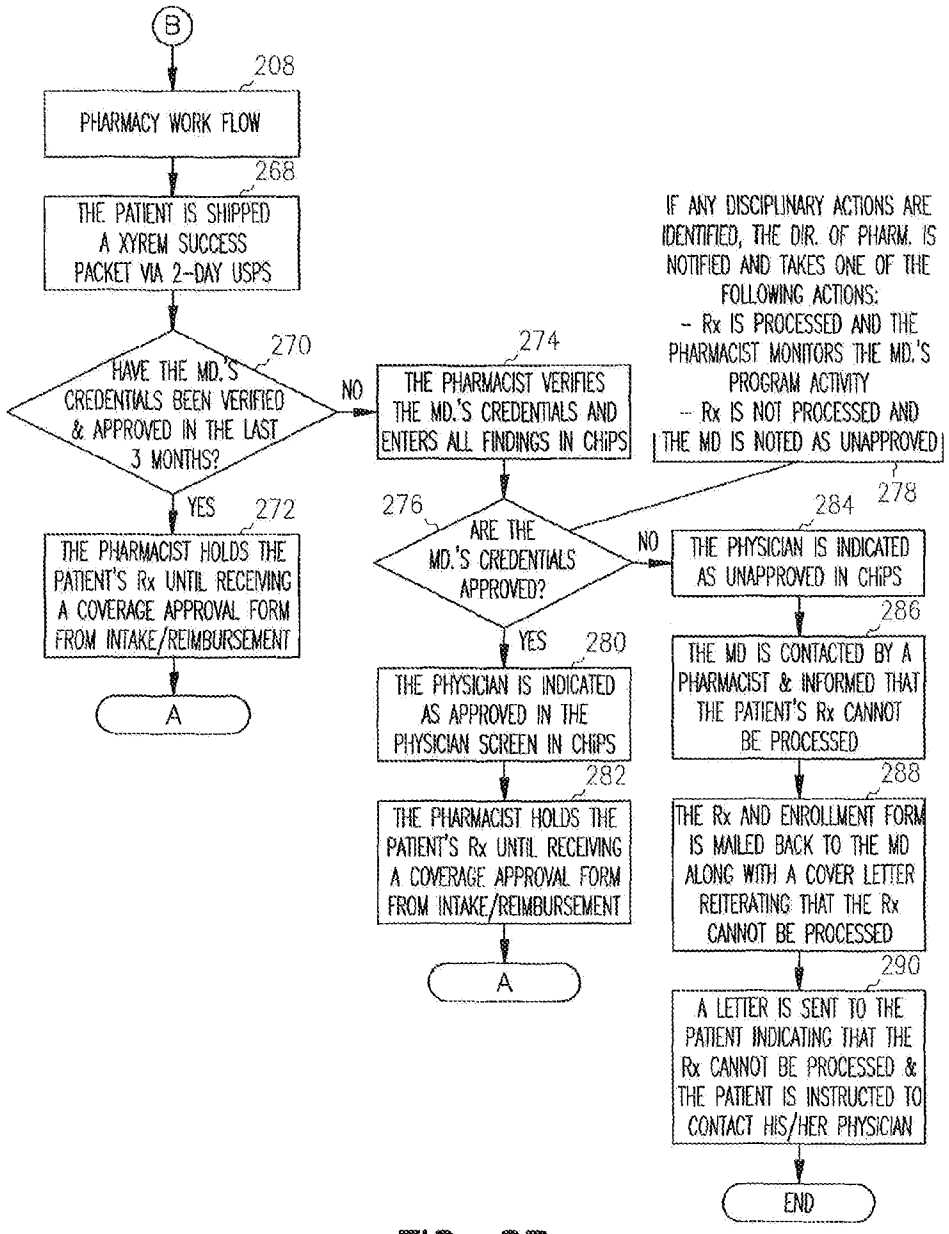
B
208
PHARMACY WORK FLOW
268
THE PATIENT IS SHIPPED A XYREM SUCCESS PACKET VIA 2-DAY USPS
270
HAVE THE MD.'S CREDENTIALS BEEN VERIFIED & APPROVED IN THE LAST 3 MONTHS?
NO
YES
272
THE PHARMACIST HOLDS THE PATIENT'S Rx UNTIL RECEIVING A COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT
A
274
THE PHARMACIST VERIFIES THE MD.'S CREDENTIALS AND ENTERS ALL FINDINGS IN CHIPS
276
ARE THE MD.'S CREDENTIALS APPROVED?
NO
YES
280
THE PHYSICIAN IS INDICATED AS APPROVED IN THE PHYSICIAN SCREEN IN CHIPS
282
THE PHARMACIST HOLDS THE PATIENT'S Rx UNTIL RECEIVING A COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT
A
IF ANY DISCIPLINARY ACTIONS ARE IDENTIFIED, THE DIR. OF PHARM. IS NOTIFIED AND TAKES ONE OF THE FOLLOWING ACTIONS:
- Rx IS PROCESSED AND THE PHARMACIST MONITORS THE MD.'S PROGRAM ACTIVITY
- Rx IS NOT PROCESSED AND THE MD IS NOTED AS UNAPPROVED
278
284
THE PHYSICIAN IS INDICATED AS UNAPPROVED IN CHIPS
286
THE MD IS CONTACTED BY A PHARMACIST & INFORMED THAT THE PATIENT'S Rx CANNOT BE PROCESSED
288
THE Rx AND ENROLLMENT FORM IS MAILED BACK TO THE MD ALONG WITH A COVER LETTER REITERATING THAT THE Rx CANNOT BE PROCESSED
290
A LETTER IS SENT TO THE PATIENT INDICATING THAT THE Rx CANNOT BE PROCESSED & THE PATIENT IS INSTRUCTED TO CONTACT HIS/HER PHYSICIAN
END

FIG. 2B

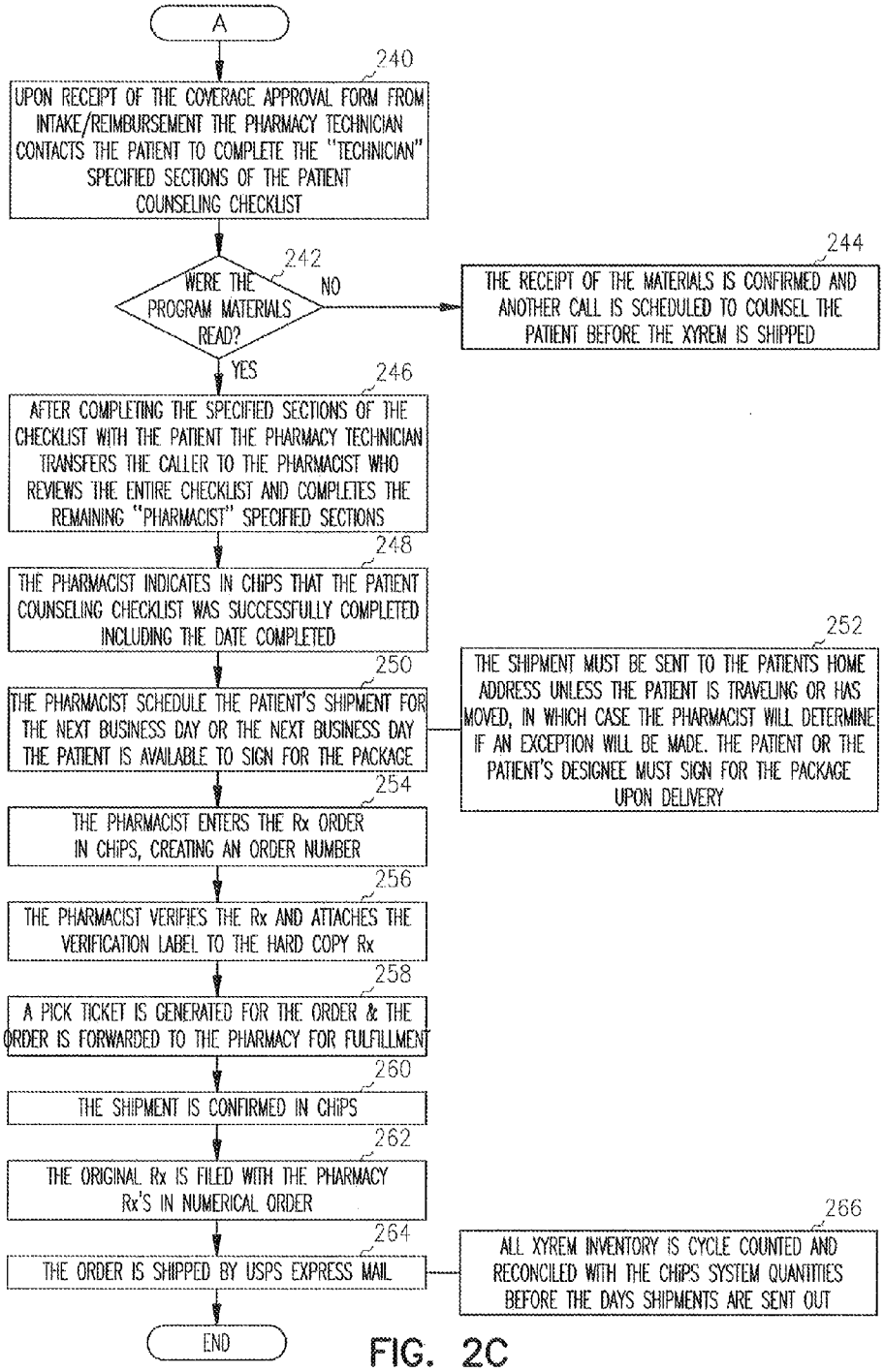
A
240
UPON RECEIPT OF THE COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE THE "TECHNICIAN" SPECIFIED SECTIONS OF THE PATIENT COUNSELING CHECKLIST
242
WERE THE PROGRAM MATERIALS READ?
NO
244
THE RECEIPT OF THE MATERIALS IS CONFIRMED AND ANOTHER CALL IS SCHEDULED TO COUNSEL THE PATIENT BEFORE THE XYREM IS SHIPPED
YES
246
AFTER COMPLETING THE SPECIFIED SECTIONS OF THE CHECKLIST WITH THE PATIENT THE PHARMACY TECHNICIAN TRANSFERS THE CALLER TO THE PHARMACIST WHO REVIEWS THE ENTIRE CHECKLIST AND COMPLETES THE REMAINING "PHARMACIST" SPECIFIED SECTIONS
248
THE PHARMACIST INDICATES IN CHIPS THAT THE PATIENT COUNSELING CHECKLIST WAS SUCCESSFULLY COMPLETED INCLUDING THE DATE COMPLETED
252
THE SHIPMENT MUST BE SENT TO THE PATIENTS HOME ADDRESS UNLESS THE PATIENT IS TRAVELING OR HAS MOVED, IN WHICH CASE THE PHARMACIST WILL DETERMINE IF AN EXCEPTION WILL BE MADE. THE PATIENT OR THE PATIENT'S DESIGNEE MUST SIGN FOR THE PACKAGE UPON DELIVERY
250
THE PHARMACIST SCHEDULE THE PATIENT'S SHIPMENT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
254
THE PHARMACIST ENTERS THE Rx ORDER IN CHIPS, CREATING AN ORDER NUMBER
256
THE PHARMACIST VERIFIES THE Rx AND ATTACHES THE VERIFICATION LABEL TO THE HARD COPY Rx
258
A PICK TICKET IS GENERATED FOR THE ORDER & THE ORDER IS FORWARDED TO THE PHARMACY FOR FULFILLMENT
260
THE SHIPMENT IS CONFIRMED IN CHIPS
262
THE ORIGINAL Rx IS FILED WITH THE PHARMACY Rx'S IN NUMERICAL ORDER
266
ALL XYREM INVENTORY IS CYCLE COUNTED AND RECONCILED WITH THE CHIPS SYSTEM QUANTITIES BEFORE THE DAYS SHIPMENTS ARE SENT OUT
264
THE ORDER IS SHIPPED BY USPS EXPRESS MAIL
END

FIG. 2C

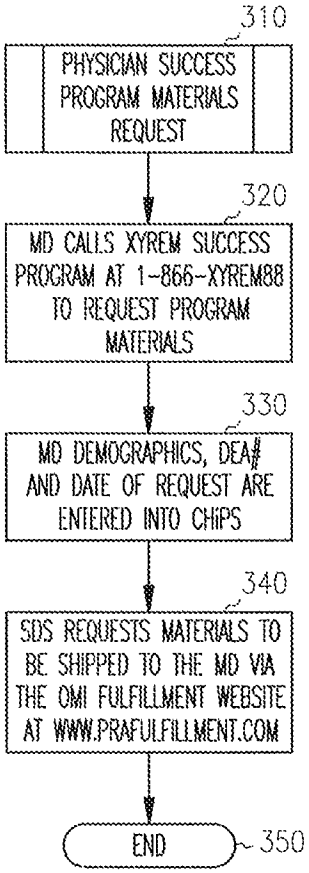
310
PHYSICIAN SUCCESS PROGRAM MATERIALS REQUEST
320
MD CALLS XYREM SUCCESS PROGRAM AT 1-866-XYREM88 TO REQUEST PROGRAM MATERIALS
330
MD DEMOGRAPHICS, DEA# AND DATE OF REQUEST ARE ENTERED INTO CHIPS
340
SDS REQUESTS MATERIALS TO BE SHIPPED TO THE MD VIA THE OMI FULFILLMENT WEBSITE AT WWW.PRAFULFILLMENT.COM
END
350

FIG. 3

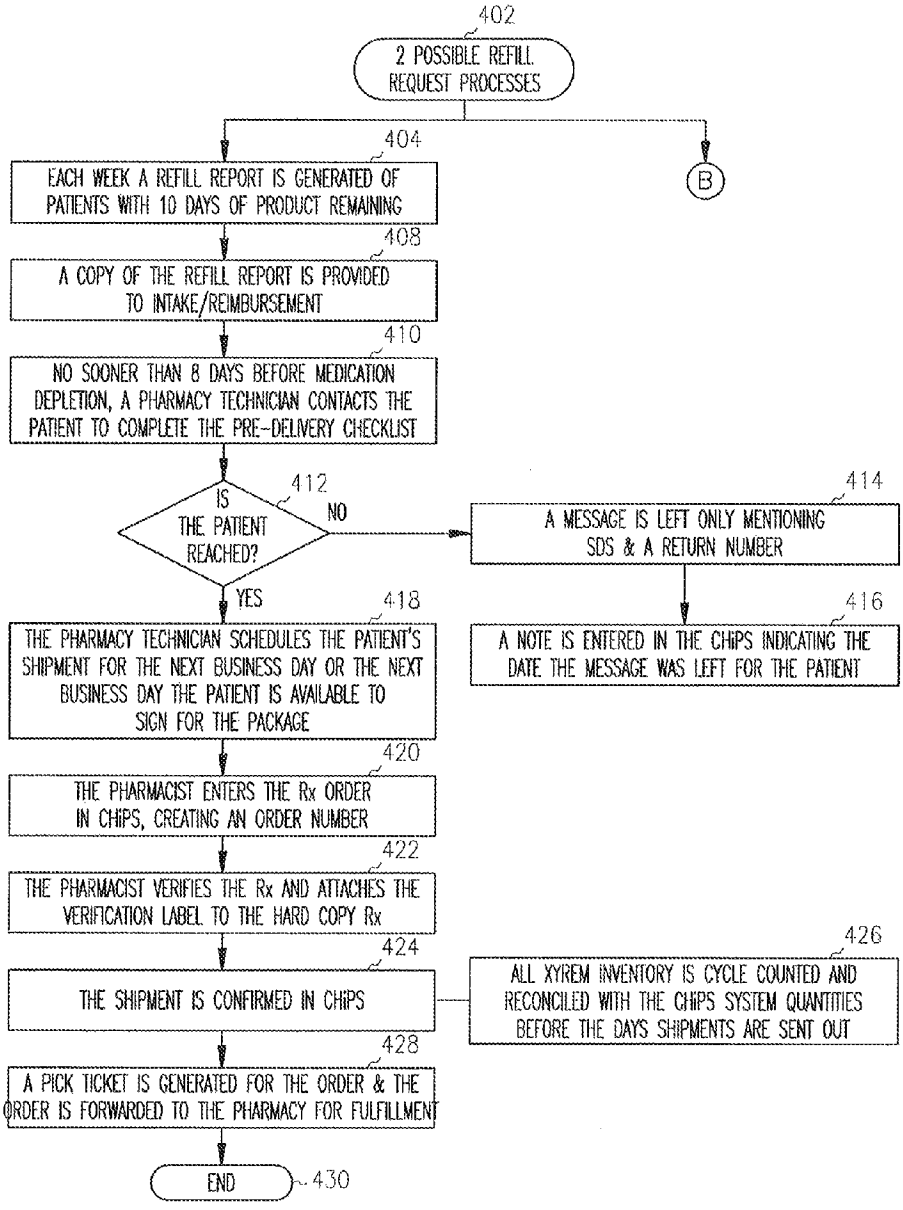
402
2 POSSIBLE REFILL REQUEST PROCESSES
404
EACH WEEK A REFILL REPORT IS GENERATED OF PATIENTS WITH 10 DAYS OF PRODUCT REMAINING
B
408
A COPY OF THE REFILL REPORT IS PROVIDED TO INTAKE/REIMBURSEMENT
410
NO SOONER THAN 8 DAYS BEFORE MEDICATION DEPLETION, A PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE THE PRE-DELIVERY CHECKLIST
412
IS THE PATIENT REACHED?
NO
414
A MESSAGE IS LEFT ONLY MENTIONING SDS & A RETURN NUMBER
YES
418
THE PHARMACY TECHNICIAN SCHEDULES THE PATIENT'S SHIPMENT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
416
A NOTE IS ENTERED IN THE CHIPS INDICATING THE DATE THE MESSAGE WAS LEFT FOR THE PATIENT
420
THE PHARMACIST ENTERS THE Rx ORDER IN CHIPS, CREATING AN ORDER NUMBER
422
THE PHARMACIST VERIFIES THE Rx AND ATTACHES THE VERIFICATION LABEL TO THE HARD COPY Rx
424
THE SHIPMENT IS CONFIRMED IN CHIPS
426
ALL XYREM INVENTORY IS CYCLE COUNTED AND RECONCILED WITH THE CHIPS SYSTEM QUANTITIES BEFORE THE DAYS SHIPMENTS ARE SENT OUT
428
A PICK TICKET IS GENERATED FOR THE ORDER & THE ORDER IS FORWARDED TO THE PHARMACY FOR FULFILLMENT
END
430

FIG. 4A

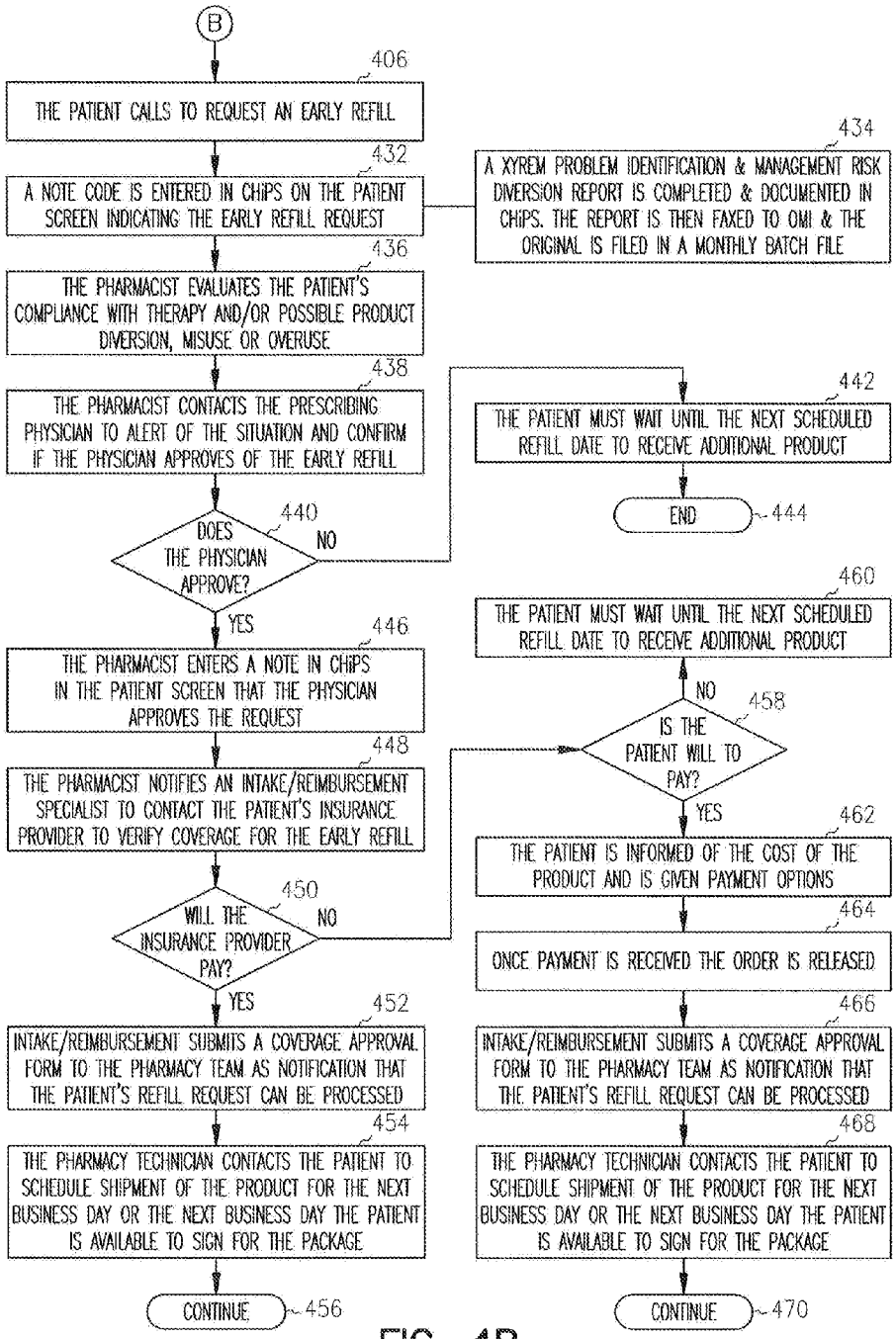
B
406
THE PATIENT CALLS TO REQUEST AN EARLY REFILL
432
A NOTE CODE IS ENTERED IN CHIPS ON THE PATIENT SCREEN INDICATING THE EARLY REFILL REQUEST
434
A XYREM PROBLEM IDENTIFICATION & MANAGEMENT RISK DIVERSION REPORT IS COMPLETED & DOCUMENTED IN CHIPS. THE REPORT IS THEN FAXED TO OMI & THE ORIGINAL IS FILED IN A MONTHLY BATCH FILE
436
THE PHARMACIST EVALUATES THE PATIENT'S COMPLIANCE WITH THERAPY AND/OR POSSIBLE PRODUCT DIVERSION, MISUSE OR OVERUSE
438
THE PHARMACIST CONTACTS THE PRESCRIBING PHYSICIAN TO ALERT OF THE SITUATION AND CONFIRM IF THE PHYSICIAN APPROVES OF THE EARLY REFILL
440
DOES THE PHYSICIAN APPROVE?
NO
442
THE PATIENT MUST WAIT UNTIL THE NEXT SCHEDULED REFILL DATE TO RECEIVE ADDITIONAL PRODUCT
END
444
YES
446
THE PHARMACIST ENTERS A NOTE IN CHIPS IN THE PATIENT SCREEN THAT THE PHYSICIAN APPROVES THE REQUEST
448
THE PHARMACIST NOTIFIES AN INTAKE/REIMBURSEMENT SPECIALIST TO CONTACT THE PATIENT'S INSURANCE PROVIDER TO VERIFY COVERAGE FOR THE EARLY REFILL
450
WILL THE INSURANCE PROVIDER PAY?
NO
460
THE PATIENT MUST WAIT UNTIL THE NEXT SCHEDULED REFILL DATE TO RECEIVE ADDITIONAL PRODUCT
458
IS THE PATIENT WILL TO PAY?
NO
YES
462
THE PATIENT IS INFORMED OF THE COST OF THE PRODUCT AND IS GIVEN PAYMENT OPTIONS
464
ONCE PAYMENT IS RECEIVED THE ORDER IS RELEASED
YES
452
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT'S REFILL REQUEST CAN BE PROCESSED
466
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT'S REFILL REQUEST CAN BE PROCESSED
454
THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO SCHEDULE SHIPMENT OF THE PRODUCT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
468
THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO SCHEDULE SHIPMENT OF THE PRODUCT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
CONTINUE
456
CONTINUE
470

FIG. 4B

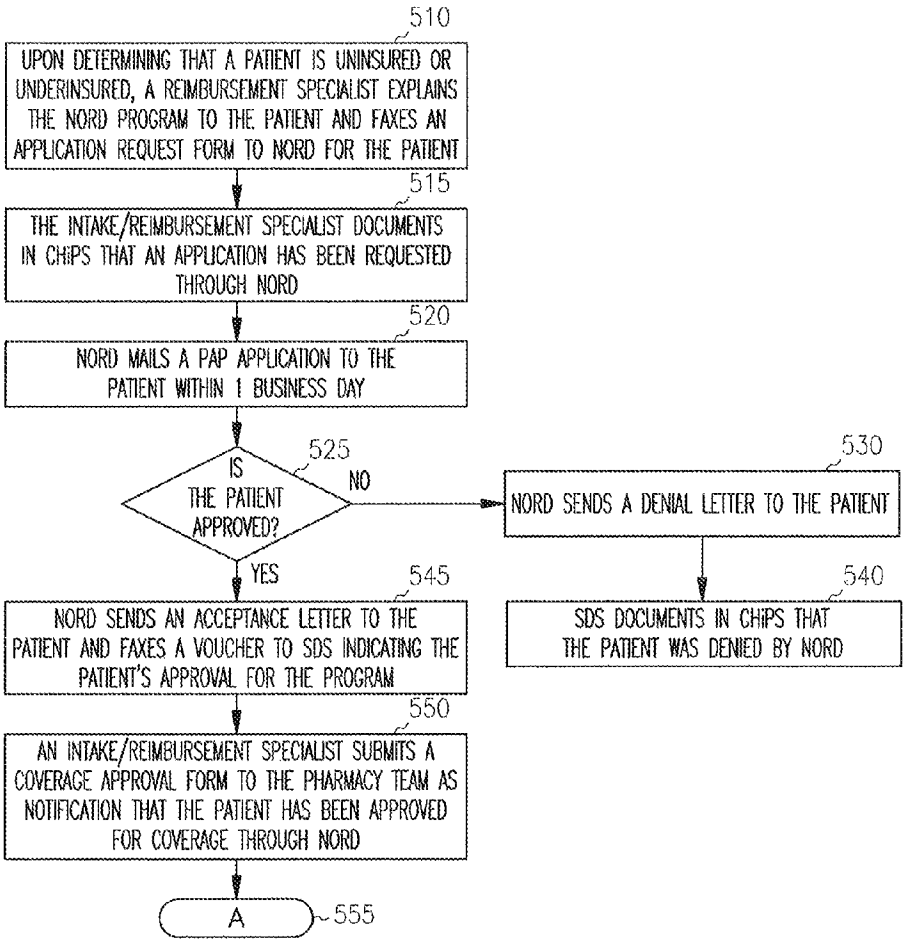
510
UPON DETERMINING THAT A PATIENT IS UNINSURED OR UNDERINSURED, A REIMBURSEMENT SPECIALIST EXPLAINS THE NORD PROGRAM TO THE PATIENT AND FAXES AN APPLICATION REQUEST FORM TO NORD FOR THE PATIENT
515
THE INTAKE/REIMBURSEMENT SPECIALIST DOCUMENTS IN CHIPS THAT AN APPLICATION HAS BEEN REQUESTED THROUGH NORD
520
NORD MAILS A PAP APPLICATION TO THE PATIENT WITHIN 1 BUSINESS DAY
525
IS THE PATIENT APPROVED?
NO
530
NORD SENDS A DENIAL LETTER TO THE PATIENT
YES
545
NORD SENDS AN ACCEPTANCE LETTER TO THE PATIENT AND FAXES A VOUCHER TO SDS INDICATING THE PATIENT'S APPROVAL FOR THE PROGRAM
540
SDS DOCUMENTS IN CHIPS THAT THE PATIENT WAS DENIED BY NORD
550
AN INTAKE/REIMBURSEMENT SPECIALIST SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT HAS BEEN APPROVED FOR COVERAGE THROUGH NORD
A
555

FIG. 5

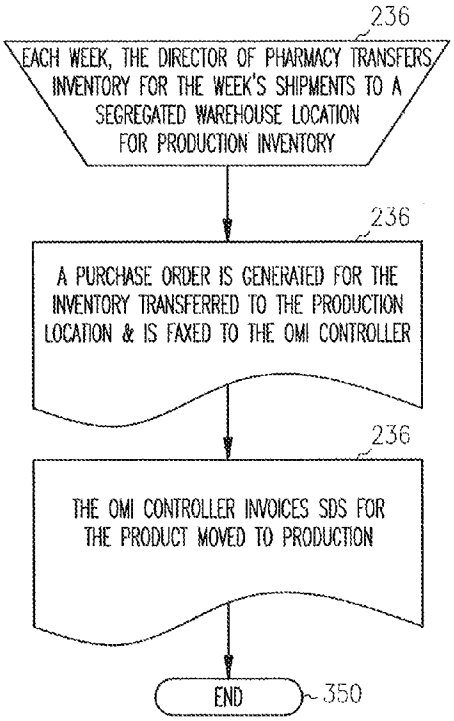

FIG. 6

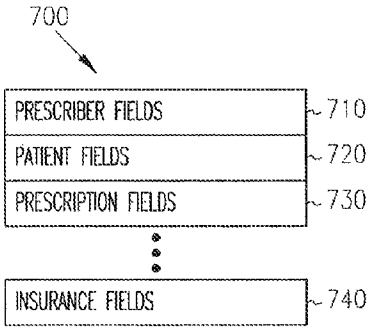

FIG. 7

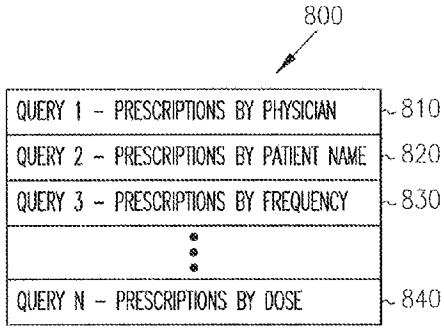

FIG. 8

900

PRESCRIPTION AND ENROLLMENT FORM

PRESCRIBER INFORMATION

PRESCRIBER'S NAME: ..... OFFICE CONTACT: .....
STREET ADDRESS: .....
CITY: ..... STATE: ..... ZIP: .....
PHONE: ..... FAX: .....
LICENSE NUMBER: ..... DEA NUMBER: .....
MD SPECIALTY: .....

PRESCRIPTION FORM

PATIENT NAME: ..... SS#: ..... DOB: ..... SEX M / F
ADDRESS: .....
CITY: ..... STATE: ..... ZIP: .....
Rx: XYREM ORAL SOLUTION (500 mg/mL) 180 ML BOTTLE QUANTITY: ..... MONTHS SUPPLY
SIG: TAKE ..... GMS P.O. DILUTED IN 60 mL WATER AT H.S. AND THEN AGAIN 2 1/2 TO 4 HOURS LATER
REFILLS (CIRCLE ONE): 0 1 2 (MAXIMUM OF 3 MONTH SUPPLY)
..... DATE: ...../...../.....
PRESCRIBER'S SIGNATURE

PHYSICIAN DECLARATION–PLEASE CHECK EACH BOX | TO BE COMPLETED AT INITIAL PRESCRIPTION ONLY

☐ I HAVE READ THE MATERIALS IN THE XYREM PHYSICIAN SUCCESS PROGRAM
☐ I VERIFY THAT THE PATIENT HAS BEEN EDUCATED WITH RESPECT TO XYREM PREPARATION, DOSING AND SCHEDULING.
☐ I UNDERSTAND THAT XYREM IS APPROVED FOR THE TREATMENT OF CATAPLEXY IN PATIENTS WITH NARCOLEPSY, AND THAT SAFETY OR EFFICACY HAS NOT BEEN ESTABLISHED FOR ANY OTHER INDICATION.
☐ I UNDERSTAND THAT THE SAFETY OF DOSES GREATER THAN 9gm/DAY HAS NOT BEEN ESTABLISHED

PATIENT INFORMATION

BEST TIME TO CONTACT PATIENT: ☐ DAY ☐ NIGHT
DAY #: ..... EVENING #: .....
INSURANCE COMPANY NAME: ..... PHONE #: .....
INSURED'S NAME: ..... RELATIONSHIP TO PATIENT: .....
IDENTIFICATION NUMBER: ..... POLICY/GROUP NUMBER: .....
PRESCRIPTION CARD: ☐ NO ☐ YES IF YES, CARRIER: ..... POLICY #: ..... GROUP: .....

PLEASE ATTACH COPIES OF PATIENT'S INSURANCE CARDS

FAX COMPLETED FORM TO XYREM SUCCESS PROGRAM (TOLL-FREE) 1-866-470-1744
FOR INFORMATION, CALL THE XYREM TEAM (TOLL FREE) AT 1-866-XYREM88 (1-866-997-3688)

FIG. 9

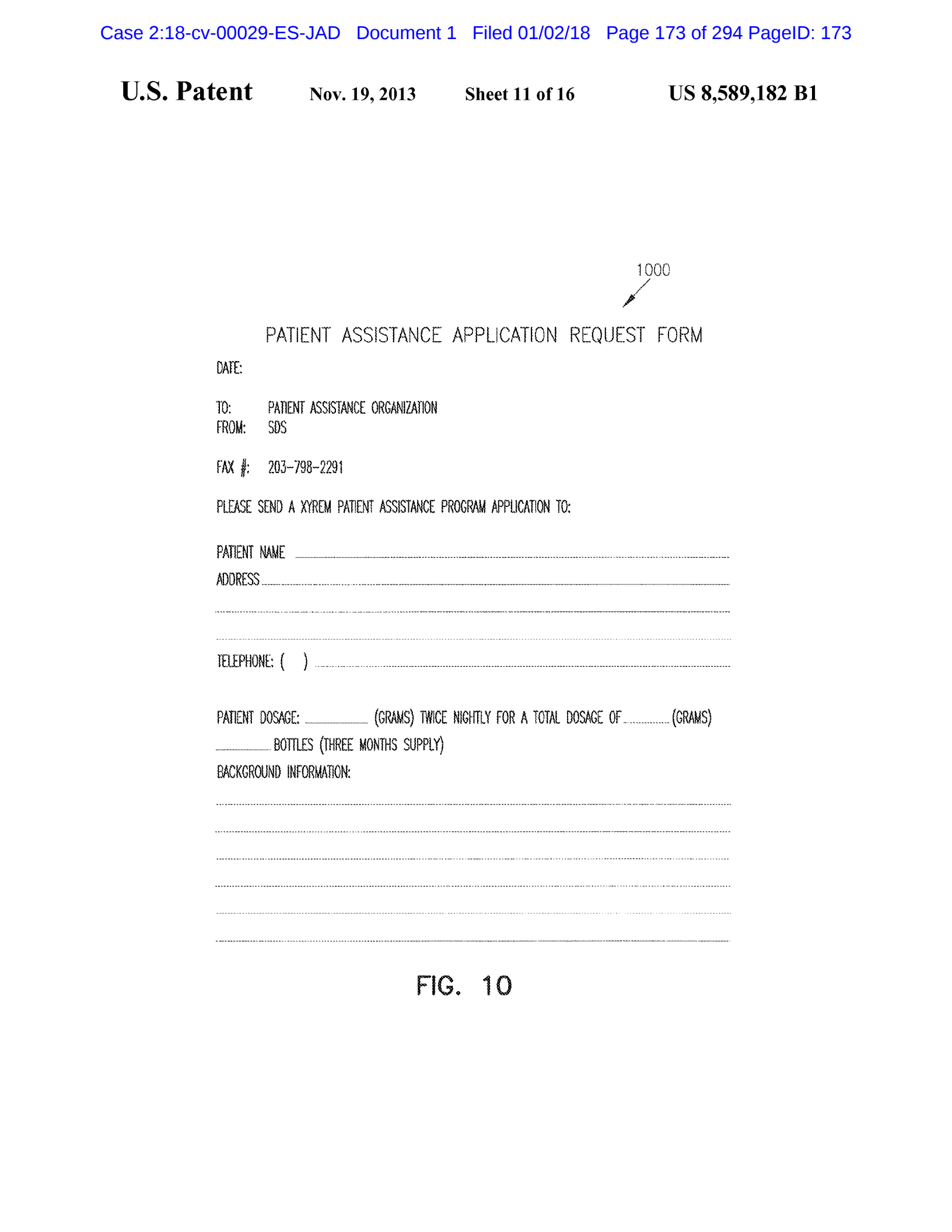
1000
PATIENT ASSISTANCE APPLICATION REQUEST FORM
DATE:
TO: PATIENT ASSISTANCE ORGANIZATION
FROM: SDS
FAX #: 203-798-2291
PLEASE SEND A XYREM PATIENT ASSISTANCE PROGRAM APPLICATION TO:
PATIENT NAME
ADDRESS
TELEPHONE: ( )
PATIENT DOSAGE: (GRAMS) TWICE NIGHTLY FOR A TOTAL DOSAGE OF (GRAMS)
BOTTLES (THREE MONTHS SUPPLY)
BACKGROUND INFORMATION:

FIG. 10

SENSITIVE DRUG PATIENT ASSISTANCE PROGRAM 1100

VOUCHER REQUEST FOR MEDICATION

PATIENT INFORMATION
<FIRST NAME><LAST NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890
DOB: 01/01/1900
SSN: 123-45-6789
DRUG ALLOTMENT: 100%
LRD: 03/01/2001

CASE CODE: ********

PHYSICIAN INFORMATION
<PHYSICIAN NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890

FIRST SHIPMENT THIS YEAR

DRUG	QUANTITY
XYREEM 180ml btl	1

VALIDATION DATE: 03/01/2001
EXPIRATION DATE: 05/31/2001
ISSUE DATE: 03/15/2001

APPROVED _____

PHARMACY USE

NORD COPY

****

(DETACH HERE)

PATIENT INFORMATION
<FIRST NAME><LAST NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890
DOB: 01/01/1900
SSN: 123-45-6789
DRUG ALLOTMENT: 100%
LRD: 03/01/2001

CASE CODE: ********

PHYSICIAN INFORMATION
<PHYSICIAN NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890

FIRST SHIPMENT THIS YEAR

DRUG	QUANTITY
XYREM 180ml btl	1

VALIDATION DATE: 03/01/2001
EXPIRATION DATE: 05/31/2001
ISSUE DATE: 03/15/2001

APPROVED _____

PHARMACY USE

FIG. 11

SENSITIVE DRUG PHYSICIAN'S CERTIFICATE
OF MEDICAL NEED

PATIENT INFORMATION

DATE: .....

NAME: .....
LAST FIRST M

DATE OF BIRTH: .....

DRUG BEING PRESCRIBED: XYREM

DIAGNOSIS/CONDITION FOR WHICH DRUG IS BEING PRESCRIBED: .....

ICD-9: .....

PHYSICIAN INFORMATION

PHYSICIAN'S NAME (PLEASE PRINT): .....

PHYSICIAN'S SIGNATURE: ..... DATE: .....

PLEASE FAX BACK TO SENSITIVE DRUG SUCCESS PROGRAM: (1-800-TOLL FREE NUMBER)

FIG. 12

ACTIVITY REPORTS

	REPORT FREQUENCY		
	WEEKLY	MONTHLY	QUARTERLY
SALES			
Rx BY ZIP (NEW AND TOTAL)	X	X	X
Rx BY PHYSICIAN BY ZIP	X	X	
$ BY ZIP	X	X	X
REGULATORY			
# OF PHYSICIAN REGISTRIES		X	
# OF DENIED PHYSICIAN REGISTRIES AND REASON		X	
# OF COMPLETED PATIENT REGISTRIES		X	
# OF PROBLEM IDENTIFICATION & MANAGEMENT RISK DIVERSION REPORTS COMPLETED	X		
# OF CYCLE COUNTS PERFORMED & ACCURACY OF EACH		X	
QUALITY ASSURANCE			
# OF PRODUCT DEFECTS/COMPLAINTS REPORTED, TYPE AND LOT #		X	
CALL CENTER			
# OF CALLS RECEIVED		X	
# OF CALLS INITIATED		X	
# OF CALLS ANSWERED IN 30 SECONDS, ETC.		X	
PERCENTAGE OF CALLS ANSWERED IN 30 SECONDS		X	
# OF ABANDONED CALLS		X	
% OF ABANDONED CALLS		X	
AVERAGE CALL LENGTH		X	
PHARMACY			
# OF FAXED Rx/ENROLLMENT FORMS		X	
# OF MAILED Rx/ENROLLEMENT FORMS		X	
# OF RxS SHIPPED W/IN 1, 2, 3, 4 ETC. DAYS (FROM THE TIME INITIAL RECEIPT TO SHIPMENT OF Rx)		X	
# OF PATIENT SUCCESS PACKETS SHIPPED		X	

FIG. 13A

ACTIVITY REPORTS

PHARMACY		X	
# OF PHYSICIAN SUCCESS PACKETS SHIPPED		X	
# OF COMPLETED SHIPMENTS		X	
# OF INCOMPLETE SHIPMENTS AND REASON		X	
# OF SHIPPING ERRORS		X	
# OF PAP SHIPMENTS		X	
# OF PAP APPLICATIONS		X	
# OF PAP APPROVALS		X	
# OF CANCELED ORDERS		X	
# OF USPS ERRORS		X	
INVENTORY		X	
# OF RETURNED PRODUCTS AND REASON		X	
# OF OUTDATED BOTTLES OF PRODUCT		X	
INVENTORY COUNTS OF CONSIGNMENT & PRODUCTION INVENTORY		X	
# OF UNITS RECEIVED		X	
LOTS RECEIVED		X	
REIMBURSEMENT		X	
# OF PENDED AND WHY		X	
# OF APPROVALS		X	
# OF DENIALS		X	
# OF REJECTIONS		X	
PAYOR TYPES		X	

FIG. 13B

ACTIVITY REPORTS

PATIENT CARE		X	
# OF ADVERSE EVENTS REPORTED AND TYPE		X	
# OF ADVERSE EVENTS SENT TO OMI		X	
# OF DOSING PROBLEMS AND TYPE		X	
# OF NONCOMPLIANCE EPISODES AND REASON		X	
# OF PATIENT COUNSELED AND REASON		X	
# OF PATIENTS DISCONTINUED AND REASON		X	
PATIENT CARE		X	
# OF PATIENTS REFERRED TO PHYSICIAN AND REASON		X	
# OF ACTIVE PATIENTS		X	
# OF NEW PATIENTS		X	
# OF RESTART PATIENTS		X	
# OF DISCONTINUED PATIENTS AND REASON		X	
DRUG INFORMATION		X	
# OF DRUG INFORMATION REQUESTS AND TYPE		X	
# OF CALLS TRIAGED TO OMI		X	

FIG. 13C

SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

RELATED APPLICATION

This application is a Continuation of U.S. Serial Application No. 13/013,680, filed on Jan. 25, 2011, which is a Continuation of U.S. application Ser. No. 12/704,097, filed on Feb. 11, 2010 and issued on Feb. 22, 2011 as U.S. Pat. No. 7,895,059, which is a Continuation of U.S. application Ser. No. 10/322,348, filed on Dec. 17, 2002 and issued on Feb. 23, 2010 as U.S. Pat. No. 7,668,730, which applications are incorporated by reference herein in their entirety.

FIELD OF THE INVENTION

The present invention relates to distribution of drugs, and in particular to the distribution of sensitive drugs.

BACKGROUND OF THE INVENTION

Sensitive drugs are controlled to minimize risk and ensure that they are not abused, or cause adverse reactions. Such sensitive drugs are approved for specific uses by the Food and Drug Administration, and must be prescribed by a licensed physician in order to be purchased by consumers. Some drugs, such as cocaine and other common street drugs are the object of abuse and illegal schemes to distribute for profit. Some schemes include Dr. shopping, diversion, and pharmacy thefts. A locked cabinet or safe is a requirement for distribution of some drugs.

Certain agents, such as gamma hydroxy buterate (GHB) are also abused, yet also are effective for therapeutic purposes such as treatment of daytime cataplexy in patients with narcolepsy. Some patients however, will obtain prescriptions from multiple doctors, and have them filled at different pharmacies. Still further, an unscrupulous physician may actually write multiple prescriptions for a patient, or multiple patients, who use cash to pay for the drugs. These patients will then sell the drug to dealers or others for profit.

There is a need for a distribution system and method that directly addresses these abuses. There is a further need for such a system and method that provides education and limits the potential for such abuse.

SUMMARY OF THE INVENTION

A drug distribution system and method utilizes a central pharmacy and database to track all prescriptions for a sensitive drug. Information is kept in a central database regarding all physicians allowed to prescribe the sensitive drug, and all patients receiving the drug. Abuses are identified by monitoring data in the database for prescription patterns by physicians and prescriptions obtained by patients. Further verification is made that the physician is eligible to prescribe the drug by consulting a separate database for a valid DEA license, and optionally state medical boards to determine whether any corrective or approved disciplinary actions relating to controlled substances have been brought against the physician. Multiple controls beyond those for traditional drugs are imposed on the distribution depending on the sensitivity of the drug.

Education is provided to both physician and patient. Prior to shipping the drug for the first time, the patient is contacted to ensure that product and abuse related educational materials have been received and/or read. The patient may provide the name of a designee to the central pharmacy who is authorized

to accept shipment of the drug. Receipt of the initial drug shipment is confirmed by contacting the patient. Either a phone call or other communication to the patient within a set time after delivery may be made to ensure receipt. Further, a courier service's tracking system is used to confirm delivery in further embodiments. If a shipment is lost, an investigation is launched to find it.

In one embodiment, the drug may be shipped by the central pharmacy to another pharmacy for patient pick-up. The second pharmacy's ability to protect against diversion before shipping the drug must be confirmed. This ability may be checked through NTIS and State Boards of Pharmacy.

Prescription refills are permitted in the number specified in the original prescription. In addition, if a prescription refill is requested by the patient prior to the anticipated due date, such refills will be questioned. A lost, stolen, destroyed or spilled prescription/supply is documented and replaced to the extent necessary to honor the prescription, and will also cause a review or full investigation.

The exclusive central database contains all relevant data related to distribution of the drug and process of distributing it, including patient, physician and prescription information. Several queries and reports are run against the database to provide information which might reveal potential abuse of the sensitive drug, such as early refills.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a block diagram of a computer system for use in implementing the system and method of the present invention.

FIGS. **2**A, **2**B and **2**C are a flowchart describing a method for sensitive drug distribution at least partially utilizing a computer system such as that shown in FIG. **1**.

FIG. **3** is a flowchart of a physician success program at least partially implemented on a computer system such as that shown in FIG. **1**.

FIGS. **4**A and **4**B are a flowchart describing a method for handling refill requests at least partially utilizing a computer system such as that shown in FIG. **1**.

FIG. **5** is a flowchart of a process for requesting special reimbursement when a patient is uninsured or underinsured at least partially utilizing a computer system as that shown in FIG. **1**.

FIG. **6** is a flowchart of a process for inventory control at least partially utilizing a computer system such as that shown in FIG. **1**.

FIG. **7** is a block diagram of database fields.

FIG. **8** is a block diagram showing a list of queries against the database fields.

FIG. **9** is a copy of one example prescription and enrollment form.

FIG. **10** is a copy of one example of a NORD application request form for patient financial assistance.

FIG. **11** is a copy of one example voucher request for medication for use with the NORD application request form of FIG. **10**.

FIG. **12** is a copy of certificate of medical need.

FIGS. **13**A, **13**B and **13**C are descriptions of sample reports obtained by querying a central database having fields represented in FIG. **7**.

DETAILED DESCRIPTION OF THE INVENTION

In the following description, reference is made to the accompanying drawings that form a part hereof, and in which is shown by way of illustration specific embodiments in

which the invention may be practiced. These embodiments are described in sufficient detail to enable those skilled in the art to practice the invention, and it is to be understood that other embodiments may be utilized and that structural, logical and electrical changes may be made without departing from the scope of the present invention. The following description is, therefore, not to be taken in a limited sense, and the scope of the present invention is defined by the appended claims.

The functions or algorithms described herein are implemented in software or a combination of software and human implemented procedures in one embodiment.

The software comprises computer executable instructions stored on computer readable media such as memory or other type of storage devices. The term "computer readable media" is also used to represent carrier waves on which the software is transmitted. Further, such functions correspond to modules, which are software, hardware, firmware of any combination thereof. Multiple functions are performed in one or more modules as desired, and the embodiments described are merely examples. The software is executed on a digital signal processor, ASIC, microprocessor, or other type of processor operating on a computer system, such as a personal computer, server or other computer system.

A sensitive drug is one which can be abused, or has addiction properties or other properties that render the drug sensitive. One example of such a drug is sodium oxybate, also known as gamma hydroxy butyrate (GHB $C_4H_7NaO_3$) which is useful for treatment of cataplexy in patients with narcolepsy. GHB is marketed under the trademark of Xyrem® (sodium oxybate oral solution), which trademark can be used interchangeably with GHB herein. Sensitive drugs also include narcotics or other drugs which require controls on their distribution and use to monitor behaviors to prevent abuse and adverse side effects.

In one embodiment, Xyrem® is subject to a restricted distribution program. One aspect of the program is to educate physicians and patients about the risks and benefits of Xyrem, including support via ongoing contact with patients and a toll free helpline. Initial prescriptions are filled only after a prescriber and patient have received and read the educational materials. Further, patient and prescribing physician registries are maintained and monitored to ensure proper distribution.

In a further embodiment, bulk sodium oxybate is manufactured at a single site, as is the finished drug product. Following manufacture of the drug product, it is stored at a facility compliant with FDA Schedule III regulations, where a consignment inventory is maintained. The inventory is owned by a company, and is managed by a central pharmacy, which maintains the consignment inventory. Xyrem® is distributed and dispensed through a primary and exclusive central pharmacy, and is not stocked in retail pharmacy outlets. It is distributed by overnight carriers, or by US mail in one embodiment to potentially invoke mail fraud laws if attempts of abuse occur.

FIG. **1** is a simplified block diagram of a computer system **100**, such as a personal computer for implementing at least a portion of the methods described herein. A central processing unit (CPU) **110** executes computer programs stored on a memory **120**. Memory **120** in one embodiment comprises one or more levels of cache as desired to speed execution of the program and access to data on which the programs operate. The CPU is directly coupled to memory **120** in one embodiment. Both CPU **110** and memory **120** are coupled to a bus **130**. A storage **140**, I/O **150** and communications **160** are also coupled to the bus **130**. Storage **140** is usually a long term storage device, such as a disk drive, tape drive, DVD, CD or other type of storage device. In one embodiment, storage **140** is used to house a database for use with the present invention. I/O **150** comprises keyboards, sound devices, displays and other mechanisms by which a user interacts with the computer system **100**. Communications **160** comprises a network, phone connection, local area network, wide area network or other mechanism for communicating with external devices. Such external devices comprise servers, other peer computers and other devices. In one embodiment, such external device comprises a database server that is used in place of the database on storage **140**. Other computer system architectures capable of executing software and interacting with a database and users may also be used. Appropriate security measures such as encryption are used to ensure confidentiality. Further, data integrity and backup measures are also used to prevent data loss.

FIGS. **2**A, **2**B and **2**C represent an initial prescription order entry process for a sensitive drug, such as Xyrem. At **202**, a medical doctor (MD) sends a Rx/enrollment form via mail, fax, email or other means to an intake/reimbursement specialist at **204**, who makes a copy of the RX/enrollment form that is stamped "copy". The original fax is forwarded to a pharmacy team. The enrollment form contains prescriber information, prescription information, checkboxes for the prescriber indicating they have read materials, educated the patient, understand the use in treatment, and understand certain safety information, and also contains patient information.

The prescriber information contains standard contact information as well as license number, DEA number and physician specialty. Patient and prescription information includes name, social security number, date of birth, gender, contact information, drug identification, patient's appropriate dosage, and number of refills allowed, along with a line for the prescriber's signature. Patient insurance information is also provided.

There are two workflows involved at the pharmacy team, intake reimbursement **206** and pharmacy workflow **208**, which may proceed in parallel or serially. The intake work flow **206** starts with an intake reimbursement specialist entering the patient and physician information into an application/database referred to as CHIPS, which is used to maintain a record of a client home infusion program (CHIP) for Xyrem®. A check is made to ensure the information is complete at **212**. If not, at **214**, an intake representative attempts to reach the MD or prescriber to obtain the missing information. If the missing information has not been obtained within a predetermined period of time, such as 24 hours at **216**, the Rx/Enrollment form is sent back to the MD with a rejection explanation. A note is entered in CHIPS that the application was rejected.

If the information is complete at **212**, the MD is contacted at **220** to verify receipt and accuracy of the patient's Rx. This contact is recorded in CHIPS. The intake and reimbursement specialist then sends a consent form and a cover letter to the patient at **224**. The insurance provider is contacted at **226** to verify coverage and benefits. At **228**, a determination is made regarding coverage for the drug. If it is not available, it is determined at **230** whether the patient is willing and able to pay. If not, a process is performed for handling patients who are uninsured or underinsured. In one embodiment, the process is referred to as a NORD process.

If the patient is willing and able to pay at **230**, the patient is informed of the cost of the product and is given payment options at **234**. At **236**, once payment is received, the intake reimbursement specialist submits a coverage approval form with the enrollment form to the pharmacy team as notification to process the patient's prescription. If coverage is approved

at **228**, the intake reimbursement specialist also submits the coverage approval form with the enrollment form to the pharmacy team as notification to process the patient's prescription. Processing of the prescription is described below.

Upon receipt and initial processing of the prescription enrollment form and sending an original to the pharmacy work flow block **208**, the patient is shipped a Xyrem® success packet via mail. In one embodiment, the Xyrem® success packet contains educational material for a patient that advises of the proper use, care and handling of the drug and consequences of diversion at **268**. The medical doctor's credentials are checked to determine if the physician has a current DEA license to prescribe controlled substances and if he or she has had any actions related to misuse/misprescribing of controlled drugs against him or her, within a predetermined time, such as three months at **270**. If they have, a pharmacist holds the prescription until receiving a coverage approval form from the intake reimbursement specialist at **272**.

If the credentials have not been recently checked, the pharmacist verifies the credentials and enters all findings in the database at **274**. If the credentials are approved at **276**, the physician is indicated as approved in a physician screen populated by information from the database at **280**. The prescription is then held pending coverage approval at **282**.

If any disciplinary actions are identified, as referenced at block **278**, management of the pharmacy is notified and either approves processing of the prescription with continued monitoring of the physician, or processing of the prescription is not performed, and the physician is noted in the database as unapproved at **284**. The enrollment form is then mailed back to the physician with a cover letter reiterating that the prescription cannot be processed at **288**. The patient is also sent a letter at **290** indicating that the prescription cannot be processed and the patient is instructed to contact their physician.

Actual filling of the approved prescription begins with receipt of the coverage approval form as indicated at **240**. The patient is contacted by the pharmacy, such as by a technician to complete a technician section of a patient counseling checklist. If a pharmacist verifies that the program materials were not read at **242**, the receipt of the material is confirmed at **244** and another call is scheduled to counsel the patient before the drug is shipped.

If the program materials, were read at **242**, the checklist is completed at **246** and the technician transfers the patient to the pharmacist who reviews the entire checklist and completes remaining pharmacist specified sections. At **248**, the pharmacists indicates in the database that the patient counseling and checklist was successfully completed, indicating the date completed.

At **250**, the pharmacist schedules the patient's shipment for the next business day or the next business day that the patient or designee is able to sign for the package. Further, as indicated at **252**, the shipment must be sent to the patient's home address unless the patient is traveling or has moved. In that event, the pharmacist may determine that an exception may be made. The patient or the patient's designee who is at least 18 years old, must sign for the package upon delivery.

At **254**, the pharmacist enters the prescription order in the database, creating an order number. The pharmacist then verifies at **256** the prescription and attaches a verification label to the hard copy prescription. At **258**, a pick ticket is generated for the order and the order is forwarded to the pharmacy for fulfillment. The shipment is confirmed in the database at **260**, and the order is shipped by USPS Express Mail. Use of the US mail invokes certain criminal penalties for unauthorized diversion. Optionally, other mail services may be used. Potential changes in the law may also bring criminal penalties into play. Following shipment, the patient is called by the central pharmacy to confirm that the prescription was received.

As noted at **266**, for the sensitive drug, Xyrem, all inventory is cycle counted and reconciled with the database system quantities before shipments for the day are sent. This provides a very precise control of the inventory.

A physician success program materials request process begins at **310** in FIG. **3**. At **320**, the MD calls to the central pharmacy to request program materials. A special phone number is provided. MD demographics, DEA number, and data or request are entered into the database at **330**. At **340**, a request is made to ship the materials to the MD via a fulfillment website, or other mechanism. The request process ends at **350**.

A refill request process begins at **302** in FIGS. **4**A and **4**B. There are two different paths for refills. A first path beginning at **404** involves generating a report from the central database of patients with a predetermined number of days or product remaining A second path beginning at **406** is followed when a patient calls to request an early refill.

In the first path, a copy of the report is provided to an intake reimbursement specialist at **408**. No sooner than 8 days before the medication depletion, a pharmacy technician contacts the patient at **410** to complete the pre-delivery checklist. At **412**, if the patient is not reached, a message is left mentioning the depletion, and a return number at **414**. A note is also entered into the database indicating the date the message was left at **416**.

If the patient is reached at **412**, the next shipment is scheduled at **418**, the prescription is entered into the database creating an order at **420**, the pharmacist verifies the prescription and attaches a verification label at **422** and the shipment is confirmed in the database at **424**. Note at **426** that the inventory is cycle counted and reconciled with the database quantities before the shipments for a day or other time period are sent. A pick ticket is generated for the order and the order is forwarded for fulfillment at **428**, with the first path ending at **430**.

The second path, beginning at **406** results in a note code being entered into the database on a patient screen indicating an early refill request at **432**. The pharmacist evaluates the patient's compliance with therapy or possible product diversion, misuse or over-use at **436**. In one embodiment, cash payers are also identified. The pharmacist then contacts the prescribing physician to alert them of the situation and confirm if the physician approves of the early refill at **438**. If the physician does not approve as indicated at **440**, the patient must wait until the next scheduled refill date to receive additional product as indicated at **442**, and the process ends at **444**.

If the physician approves at **440**, the pharmacist enters a note in the database on a patient screen that the physician approves the request at **446**. The pharmacist notifies an intake reimbursement specialist to contact the patient's insurance provider to verify coverage for the early refill at **448**. If the insurance provider will pay as determined at **450**, the specialist submits the coverage approval form as notification that the refill may be processed at **452**. At **454**, the pharmacy technician contacts the patient to schedule shipment of the product for the next business day, and the process of filling the order is continued at **456** by following the process beginning at **240**.

If the insurance provider will not pay at **450**, it is determined whether the patient is willing and/or able to pay at **458**. If not, the patient must wait until the next scheduled refill date to receive additional product at **460**. If it was determined at **458** that the patient was willing and able to pay, the patient is informed of the cost of the product and is given payment

options at **462**. Once payment is received as indicated at **464**, the specialist submits a coverage approval form to the pharmacy team as notification that the refill request can be processed at **466**. At **468**, the pharmacy technician contacts the patient to schedule shipment. The process of filling the order is continued at **470** by following the process beginning at **240**.

A process, referred to as a NORD process in one embodiment is used to determine whether donated, third party funds are available for paying for prescriptions where neither insurance will, nor the patient can pay. The process begins at **510** upon determining that a patient is uninsured or underinsured. A reimbursement specialist explains the NORD program to the patient and faxes an application request form to NORD for the patient. At **515**, the intake reimbursement specialist documents in the database that an application has been received through NORD. At **520**, NORD mails an application to the patient within one business day.

A determination is made at **525** by NORD whether the patient is approved. If not, at **530**, NORD sends a denial letter to the patient, and it is documented in the database at **540** that the patient was denied by NORD. If the patient is approved, NORD sends an acceptance letter to the patient and faxes a voucher to the central pharmacy (SDS in one embodiment) to indicate the approval at **545**. At **550**, an intake reimbursement specialist submits a coverage approval form to the pharmacy team as notification that the patient has been approved for coverage. The process of filling the order is continued at **555** by following the process beginning at **240**.

An inventory control process is illustrated in FIG. **6** beginning at **610**. Each week, a responsible person at the central pharmacy, such as the director of the pharmacy transfers inventory for the week's shipments to a segregated warehouse location for production inventory. At **620**, a purchase order is generated for the inventory transferred to the production location and is sent, such as by fax, to a controller, such as the controller of the company that obtained approval for distribution and use of the sensitive drug. At **630**, the controller invoices the central pharmacy for the product moved to production. The process ends at **640**.

The central database described above is a relational database running on the system of FIG. **1**, or a server based system having a similar architecture coupled to workstations via a network, as represented by communications **160**. The database is likely stored in storage **140**, and contains multiple fields of information as indicated at **700** in FIG. **7**. The organization and groupings of the fields are shown in one format for convenience. It is recognized that many different organizations or schemas may be utilized. In one embodiment, the groups of fields comprise prescriber fields **710**, patient fields **720**, prescription fields **730** and insurance fields **740**. For purposes of illustration, all the entries described with respect to the above processes are included in the fields. In further embodiments, no such groupings are made, and the data is organized in a different manner.

Several queries are illustrated at **800** in FIG. **8**. There may be many other queries as required by individual state reporting requirements. A first query at **810** is used to identify prescriptions written by physician. The queries may be written in structured query language, natural query languages or in any other manner compatible with the database. A second query **820** is used to pull information from the database related to prescriptions by patient name. A third query **830** is used to determine prescriptions by frequency, and a n^{th} query finds prescriptions by dose at **840**. Using query languages combined with the depth of data in the central database allows many other methods of investigating for potential abuse of the drugs. The central database ensures that all prescriptions, prescribers and patients are tracked and subject to such investigations. In further embodiments, the central database may be distributed among multiple computers provided a query operates over all data relating to such prescriptions, prescribers and patients for the drug.

An example of one prescription and enrollment form is shown at **900** in FIG. **9**. As previously indicated, several fields are included for prescriber information, prescription information and patient information.

FIG. **10** is a copy of one example NORD application request form **1000** used to request that an application be sent to a patient for financial assistance.

FIG. **11** is a copy of one example application **1100** for financial assistance as requested by form **1000**. The form requires both patient and physician information. Social security number information is also requested. The form provides information for approving the financial assistance and for tracking assistance provided.

FIG. **12** is a copy of one example voucher request for medication for use with the NORD application request form of FIG. **10**. In addition to patient and physician information, prescription information and diagnosis information is also provided.

FIGS. **13**A, **13**B and **13**C are descriptions of sample reports obtained by querying a central database having fields represented in FIG. **7**. The activities grouped by sales, regulatory, quality assurance, call center, pharmacy, inventory, reimbursement, patient care and drug information. Each report has an associated frequency or frequencies. The reports are obtained by running queries against the database, with the queries written in one of many query languages.

While the invention has been described with respect to a Schedule III drug, it is useful for other sensitive drugs that are DEA or Federally scheduled drugs in Schedule II-V, as well as still other sensitive drugs where multiple controls are desired for distribution and use.

The invention claimed is:

1. A method of treatment of a narcoleptic patient with a prescription drug that has a potential for misuse, abuse or diversion, wherein the prescription drug is sold or distributed by a company that obtained approval for distribution of the prescription drug, comprising:

receiving, using a computer processor, into a single computer database of the company that obtained approval for distribution of the prescription drug, from any and all patients being prescribed the company's prescription drug, all prescriptions for the company's prescription drug with the potential for abuse, misuse or diversion;

entering, using the computer processor, into the single computer database information sufficient to identify the narcoleptic patient for whom the company's prescription drug is prescribed;

entering, using the computer processor, into the single computer database information sufficient to identify any and all physicians or other prescribers of the company's prescription drug and information to show that the physicians or other prescribers are authorized to prescribe the company's prescription drug;

entering and maintaining, using the computer processor, in the single computer database information that indicates that the narcoleptic patient or prescriber has abused, misused, or diverted the company's prescription drug; and

checking for abuse, using the computer processor and the single computer database, and authorizing filling of the prescriptions for the company's prescription drug only if there is no record of incidents that indicate abuse, mis-

use, or diversion by the narcoleptic patient and prescriber, and if there is a record of such incidents, the single computer database indicates that such incidents have been investigated, and the single computer database indicates that such incidents do not involve abuse, misuse or diversion.

2. The method of claim **1**, comprising delivering the prescription drug to the narcoleptic patient in order to treat the narcoleptic patient with the prescription drug.

3. The method of claim **1**, wherein a pharmacy enters data into the single computer database.

4. The method of claim **1**, comprising selectively blocking shipment of the prescription drug to the narcoleptic patient.

5. The method of claim **1**, wherein an abuse pattern is associated with the narcoleptic patient, and shipment of the prescription drug is blocked based upon such association.

6. The method of claim **1**, wherein the prescription drug comprises a gamma hydroxy butyrate (GHB) drug product.

7. The method of claim **6**, wherein said GHB drug product treats cataplexy in said narcoleptic patient.

8. A method of treatment of a narcoleptic patient with a prescription drug that has the potential for misuse, abuse or diversion, wherein the prescription drug is sold or distributed by a company that obtained approval for distribution of the prescription drug, comprising:

receiving, using a computer processor, into a single computer database of the company that obtained approval for distribution of the prescription drug, from any and all patients being prescribed the company's prescription drug, all prescriptions for a prescription drug with the potential for abuse, misuse or diversion sold or distributed under a single trademark;

entering, using the computer processor, into the single computer database information sufficient to identify the narcoleptic patient for whom said prescription drug was prescribed;

entering, using the computer processor, into the single computer database information sufficient to identify any and all physicians or other prescribers of said prescription drug and information to show that the any and all physicians or other prescribers were authorized to prescribe said prescription drug;

entering and maintaining, using the computer processor, in the single database information which may suggest that the narcoleptic patient or prescriber has abused, misused, or diverted said prescription drug;

checking for abuse, using the computer processor and the single computer database, and authorizing filling of the prescriptions for said prescription drug only if there is no record of incidents that may suggest abuse, misuse, or diversion by the narcoleptic patient and prescriber, and if there is a record of such incidents, the single computer database indicates that such incidents have been investigated, and the single computer database indicates that such incidents do not involve abuse, misuse or diversion.

9. The method of claim **8**, comprising delivering the prescription drug to the narcoleptic patient in order to treat the narcoleptic patient with the prescription drug.

10. The method of claim **8**, wherein a pharmacy enters data into the single computer database.

11. The method of claim **8**, comprising selectively blocking shipment of the prescription drug to the narcoleptic patient.

12. The method of claim **8**, wherein an abuse pattern is associated with the patient, and shipment of the prescription drug is blocked based upon such association.

13. The method of claim **8**, wherein the prescription drug comprises a gamma hydroxy butyrate (GHB) drug product.

14. The method of claim **13**, wherein said GHB drug product treats cataplexy in said narcoleptic patient.

15. A method of treatment of a narcoleptic patient with a prescription drug that has the potential for misuse, abuse or diversion, wherein the prescription drug is sold or distributed by a company that obtained approval for distribution of the prescription drug, comprising:

receiving, using a computer processor, into a single computer database of the company that obtained approval for distribution of the prescription drug, all prescriptions for the prescription drug from any and all patients being prescribed the company's prescription drug, wherein the company's prescription drug has been manufactured at a single manufacturing site, and wherein the company's prescription drug has the potential for abuse, misuse or diversion;

entering, using the computer processor, into the single database information sufficient to identify the narcoleptic patient for whom the company's prescription drug was prescribed,

entering, using the computer processor, into the single database information sufficient to identify the physician or other prescriber of the company's prescription drug and information to show that the physician or other prescriber was authorized to prescribe the company's prescription drug;

entering and maintaining, using the computer processor, in the single database information which may suggest that the narcoleptic patient or prescriber has abused, misused, or diverted the company's prescription drug;

checking for abuse, using the computer processor and the single computer database, and authorizing filling of the prescription for the company's prescription drug only if there is no record of incidents that may suggest abuse, misuse, or diversion by the narcoleptic patient and prescriber and if there is a record of such incidents, the single computer database indicates that any such incidents have been investigated and found not to involve abuse, misuse or diversion; and

providing the company's prescription drug to the narcoleptic patient in order to treat the narcoleptic patient with the company's prescription drug;

wherein the company's prescription drug that has the potential for misuse, abuse or diversion is a gamma hydroxybutyrate (GHB) drug product; and

wherein said GHB drug product treats cataplexy in said narcoleptic patient.

16. The method of claim **15**, wherein a pharmacy enters data into the single computer database.

17. The method of claim **15**, comprising selectively blocking shipment of the prescription drug to the narcoleptic patient.

18. The method of claim **15**, wherein an abuse pattern is associated with the patient, and shipment of the prescription drug is blocked based upon such association.

19. A method of treatment of a narcoleptic patient with a single prescription drug that has a potential for misuse, abuse or diversion, comprising:

receiving, using a computer processor, into a single computer database and storing in a computer memory all prescriptions for the single prescription drug received at a pharmacy and sold or distributed by a company that obtained approval for distribution of the prescription drug, the single prescription drug having the potential for abuse, misuse or diversion, wherein the pharmacy is

permitted to distribute the single prescription drug based on two or more of the following: processing of a prescription enrollment form for the single prescription drug; agreeing to document adverse events relating to the single prescription drug; providing educational materials relating to the single prescription drug; and verifying that the single prescription drug is medically necessary;

entering, using the computer processor, into the single computer database information sufficient to identify the narcoleptic patient for whom the company's prescription drug is prescribed;

entering, using the computer processor, into the single computer database information sufficient to identify a physician or other prescriber of the company's prescription drug and information to show that the physician or other prescriber is authorized to prescribe the company's prescription drug, including verifying that the prescriber's drug enforcement agency (DEA) number and state license are current and that there are no pending disciplinary actions against the prescriber;

verifying two or more of the following using the computer processor prior to providing the single prescription drug to the narcoleptic patient: patient name; patient address; that the patient has received educational material regarding the single prescription drug; a quantity of the single prescription drug; and dosing directions for the single prescription drug;

entering and maintaining, using the computer processor, in the single computer database information that indicates that the narcoleptic patient or prescriber has abused, misused, or diverted the company's single prescription drug; and

checking for abuse, using the computer processor and the single computer database, and authorizing filling of the prescriptions for the company's single prescription drug only if there is no record of incidents that indicate abuse, misuse, or diversion by the narcoleptic patient and prescriber, and if there is a record of such incidents, the single computer database indicates that such incidents have been investigated, and the single computer database indicates that such incidents do not involve abuse, misuse or diversion.

20. The method of claim **19**, comprising delivering the prescription drug to the narcoleptic patient in order to treat the narcoleptic patient with the prescription drug.

21. The method of claim **19**, wherein a pharmacy enters data into the single computer database.

22. The method of claim **19**, comprising selectively blocking shipment of the prescription drug to the narcoleptic patient.

23. The method of claim **19**, wherein an abuse pattern is associated with the narcoleptic patient, and shipment of the single prescription drug is blocked based upon such association.

24. The method of claim **19**, wherein the single prescription drug comprises a gamma hydroxy butyrate (GHB) drug product.

25. The method of claim **19**, wherein said GHB drug product treats cataplexy in said narcoleptic patient.

26. The method of claim **1**, comprising identifying, using the computer processor, information relating to the prescriptions and the information relating to the narcoleptic patient, and using the information for reconciling inventory for the company's prescription drug before shipments for a day or other time period are sent.

* * * * *

EXHIBIT G

US008731963B1

(12) **United States Patent**
Reardan et al.

(10) **Patent No.: US 8,731,963 B1**
(45) **Date of Patent: *May 20, 2014**

(54) **SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/592,202**

(22) Filed: **Aug. 22, 2012**

Related U.S. Application Data

(63) Continuation of application No. 13/013,680, filed on Jan. 25, 2011, now abandoned, which is a continuation of application No. 12/704,097, filed on Feb. 11, 2010, now Pat. No. 7,895,059, which is a continuation of application No. 10/322,348, filed on Dec. 17, 2002, now Pat. No. 7,668,730.

(51) **Int. Cl.**
G06Q 10/00 (2012.01)

(52) **U.S. Cl.**
USPC **705/2**; 705/3; 707/803

(58) **Field of Classification Search**
USPC 707/803; 705/2, 3
See application file for complete search history.

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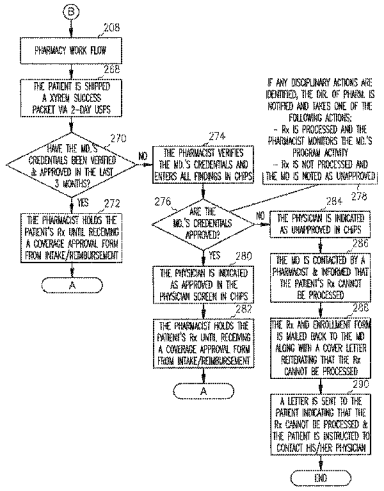
(57) **ABSTRACT**

A drug distribution system and method utilizes a central pharmacy and database to track all prescriptions for a sensitive drug. Information is kept in the database regarding all physicians allowed to prescribe the sensitive drug, and all patients receiving the drug. Abuses are identified by monitoring data in the database for prescription patterns by physicians and prescriptions obtained by patients. Further verification is made that the physician is eligible to prescribe the drug by consulting a separate database, and optionally whether any actions are taken against the physician. Multiple controls beyond those for normal drugs are imposed on the distribution depending on the sensitivity of the drug.

28 Claims, 16 Drawing Sheets



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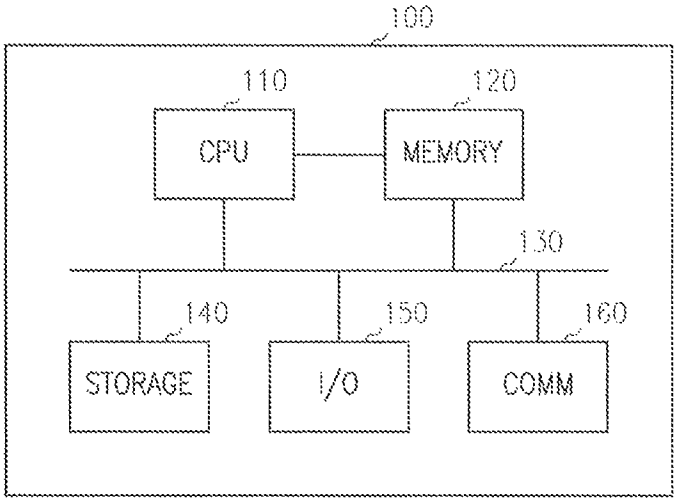

FIG. 1

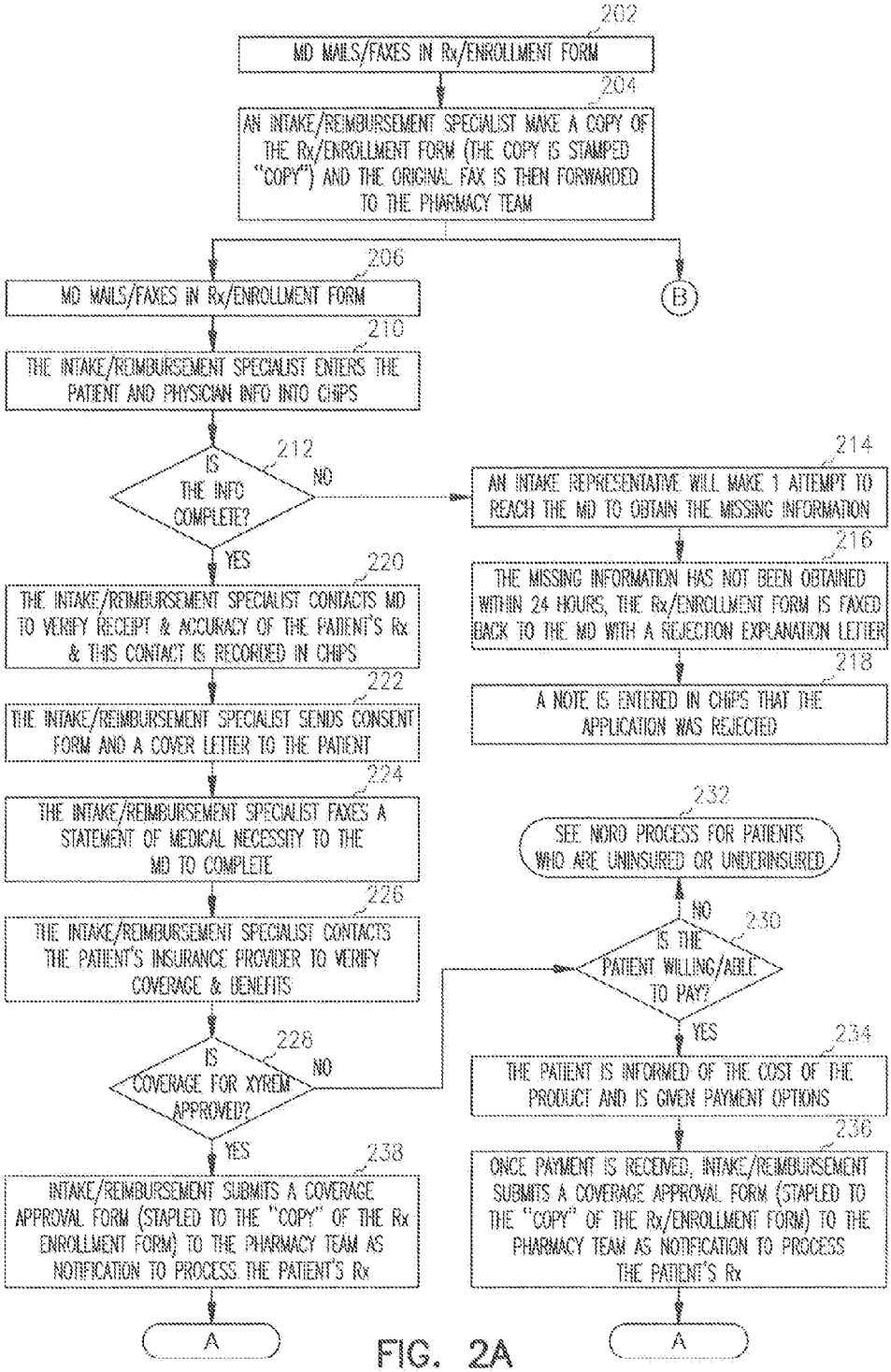
202
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
204
AN INTAKE/REIMBURSEMENT SPECIALIST MAKE A COPY OF THE Rx/ENROLLMENT FORM (THE COPY IS STAMPED "COPY") AND THE ORIGINAL FAX IS THEN FORWARDED TO THE PHARMACY TEAM
206
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
B
210
THE INTAKE/REIMBURSEMENT SPECIALIST ENTERS THE PATIENT AND PHYSICIAN INFO INTO CHIPS
212
IS THE INFO COMPLETE?
NO
YES
214
AN INTAKE REPRESENTATIVE WILL MAKE 1 ATTEMPT TO REACH THE MD TO OBTAIN THE MISSING INFORMATION
216
THE MISSING INFORMATION HAS NOT BEEN OBTAINED WITHIN 24 HOURS, THE Rx/ENROLLMENT FORM IS FAXED BACK TO THE MD WITH A REJECTION EXPLANATION LETTER
218
A NOTE IS ENTERED IN CHIPS THAT THE APPLICATION WAS REJECTED
220
THE INTAKE/REIMBURSEMENT SPECIALIST CONTACTS MD TO VERIFY RECEIPT & ACCURACY OF THE PATIENT'S Rx & THIS CONTACT IS RECORDED IN CHIPS
222
THE INTAKE/REIMBURSEMENT SPECIALIST SENDS CONSENT FORM AND A COVER LETTER TO THE PATIENT
224
THE INTAKE/REIMBURSEMENT SPECIALIST FAXES A STATEMENT OF MEDICAL NECESSITY TO THE MD TO COMPLETE
226
THE INTAKE/REIMBURSEMENT SPECIALIST CONTACTS THE PATIENT'S INSURANCE PROVIDER TO VERIFY COVERAGE & BENEFITS
228
IS COVERAGE FOR XYREM APPROVED?
NO
YES
238
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM (STAPLED TO THE "COPY" OF THE Rx ENROLLMENT FORM) TO THE PHARMACY TEAM AS NOTIFICATION TO PROCESS THE PATIENT'S Rx
A
232
SEE NORD PROCESS FOR PATIENTS WHO ARE UNINSURED OR UNDERINSURED
NO
230
IS THE PATIENT WILLING/ABLE TO PAY?
YES
234
THE PATIENT IS INFORMED OF THE COST OF THE PRODUCT AND IS GIVEN PAYMENT OPTIONS
236
ONCE PAYMENT IS RECEIVED, INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM (STAPLED TO THE "COPY" OF THE Rx/ENROLLMENT FORM) TO THE PHARMACY TEAM AS NOTIFICATION TO PROCESS THE PATIENT'S Rx
A

FIG. 2A

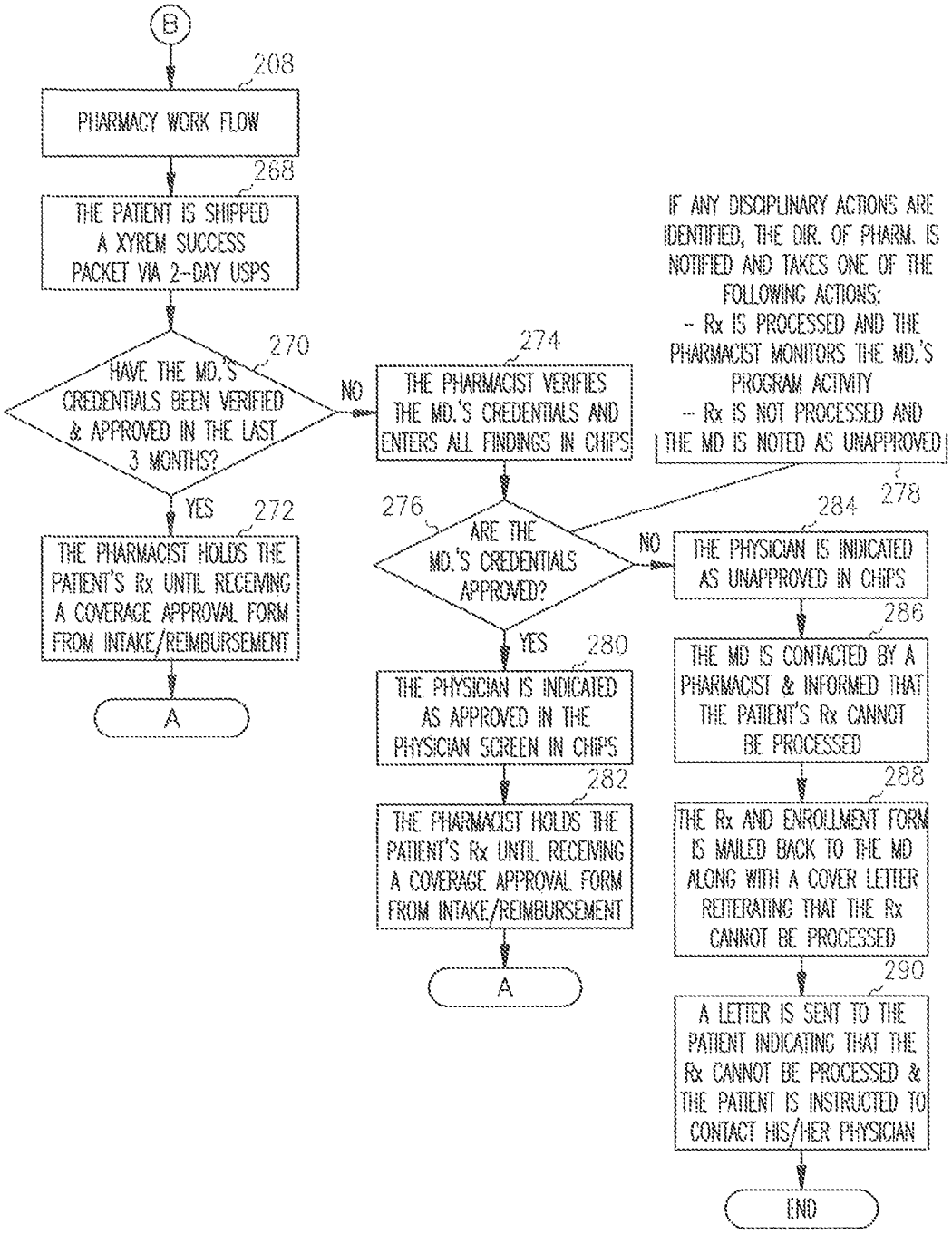
B
208
PHARMACY WORK FLOW
268
THE PATIENT IS SHIPPED A XYREM SUCCESS PACKET VIA 2-DAY USPS
270
HAVE THE MD.'S CREDENTIALS BEEN VERIFIED & APPROVED IN THE LAST 3 MONTHS?
NO
YES
272
THE PHARMACIST HOLDS THE PATIENT'S Rx UNTIL RECEIVING A COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT
A
274
THE PHARMACIST VERIFIES THE MD.'S CREDENTIALS AND ENTERS ALL FINDINGS IN CHIPS
276
ARE THE MD.'S CREDENTIALS APPROVED?
NO
YES
280
THE PHYSICIAN IS INDICATED AS APPROVED IN THE PHYSICIAN SCREEN IN CHIPS
282
THE PHARMACIST HOLDS THE PATIENT'S Rx UNTIL RECEIVING A COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT
A
IF ANY DISCIPLINARY ACTIONS ARE IDENTIFIED, THE DIR. OF PHARM. IS NOTIFIED AND TAKES ONE OF THE FOLLOWING ACTIONS:
- Rx IS PROCESSED AND THE PHARMACIST MONITORS THE MD.'S PROGRAM ACTIVITY
- Rx IS NOT PROCESSED AND THE MD IS NOTED AS UNAPPROVED
278
284
THE PHYSICIAN IS INDICATED AS UNAPPROVED IN CHIPS
286
THE MD IS CONTACTED BY A PHARMACIST & INFORMED THAT THE PATIENT'S Rx CANNOT BE PROCESSED
288
THE Rx AND ENROLLMENT FORM IS MAILED BACK TO THE MD ALONG WITH A COVER LETTER REITERATING THAT THE Rx CANNOT BE PROCESSED
290
A LETTER IS SENT TO THE PATIENT INDICATING THAT THE Rx CANNOT BE PROCESSED & THE PATIENT IS INSTRUCTED TO CONTACT HIS/HER PHYSICIAN
END

FIG. 2B

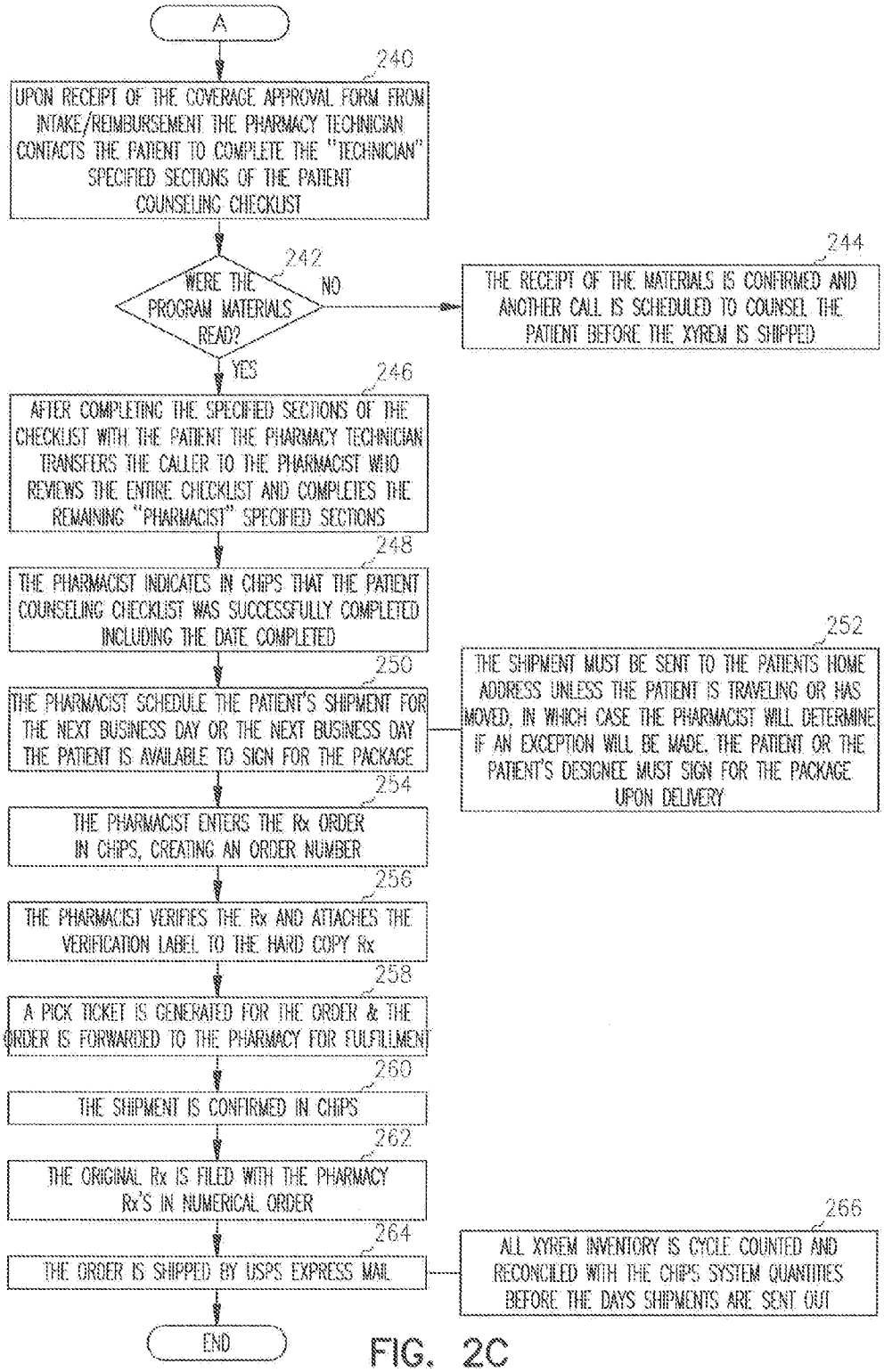
A
240
UPON RECEIPT OF THE COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE THE "TECHNICIAN" SPECIFIED SECTIONS OF THE PATIENT COUNSELING CHECKLIST
242
WERE THE PROGRAM MATERIALS READ?
NO
244
THE RECEIPT OF THE MATERIALS IS CONFIRMED AND ANOTHER CALL IS SCHEDULED TO COUNSEL THE PATIENT BEFORE THE XYREM IS SHIPPED
YES
246
AFTER COMPLETING THE SPECIFIED SECTIONS OF THE CHECKLIST WITH THE PATIENT THE PHARMACY TECHNICIAN TRANSFERS THE CALLER TO THE PHARMACIST WHO REVIEWS THE ENTIRE CHECKLIST AND COMPLETES THE REMAINING "PHARMACIST" SPECIFIED SECTIONS
248
THE PHARMACIST INDICATES IN CHIPS THAT THE PATIENT COUNSELING CHECKLIST WAS SUCCESSFULLY COMPLETED INCLUDING THE DATE COMPLETED
252
THE SHIPMENT MUST BE SENT TO THE PATIENTS HOME ADDRESS UNLESS THE PATIENT IS TRAVELING OR HAS MOVED, IN WHICH CASE THE PHARMACIST WILL DETERMINE IF AN EXCEPTION WILL BE MADE. THE PATIENT OR THE PATIENT'S DESIGNEE MUST SIGN FOR THE PACKAGE UPON DELIVERY
250
THE PHARMACIST SCHEDULE THE PATIENT'S SHIPMENT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
254
THE PHARMACIST ENTERS THE Rx ORDER IN CHIPS, CREATING AN ORDER NUMBER
256
THE PHARMACIST VERIFIES THE Rx AND ATTACHES THE VERIFICATION LABEL TO THE HARD COPY Rx
258
A PICK TICKET IS GENERATED FOR THE ORDER & THE ORDER IS FORWARDED TO THE PHARMACY FOR FULFILLMENT
260
THE SHIPMENT IS CONFIRMED IN CHIPS
262
THE ORIGINAL Rx IS FILED WITH THE PHARMACY Rx'S IN NUMERICAL ORDER
266
ALL XYREM INVENTORY IS CYCLE COUNTED AND RECONCILED WITH THE CHIPS SYSTEM QUANTITIES BEFORE THE DAYS SHIPMENTS ARE SENT OUT
264
THE ORDER IS SHIPPED BY USPS EXPRESS MAIL
END

FIG. 2C

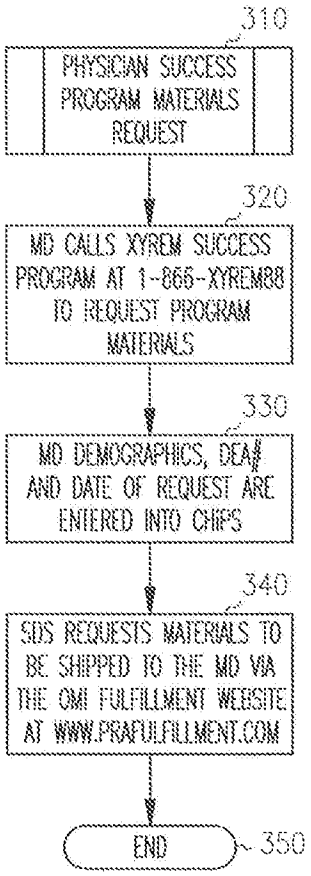
310
PHYSICIAN SUCCESS PROGRAM MATERIALS REQUEST
320
MD CALLS XYREM SUCCESS PROGRAM AT 1-866-XYREM88 TO REQUEST PROGRAM MATERIALS
330
MD DEMOGRAPHICS, DEA# AND DATE OF REQUEST ARE ENTERED INTO CHPS
340
SDS REQUESTS MATERIALS TO BE SHIPPED TO THE MD VIA THE OMI FULFILLMENT WEBSITE AT WWW.PRAFULFILLMENT.COM
END
350

FIG. 3

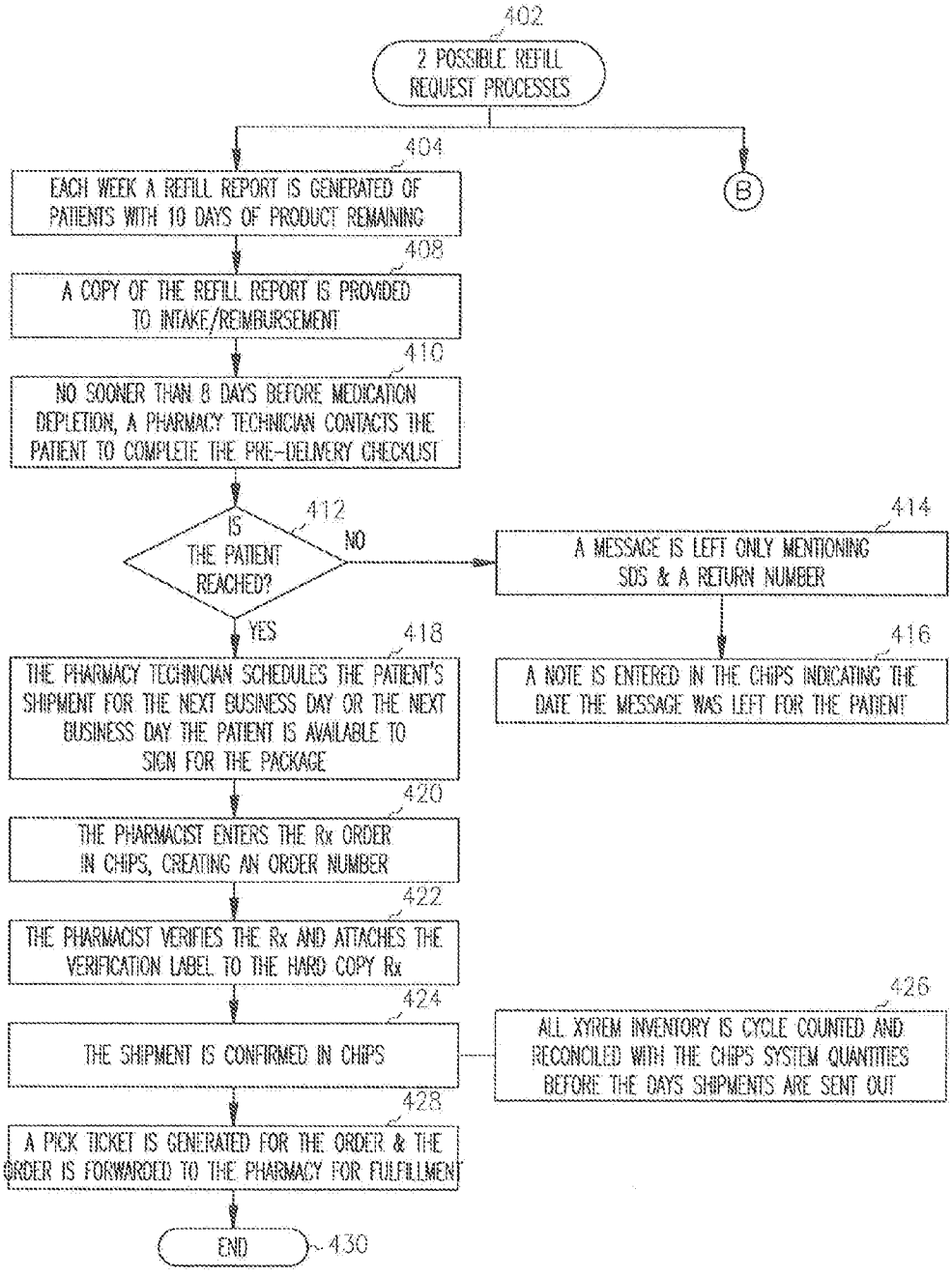
402
2 POSSIBLE REFILL REQUEST PROCESSES
404
EACH WEEK A REFILL REPORT IS GENERATED OF PATIENTS WITH 10 DAYS OF PRODUCT REMAINING
B
408
A COPY OF THE REFILL REPORT IS PROVIDED TO INTAKE/REIMBURSEMENT
410
NO SOONER THAN 8 DAYS BEFORE MEDICATION DEPLETION, A PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE THE PRE-DELIVERY CHECKLIST
412
IS THE PATIENT REACHED?
NO
414
A MESSAGE IS LEFT ONLY MENTIONING SDS & A RETURN NUMBER
YES
418
THE PHARMACY TECHNICIAN SCHEDULES THE PATIENT'S SHIPMENT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
416
A NOTE IS ENTERED IN THE CHIPS INDICATING THE DATE THE MESSAGE WAS LEFT FOR THE PATIENT
420
THE PHARMACIST ENTERS THE Rx ORDER IN CHIPS, CREATING AN ORDER NUMBER
422
THE PHARMACIST VERIFIES THE Rx AND ATTACHES THE VERIFICATION LABEL TO THE HARD COPY Rx
424
THE SHIPMENT IS CONFIRMED IN CHIPS
426
ALL XYREM INVENTORY IS CYCLE COUNTED AND RECONCILED WITH THE CHIPS SYSTEM QUANTITIES BEFORE THE DAYS SHIPMENTS ARE SENT OUT
428
A PICK TICKET IS GENERATED FOR THE ORDER & THE ORDER IS FORWARDED TO THE PHARMACY FOR FULFILLMENT
END
430

FIG. 4A

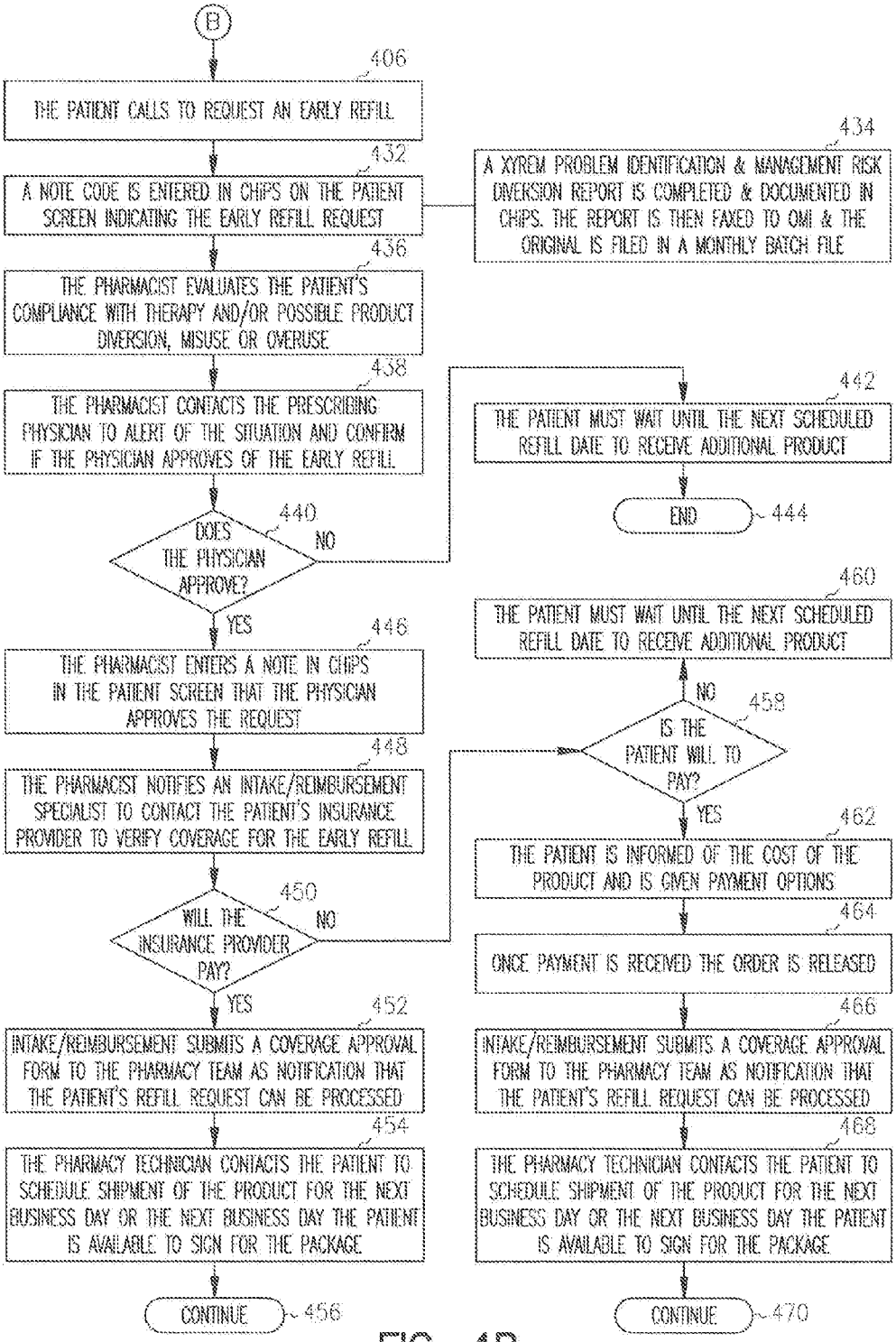
B
406
THE PATIENT CALLS TO REQUEST AN EARLY REFILL
432
A NOTE CODE IS ENTERED IN CHIPS ON THE PATIENT SCREEN INDICATING THE EARLY REFILL REQUEST
434
A XYROM PROBLEM IDENTIFICATION & MANAGEMENT RISK DIVERSION REPORT IS COMPLETED & DOCUMENTED IN CHIPS. THE REPORT IS THEN FAXED TO OMI & THE ORIGINAL IS FILED IN A MONTHLY BATCH FILE
436
THE PHARMACIST EVALUATES THE PATIENT'S COMPLIANCE WITH THERAPY AND/OR POSSIBLE PRODUCT DIVERSION, MISUSE OR OVERUSE
438
THE PHARMACIST CONTACTS THE PRESCRIBING PHYSICIAN TO ALERT OF THE SITUATION AND CONFIRM IF THE PHYSICIAN APPROVES OF THE EARLY REFILL
440
DOES THE PHYSICIAN APPROVE?
NO
YES
442
THE PATIENT MUST WAIT UNTIL THE NEXT SCHEDULED REFILL DATE TO RECEIVE ADDITIONAL PRODUCT
END
444
446
THE PHARMACIST ENTERS A NOTE IN CHIPS IN THE PATIENT SCREEN THAT THE PHYSICIAN APPROVES THE REQUEST
448
THE PHARMACIST NOTIFIES AN INTAKE/REIMBURSEMENT SPECIALIST TO CONTACT THE PATIENT'S INSURANCE PROVIDER TO VERIFY COVERAGE FOR THE EARLY REFILL
450
WILL THE INSURANCE PROVIDER PAY?
NO
YES
452
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT'S REFILL REQUEST CAN BE PROCESSED
454
THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO SCHEDULE SHIPMENT OF THE PRODUCT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
CONTINUE
456
460
THE PATIENT MUST WAIT UNTIL THE NEXT SCHEDULED REFILL DATE TO RECEIVE ADDITIONAL PRODUCT
NO
458
IS THE PATIENT WILL TO PAY?
YES
462
THE PATIENT IS INFORMED OF THE COST OF THE PRODUCT AND IS GIVEN PAYMENT OPTIONS
464
ONCE PAYMENT IS RECEIVED THE ORDER IS RELEASED
466
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT'S REFILL REQUEST CAN BE PROCESSED
468
THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO SCHEDULE SHIPMENT OF THE PRODUCT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
CONTINUE
470

FIG. 4B

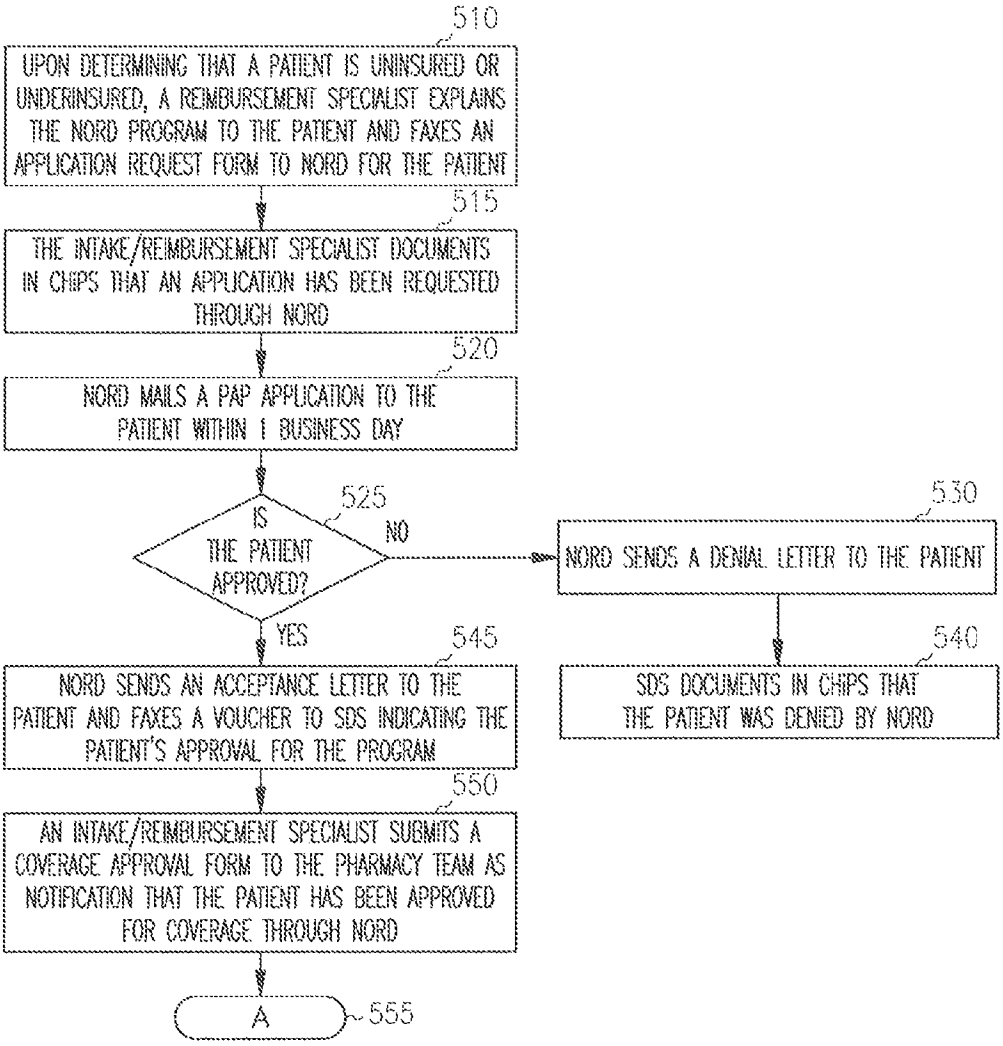
510
UPON DETERMINING THAT A PATIENT IS UNINSURED OR UNDERINSURED, A REIMBURSEMENT SPECIALIST EXPLAINS THE NORD PROGRAM TO THE PATIENT AND FAXES AN APPLICATION REQUEST FORM TO NORD FOR THE PATIENT
515
THE INTAKE/REIMBURSEMENT SPECIALIST DOCUMENTS IN CHIPS THAT AN APPLICATION HAS BEEN REQUESTED THROUGH NORD
520
NORD MAILS A PAP APPLICATION TO THE PATIENT WITHIN 1 BUSINESS DAY
525
IS THE PATIENT APPROVED?
NO
530
NORD SENDS A DENIAL LETTER TO THE PATIENT
YES
545
NORD SENDS AN ACCEPTANCE LETTER TO THE PATIENT AND FAXES A VOUCHER TO SDS INDICATING THE PATIENT'S APPROVAL FOR THE PROGRAM
540
SDS DOCUMENTS IN CHIPS THAT THE PATIENT WAS DENIED BY NORD
550
AN INTAKE/REIMBURSEMENT SPECIALIST SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT HAS BEEN APPROVED FOR COVERAGE THROUGH NORD
A
555

FIG. 5

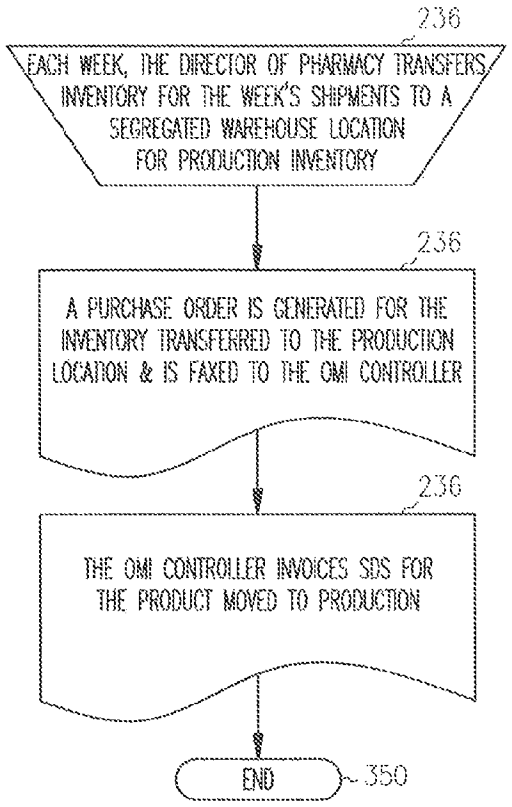

FIG. 6

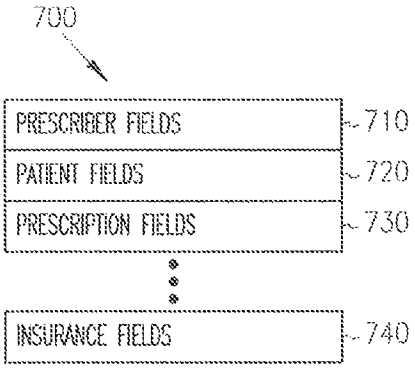

FIG. 7

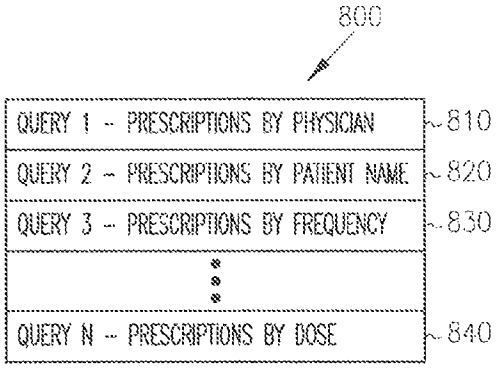

FIG. 8

900

PRESCRIPTION AND ENROLLMENT FORM

PRESCRIBER INFORMATION

PRESCRIBER'S NAME: ..... OFFICE CONTACT: .....
STREET ADDRESS: .....
CITY: ..... STATE: ..... ZIP: .....
PHONE: ..... FAX: .....
LICENSE NUMBER: ..... DEA NUMBER: .....
MD SPECIALTY: .....

PRESCRIPTION FORM

PATIENT NAME: ..... SS#: ..... DOB: ..... SEX M / F
ADDRESS: .....
CITY: ..... STATE: ..... ZIP: .....
Rx: XYREM ORAL SOLUTION (500 mg/mL) 180 ML BOTTLE QUANTITY: ..... MONTHS SUPPLY
SIG: TAKE ..... GMS P.O. DILUTED IN 60 mL WATER AT H.S. AND THEN AGAIN 2 1/2 TO 4 HOURS LATER
REFILLS (CIRCLE ONE): 0 1 2 (MAXIMUM OF 3 MONTH SUPPLY)
..... DATE: ...../...../.....
PRESCRIBER'S SIGNATURE

PHYSICIAN DECLARATION–PLEASE CHECK EACH BOX | TO BE COMPLETED AT INITIAL PRESCRIPTION ONLY

☐ I HAVE READ THE MATERIALS IN THE XYREM PHYSICIAN SUCCESS PROGRAM
☐ I VERIFY THAT THE PATIENT HAS BEEN EDUCATED WITH RESPECT TO XYREM PREPARATION, DOSING AND SCHEDULING.
☐ I UNDERSTAND THAT XYREM IS APPROVED FOR THE TREATMENT OF CATAPLEXY IN PATIENTS WITH NARCOLEPSY, AND THAT SAFETY OR EFFICACY HAS NOT BEEN ESTABLISHED FOR ANY OTHER INDICATION.
☐ I UNDERSTAND THAT THE SAFETY OF DOSES GREATER THAN 9gm/DAY HAS NOT BEEN ESTABLISHED

PATIENT INFORMATION

BEST TIME TO CONTACT PATIENT: ☐ DAY ☐ NIGHT
DAY #: ..... EVENING #: .....
INSURANCE COMPANY NAME: ..... PHONE #: .....
INSURED'S NAME: ..... RELATIONSHIP TO PATIENT: .....
IDENTIFICATION NUMBER: ..... POLICY/GROUP NUMBER: .....
PRESCRIPTION CARD: ☐ NO ☐ YES IF YES, CARRIER: ..... POLICY #: ..... GROUP: .....

PLEASE ATTACH COPIES OF PATIENT'S INSURANCE CARDS

FAX COMPLETED FORM TO XYREM SUCCESS PROGRAM (TOLL-FREE) 1-866-470-1744

FOR INFORMATION, CALL THE XYREM TEAM (TOLL FREE) AT 1-866-XYREM88 (1-866-997-3688)

FIG. 9

1000

PATIENT ASSISTANCE APPLICATION REQUEST FORM

DATE:

TO: PATIENT ASSISTANCE ORGANIZATION
FROM: SDS

FAX #: 203-798-2291

PLEASE SEND A XYREM PATIENT ASSISTANCE PROGRAM APPLICATION TO:

PATIENT NAME .....

ADDRESS .....

.....

.....

TELEPHONE: ( ) .....

PATIENT DOSAGE: _____ (GRAMS) TWICE NIGHTLY FOR A TOTAL DOSAGE OF ..... (GRAMS)

_____ BOTTLES (THREE MONTHS SUPPLY)

BACKGROUND INFORMATION:

.....

.....

.....

.....

.....

.....

FIG. 10

SENSITIVE DRUG PATIENT ASSISTANCE PROGRAM 1100

VOUCHER REQUEST FOR MEDICATION

PATIENT INFORMATION
<FIRST NAME><LAST NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890
DOB: 01/01/1900
SSN: 123-45-6789
DRUG ALLOTMENT: 100%
LRD: 03/01/2001

CASE CODE: ********

PHYSICIAN INFORMATION
<PHYSICIAN NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890

FIRST SHIPMENT THIS YEAR

DRUG	QUANTITY
XYREEM 180ml btl	1

VALIDATION DATE: 03/01/2001
EXPIRATION DATE: 05/31/2001
ISSUE DATE: 03/15/2001

APPROVED _____

PHARMACY USE

NORD COPY

****

(DETACH HERE)

PATIENT INFORMATION
<FIRST NAME><LAST NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890
DOB: 01/01/1900
SSN: 123-45-6789
DRUG ALLOTMENT: 100%
LRD: 03/01/2001

CASE CODE: ********

PHYSICIAN INFORMATION
<PHYSICIAN NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890

FIRST SHIPMENT THIS YEAR

DRUG	QUANTITY
XYREM 180ml btl	1

VALIDATION DATE: 03/01/2001
EXPIRATION DATE: 05/31/2001
ISSUE DATE: 03/15/2001

APPROVED _____

PHARMACY USE

FIG. 11

SENSITIVE DRUG PHYSICIAN'S CERTIFICATE
OF MEDICAL NEED

PATIENT INFORMATION

DATE: .....

NAME: .....
LAST FIRST M

DATE OF BIRTH: .....

DRUG BEING PRESCRIBED: XYREM

DIAGNOSIS/CONDITION FOR WHICH DRUG IS BEING PRESCRIBED: .....

ICD-9: .....

PHYSICIAN INFORMATION

PHYSICIAN'S NAME (PLEASE PRINT): .....

PHYSICIAN'S SIGNATURE: ..... DATE: .....

PLEASE FAX BACK TO SENSITIVE DRUG SUCCESS PROGRAM: (1-800-TOLL FREE NUMBER)

FIG. 12

ACTIVITY REPORTS

	REPORT FREQUENCY		
	WEEKLY	MONTHLY	QUARTERLY
SALES			
Rx BY ZIP (NEW AND TOTAL)	X	X	X
Rx BY PHYSICIAN BY ZIP	X	X	
$ BY ZIP	X	X	X
REGULATORY			
# OF PHYSICIAN REGISTRIES		X	
# OF DENIED PHYSICIAN REGISTRIES AND REASON		X	
# OF COMPLETED PATIENT REGISTRIES		X	
# OF PROBLEM IDENTIFICATION & MANAGEMENT RISK DIVERSION REPORTS COMPLETED	X		
# OF CYCLE COUNTS PERFORMED & ACCURACY OF EACH		X	
QUALITY ASSURANCE			
# OF PRODUCT DEFECTS/COMPLAINTS REPORTED, TYPE AND LOT #		X	
CALL CENTER			
# OF CALLS RECEIVED		X	
# OF CALLS INITIATED		X	
# OF CALLS ANSWERED IN 30 SECONDS, ETC.		X	
PERCENTAGE OF CALLS ANSWERED IN 30 SECONDS		X	
# OF ABANDONED CALLS		X	
% OF ABANDONED CALLS		X	
AVERAGE CALL LENGTH		X	
PHARMACY			
# OF FAXED Rx/ENROLLMENT FORMS		X	
# OF MAILED Rx/ENROLLMENT FORMS		X	
# OF RxS SHIPPED WITH 1, 2, 3, 4 ETC. DAYS (FROM THE TIME INITIAL RECEIPT TO SHIPMENT OF Rx)		X	
# OF PATIENT SUCCESS PACKETS SHIPPED		X	

FIG. 13A

ACTIVITY REPORTS

PHARMACY		X	
# OF PHYSICIAN SUCCESS PACKETS SHIPPED		X	
# OF COMPLETED SHIPMENTS		X	
# OF INCOMPLETE SHIPMENTS AND REASON		X	
# OF SHIPPING ERRORS		X	
# OF PAP SHIPMENTS		X	
# OF PAP APPLICATIONS		X	
# OF PAP APPROVALS		X	
# OF CANCELED ORDERS		X	
# OF USPS ERRORS		X	
INVENTORY		X	
# OF RETURNED PRODUCTS AND REASON		X	
# OF OUTDATED BOTTLES OF PRODUCT		X	
INVENTORY COUNTS OF CONSIGNMENT & PRODUCTION INVENTORY		X	
# OF UNITS RECEIVED		X	
LOTS RECEIVED		X	
REIMBURSEMENT		X	
# OF PENDED AND WHY		X	
# OF APPROVALS		X	
# OF DENIALS		X	
# OF REJECTIONS		X	
PAYOR TYPES		X	

FIG. 13B

ACTIVITY REPORTS

PATIENT CARE			
# OF ADVERSE EVENTS REPORTED AND TYPE		X	
# OF ADVERSE EVENTS SENT TO OMI		X	
# OF DOSING PROBLEMS AND TYPE		X	
# OF NONCOMPLIANCE EPISODES AND REASON		X	
# OF PATIENT COUNSELED AND REASON		X	
# OF PATIENTS DISCONTINUED AND REASON		X	
PATIENT CARE		X	
# OF PATIENTS REFERRED TO PHYSICIAN AND REASON		X	
# OF ACTIVE PATIENTS		X	
# OF NEW PATIENTS		X	
# OF RESTART PATIENTS		X	
# OF DISCONTINUED PATIENTS AND REASON		X	
DRUG INFORMATION		X	
# OF DRUG INFORMATION REQUESTS AND TYPE		X	
# OF CALLS TRIAGED TO OMI		X	

FIG. 13C

SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

RELATED APPLICATION

This application a Continuation of U.S. application Ser. No. 13/013,680, filed on Jan. 25, 2011, which is a Continuation of U.S. application Ser. No. 12/704,097, filed on Feb. 11, 2010 and issued on Feb. 22, 2011 as U.S. Pat. No. 7,895,059, which is a Continuation of U.S. application Ser. No. 10/322,348, filed on Dec. 17, 2002 and issued on Feb. 23, 2010 as U.S. Pat. No. 7,668,730, which applications are incorporated by reference herein in their entirety.

FIELD OF THE INVENTION

The present invention relates to distribution of drugs, and in particular to the distribution of sensitive drugs.

BACKGROUND OF THE INVENTION

Sensitive drugs are controlled to minimize risk and ensure that they are not abused, or cause adverse reactions. Such sensitive drugs are approved for specific uses by the Food and Drug Administration, and must be prescribed by a licensed physician in order to be purchased by consumers. Some drugs, such as cocaine and other common street drugs are the object of abuse and illegal schemes to distribute for profit. Some schemes include Dr. shopping, diversion, and pharmacy thefts. A locked cabinet or safe is a requirement for distribution of some drugs.

Certain agents, such as gamma hydroxy buterate (GHB) are also abused, yet also are effective for therapeutic purposes such as treatment of daytime cataplexy in patients with narcolepsy. Some patients however, will obtain prescriptions from multiple doctors, and have them filled at different pharmacies. Still further, an unscrupulous physician may actually write multiple prescriptions for a patient, or multiple patients, who use cash to pay for the drugs. These patients will then sell the drug to dealers or others for profit.

There is a need for a distribution system and method that directly addresses these abuses. There is a further need for such a system and method that provides education and limits the potential for such abuse.

SUMMARY OF THE INVENTION

A drug distribution system and method utilizes a central pharmacy and database to track all prescriptions for a sensitive drug. Information is kept in a central database regarding all physicians allowed to prescribe the sensitive drug, and all patients receiving the drug. Abuses are identified by monitoring data in the database for prescription patterns by physicians and prescriptions obtained by patients. Further verification is made that the physician is eligible to prescribe the drug by consulting a separate database for a valid DEA license, and optionally state medical boards to determine whether any corrective or approved disciplinary actions relating to controlled substances have been brought against the physician. Multiple controls beyond those for traditional drugs are imposed on the distribution depending on the sensitivity of the drug.

Education is provided to both physician and patient. Prior to shipping the drug for the first time, the patient is contacted to ensure that product and abuse related educational materials have been received and/or read. The patient may provide the name of a designee to the central pharmacy who is authorized to accept shipment of the drug. Receipt of the initial drug shipment is confirmed by contacting the patient. Either a phone call or other communication to the patient within a set time after delivery may be made to ensure receipt. Further, a courier service's tracking system is used to confirm delivery in further embodiments. If a shipment is lost, an investigation is launched to find it.

In one embodiment, the drug may be shipped by the central pharmacy to another pharmacy for patient pick-up. The second pharmacy's ability to protect against diversion before shipping the drug must be confirmed. This ability may be checked through NTIS and State Boards of Pharmacy.

Prescription refills are permitted in the number specified in the original prescription. In addition, if a prescription refill is requested by the patient prior to the anticipated due date, such refills will be questioned. A lost, stolen, destroyed or spilled prescription/supply is documented and replaced to the extent necessary to honor the prescription, and will also cause a review or full investigation.

The exclusive central database contains all relevant data related to distribution of the drug and process of distributing it, including patient, physician and prescription information. Several queries and reports are run against the database to provide information which might reveal potential abuse of the sensitive drug, such as early refills.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a block diagram of a computer system for use in implementing the system and method of the present invention.

FIGS. **2**A, **2**B and **2**C are a flowchart describing a method for sensitive drug distribution at least partially utilizing a computer system such as that shown in FIG. **1**.

FIG. **3** is a flowchart of a physician success program at least partially implemented on a computer system such as that shown in FIG. **1**.

FIGS. **4**A and **4**B are a flowchart describing a method for handling refill requests at least partially utilizing a computer system such as that shown in FIG. **1**.

FIG. **5** is a flowchart of a process for requesting special reimbursement when a patient is uninsured or underinsured at least partially utilizing a computer system as that shown in FIG. **1**.

FIG. **6** is a flowchart of a process for inventory control at least partially utilizing a computer system such as that shown in FIG. **1**.

FIG. **7** is a block diagram of database fields.

FIG. **8** is a block diagram showing a list of queries against the database fields.

FIG. **9** is a copy of one example prescription and enrollment form.

FIG. **10** is a copy of one example of a NORD application request form for patient financial assistance.

FIG. **11** is a copy of one example voucher request for medication for use with the NORD application request form of FIG. **10**.

FIG. **12** is a copy of certificate of medical need.

FIGS. **13**A, **13**B and **13**C are descriptions of sample reports obtained by querying a central database having fields represented in FIG. **7**.

DETAILED DESCRIPTION OF THE INVENTION

In the following description, reference is made to the accompanying drawings that form a part hereof, and in which is shown by way of illustration specific embodiments in

which the invention may be practiced. These embodiments are described in sufficient detail to enable those skilled in the art to practice the invention, and it is to be understood that other embodiments may be utilized and that structural, logical and electrical changes may be made without departing from the scope of the present invention. The following description is, therefore, not to be taken in a limited sense, and the scope of the present invention is defined by the appended claims.

The functions or algorithms described herein are implemented in software or a combination of software and human implemented procedures in one embodiment. The software comprises computer executable instructions stored on computer readable media such as memory or other type of storage devices. The term "computer readable media" is also used to represent carrier waves on which the software is transmitted. Further, such functions correspond to modules, which are software, hardware, firmware of any combination thereof. Multiple functions are performed in one or more modules as desired, and the embodiments described are merely examples. The software is executed on a digital signal processor, ASIC, microprocessor, or other type of processor operating on a computer system, such as a personal computer, server or other computer system.

A sensitive drug is one which can be abused, or has addiction properties or other properties that render the drug sensitive. One example of such a drug is sodium oxybate, also known as gamma hydroxy butyrate (GHB $C_4H_7NaO_3$) which is useful for treatment of cataplexy in patients with narcolepsy. GHB is marketed under the trademark of Xyrem® (sodium oxybate oral solution), which trademark can be used interchangeably with GHB herein. Sensitive drugs also include narcotics or other drugs which require controls on their distribution and use to monitor behaviors to prevent abuse and adverse side effects.

In one embodiment, Xyrem® is subject to a restricted distribution program. One aspect of the program is to educate physicians and patients about the risks and benefits of Xyrem, including support via ongoing contact with patients and a toll free helpline. Initial prescriptions are filled only after a prescriber and patient have received and read the educational materials. Further, patient and prescribing physician registries are maintained and monitored to ensure proper distribution.

In a further embodiment, bulk sodium oxybate is manufactured at a single site, as is the finished drug product. Following manufacture of the drug product, it is stored at a facility compliant with FDA Schedule III regulations, where a consignment inventory is maintained. The inventory is owned by a company, and is managed by a central pharmacy, which maintains the consignment inventory. Xyrem® is distributed and dispensed through a primary and exclusive central pharmacy, and is not stocked in retail pharmacy outlets. It is distributed by overnight carriers, or by US mail in one embodiment to potentially invoke mail fraud laws if attempts of abuse occur.

FIG. **1** is a simplified block diagram of a computer system **100**, such as a personal computer for implementing at least a portion of the methods described herein. A central processing unit (CPU) **110** executes computer programs stored on a memory **120**. Memory **120** in one embodiment comprises one or more levels of cache as desired to speed execution of the program and access to data on which the programs operate. The CPU is directly coupled to memory **120** in one embodiment. Both CPU **110** and memory **120** are coupled to a bus **130**. A storage **140**, I/O **150** and communications **160** are also coupled to the bus **130**. Storage **140** is usually a long term storage device, such as a disk drive, tape drive, DVD, CD or other type of storage device. In one embodiment, storage **140** is used to house a database for use with the present invention. I/O **150** comprises keyboards, sound devices, displays and other mechanisms by which a user interacts with the computer system **100**. Communications **160** comprises a network, phone connection, local area network, wide area network or other mechanism for communicating with external devices. Such external devices comprise servers, other peer computers and other devices. In one embodiment, such external device comprises a database server that is used in place of the database on storage **140**. Other computer system architectures capable of executing software and interacting with a database and users may also be used. Appropriate security measures such as encryption are used to ensure confidentiality. Further, data integrity and backup measures are also used to prevent data loss.

FIGS. **2**A, **2**B and **2**C represent an initial prescription order entry process for a sensitive drug, such as Xyrem. At **202**, a medical doctor (MD) sends a Rx/enrollment form via mail, fax, email or other means to an intake/reimbursement specialist at **204**, who makes a copy of the RX/enrollment form that is stamped "copy". The original fax is forwarded to a pharmacy team. The enrollment form contains prescriber information, prescription information, checkboxes for the prescriber indicating they have read materials, educated the patient, understand the use in treatment, and understand certain safety information, and also contains patient information.

The prescriber information contains standard contact information as well as license number, DEA number and physician specialty. Patient and prescription information includes name, social security number, date of birth, gender, contact information, drug identification, patient's appropriate dosage, and number of refills allowed, along with a line for the prescriber's signature. Patient insurance information is also provided.

There are two workflows involved at the pharmacy team, intake reimbursement **206** and pharmacy workflow **208**, which may proceed in parallel or serially. The intake work flow **206** starts with an intake reimbursement specialist entering the patient and physician information into an application/database referred to as CHIPS, which is used to maintain a record of a client home infusion program (CHIP) for Xyrem®. A check is made to ensure the information is complete at **212**. If not, at **214**, an intake representative attempts to reach the MD or prescriber to obtain the missing information. If the missing information has not been obtained within a predetermined period of time, such as 24 hours at **216**, the Rx/Enrollment form is sent back to the MD with a rejection explanation. A note is entered in CHIPS that the application was rejected.

If the information is complete at **212**, the MD is contacted at **220** to verify receipt and accuracy of the patient's Rx. This contact is recorded in CHIPS. The intake and reimbursement specialist then sends a consent form and a cover letter to the patient at **224**. The insurance provider is contacted at **226** to verify coverage and benefits. At **228**, a determination is made regarding coverage for the drug. If it is not available, it is determined at **230** whether the patient is willing and able to pay. If not, a process is performed for handling patients who are uninsured or underinsured. In one embodiment, the process is referred to as a NORD process.

If the patient is willing and able to pay at **230**, the patient is informed of the cost of the product and is given payment options at **234**. At **236**, once payment is received, the intake reimbursement specialist submits a coverage approval form with the enrollment form to the pharmacy team as notification to process the patient's prescription. If coverage is approved

at **228**, the intake reimbursement specialist also submits the coverage approval form with the enrollment form to the pharmacy team as notification to process the patient's prescription. Processing of the prescription is described below.

Upon receipt and initial processing of the prescription enrollment form and sending an original to the pharmacy work flow block **208**, the patient is shipped a Xyrem® success packet via mail. In one embodiment, the Xyrem® success packet contains educational material for a patient that advises of the proper use, care and handling of the drug and consequences of diversion at **268**. The medical doctor's credentials are checked to determine if the physician has a current DEA license to prescribe controlled substances and if he or she has had any actions related to misuse/misprescribing of controlled drugs against him or her, within a predetermined time, such as three months at **270**. If they have, a pharmacist holds the prescription until receiving a coverage approval form from the intake reimbursement specialist at **272**.

If the credentials have not been recently checked, the pharmacist verifies the credentials and enters all findings in the database at **274**. If the credentials are approved at **276**, the physician is indicated as approved in a physician screen populated by information from the database at **280**. The prescription is then held pending coverage approval at **282**.

If any disciplinary actions are identified, as referenced at block **278**, management of the pharmacy is notified and either approves processing of the prescription with continued monitoring of the physician, or processing of the prescription is not performed, and the physician is noted in the database as unapproved at **284**. The enrollment form is then mailed back to the physician with a cover letter reiterating that the prescription cannot be processed at **288**. The patient is also sent a letter at **290** indicating that the prescription cannot be processed and the patient is instructed to contact their physician.

Actual filling of the approved prescription begins with receipt of the coverage approval form as indicated at **240**. The patient is contacted by the pharmacy, such as by a technician to complete a technician section of a patient counseling checklist. If a pharmacist verifies that the program materials were not read at **242**, the receipt of the material is confirmed at **244** and another call is scheduled to counsel the patient before the drug is shipped.

If the program materials, were read at **242**, the checklist is completed at **246** and the technician transfers the patient to the pharmacist who reviews the entire checklist and completes remaining pharmacist specified sections. At **248**, the pharmacists indicates in the database that the patient counseling and checklist was successfully completed, indicating the date completed.

At **250**, the pharmacist schedules the patient's shipment for the next business day or the next business day that the patient or designee is able to sign for the package. Further, as indicated at **252**, the shipment must be sent to the patient's home address unless the patient is traveling or has moved. In that event, the pharmacist may determine that an exception may be made. The patient or the patient's designee who is at least 18 years old, must sign for the package upon delivery.

At **254**, the pharmacist enters the prescription order in the database, creating an order number. The pharmacist then verifies at **256** the prescription and attaches a verification label to the hard copy prescription. At **258**, a pick ticket is generated for the order and the order is forwarded to the pharmacy for fulfillment. The shipment is confirmed in the database at **260**, and the order is shipped by USPS Express Mail. Use of the US mail invokes certain criminal penalties for unauthorized diversion. Optionally, other mail services may be used. Potential changes in the law may also bring criminal penalties into play. Following shipment, the patient is called by the central pharmacy to confirm that the prescription was received.

As noted at **266**, for the sensitive drug, Xyrem, all inventory is cycle counted and reconciled with the database system quantities before shipments for the day are sent. This provides a very precise control of the inventory.

A physician success program materials request process begins at **310** in FIG. **3**. At **320**, the MD calls to the central pharmacy to request program materials. A special phone number is provided. MD demographics, DEA number, and data or request are entered into the database at **330**. At **340**, a request is made to ship the materials to the MD via a fulfillment website, or other mechanism. The request process ends at **350**.

A refill request process begins at **302** in FIGS. **4**A and **4**B. There are two different paths for refills. A first path beginning at **404** involves generating a report from the central database of patients with a predetermined number of days or product remaining. A second path beginning at **406** is followed when a patient calls to request an early refill.

In the first path, a copy of the report is provided to an intake reimbursement specialist at **408**. No sooner than 8 days before the medication depletion, a pharmacy technician contacts the patient at **410** to complete the pre-delivery **30** checklist. At **412**, if the patient is not reached, a message is left mentioning the depletion, and a return number at **414**. A note is also entered into the database indicating the date the message was left at **416**.

If the patient is reached at **412**, the next shipment is scheduled at **418**, the prescription is entered into the database creating an order at **420**, the pharmacist verifies the prescription and attaches a verification label at **422** and the shipment is confirmed in the database at **424**. Note at **426** that the inventory is cycle counted and reconciled with the database quantities before the shipments for a day or other time period are sent. A pick ticket is generated for the order and the order is forwarded for fulfillment at **428**, with the first path ending at **430**.

The second path, beginning at **406** results in a note code being entered into the database on a patient screen indicating an early refill request at **432**. The pharmacist evaluates the patient's compliance with therapy or possible product diversion, misuse or over-use at **436**. In one embodiment, cash payers are also identified. The pharmacist then contacts the prescribing physician to alert them of the situation and confirm if the physician approves of the early refill at **438**. If the physician does not approve as indicated at **440**, the patient must wait until the next scheduled refill date to receive additional product as indicated at **442**, and the process ends at **444**.

If the physician approves at **440**, the pharmacist enters a note in the database on a patient screen that the physician approves the request at **446**. The pharmacist notifies an intake reimbursement specialist to contact the patient's insurance provider to verify coverage for the early refill at **448**. If the insurance provider will pay as determined at **450**, the specialist submits the coverage approval form as notification that the refill may be processed at **452**. At **454**, the pharmacy technician contacts the patient to schedule shipment of the product for the next business day, and the process of filling the order is continued at **456** by following the process beginning at **240**.

If the insurance provider will not pay at **450**, it is determined whether the patient is willing and/or able to pay at **458**. If not, the patient must wait until the next scheduled refill date to receive additional product at **460**. If it was determined at **458** that the patient was willing and able to pay, the patient is informed of the cost of the product and is given payment

options at **462**. Once payment is received as indicated at **464**, the specialist submits a coverage approval form to the pharmacy team as notification that the refill request can be processed at **466**. At **468**, the pharmacy technician contacts the patient to schedule shipment. The process of filling the order is continued at **470** by following the process beginning at **240**.

A process, referred to as a NORD process in one embodiment is used to determine whether donated, third party funds are available for paying for prescriptions where neither insurance will, nor the patient can pay. The process begins at **510** upon determining that a patient is uninsured or underinsured. A reimbursement specialist explains the NORD program to the patient and faxes an application request form to NORD for the patient. At **515**, the intake reimbursement specialist documents in the database that an application has been received through NORD. At **520**, NORD mails an application to the patient within one business day.

A determination is made at **525** by NORD whether the patient is approved. If not, at **530**, NORD sends a denial letter to the patient, and it is documented in the database at **540** that the patient was denied by NORD. If the patient is approved, NORD sends an acceptance letter to the patient and faxes a voucher to the central pharmacy (SDS in one embodiment) to indicate the approval at **545**. At **550**, an intake reimbursement specialist submits a coverage approval form to the pharmacy team as notification that the patient has been approved for coverage. The process of filling the order is continued at **555** by following the process beginning at **240**.

An inventory control process is illustrated in FIG. **6** beginning at **610**. Each week, a responsible person at the central pharmacy, such as the director of the pharmacy transfers inventory for the week's shipments to a segregated warehouse location for production inventory. At **620**, a purchase order is generated for the inventory transferred to the production location and is sent, such as by fax, to a controller, such as the controller of the company that obtained approval for distribution and use of the sensitive drug. At **630**, the controller invoices the central pharmacy for the product moved to production. The process ends at **640**.

The central database described above is a relational database running on the system of FIG. **1**, or a server based system having a similar architecture coupled to workstations via a network, as represented by communications **160**. The database is likely stored in storage **140**, and contains multiple fields of information as indicated at **700** in FIG. **7**. The organization and groupings of the fields are shown in one format for convenience. It is recognized that many different organizations or schemas may be utilized. In one embodiment, the groups of fields comprise prescriber fields **710**, patient fields **720**, prescription fields **730** and insurance fields **740**. For purposes of illustration, all the entries described with respect to the above processes are included in the fields. In further embodiments, no such groupings are made, and the data is organized in a different manner.

Several queries are illustrated at **800** in FIG. **8**. There may be many other queries as required by individual state reporting requirements. A first query at **810** is used to identify prescriptions written by physician. The queries may be written in structured query language, natural query languages or in any other manner compatible with the database. A second query **820** is used to pull information from the database related to prescriptions by patient name. A third query **830** is used to determine prescriptions by frequency, and a n^{th} query finds prescriptions by dose at **840**. Using query languages combined with the depth of data in the central database allows many other methods of investigating for potential abuse of the drugs. The central database ensures that all prescriptions, prescribers and patients are tracked and subject to such investigations. In further embodiments, the central database may be distributed among multiple computers provided a query operates over all data relating to such prescriptions, prescribers and patients for the drug.

An example of one prescription and enrollment form is shown at **900** in FIG. **9**. As previously indicated, several fields are included for prescriber information, prescription information and patient information.

FIG. **10** is a copy of one example NORD application request form **1000** used to request that an application be sent to a patient for financial assistance.

FIG. **11** is a copy of one example application **1100** for financial assistance as requested by form **1000**. The form requires both patient and physician information. Social security number information is also requested. The form provides information for approving the financial assistance and for tracking assistance provided.

FIG. **12** is a copy of one example voucher request for medication for use with the NORD application request form of FIG. **10**. In addition to patient and physician information, prescription information and diagnosis information is also provided.

FIGS. **13**A, **13**B and **13**C are descriptions of sample reports obtained by querying a central database having fields represented in FIG. **7**. The activities grouped by sales, regulatory, quality assurance, call center, pharmacy, inventory, reimbursement, patient care and drug information. Each report has an associated frequency or frequencies. The reports are obtained by running queries against the database, with the queries written in one of many query languages.

While the invention has been described with respect to a Schedule III drug, it is useful for other sensitive drugs that are DEA or Federally scheduled drugs in Schedule II-V, as well as still other sensitive drugs where multiple controls are desired for distribution and use.

The invention claimed is:

1. A computer-implemented system for treatment of a narcoleptic patient with a prescription drug that has a potential for misuse, abuse or diversion, comprising:

one or more computer memories for storing a single computer database having a database schema that contains and interrelates prescription fields, patient fields, and prescriber fields;

said prescription fields, contained within the database schema, storing prescriptions for the prescription drug with the potential for abuse, misuse or diversion, wherein the prescription drug is sold or distributed by a company that obtained approval for distribution of the prescription drug;

said patient fields, contained within the database schema, storing information sufficient to identify the narcoleptic patient for whom the company's prescription drug is prescribed;

said prescriber fields, contained within the database schema, storing information sufficient to identify a physician or other prescriber of the company's prescription drug and information to show that the physician or other prescriber is authorized to prescribe the company's prescription drug;

a data processor configured to:

process a database query that operates over all data related to the prescription fields, prescriber fields, and patient fields for the prescription drug; and

reconcile inventory of the prescription drug before the shipments for a day or other time period are sent by using

said database query to identify information in the prescription fields and patient fields;

wherein the data processor is configured to process a second database query that identifies that the narcoleptic patient is a cash payer and a physician that is interrelated with the narcoleptic patient through the schema of the single computer database;

said identifying that the narcoleptic patient is a cash payer by said second database query being an indicator of a potential misuse, abuse or diversion by the narcoleptic patient and being used to notify the physician that is interrelated with the narcoleptic patient through the schema of the single computer database.

2. The system of claim **1**, wherein the data processor selectively blocks shipment of the prescription drug to the patient based upon said identifying by the database query.

3. The system of claim **1**, wherein the prescription drug is shipped to the narcoleptic patient if no potential misuse, abuse or diversion is found for the narcoleptic patient.

4. The system of claim **1**, wherein the single computer database is an exclusive database that receives data associated with all patients being prescribed the prescription drug that is associated with the company.

5. The system of claim **1**, wherein an exclusive central pharmacy controls the single computer database.

6. The system of claim **1** wherein the prescription drug comprises gamma hydroxyl butyrate (GHB).

7. The system of claim **1**, wherein the single computer database comprises a relational database.

8. The system of claim **1**, wherein the single computer database is distributed among multiple computers and the database query operates over all data relating to said prescription fields, prescriber fields, and patient fields for the prescription drug.

9. The system of claim **1**, wherein the data processor is configured to initiate an inquiry to a prescriber when one or more prescription fields, patient fields, or prescriber fields are incomplete in the computer database.

10. The system of claim **1**, wherein the data processor is configured to process a third database query that identifies an expected date for a refill of the prescription drug.

11. The system of claim **10**, wherein the expected date is based on a prescription for the prescription drug and a date of a previous filling of the prescription.

12. The system of claim **11**, wherein the prescription identifies an amount of the prescription drug to be provided and a schedule for consumption of the prescription drug.

13. The system of claim **1**, wherein the database schema further contains and interrelates insurance fields, wherein the insurance fields, contained within the database schema, store information sufficient to identify an insurer to be contacted for payment for prescription drugs of an associated patient.

14. The system of claim **1**, wherein the single computer database is used to identify a current pattern or an anticipated pattern of abuse of the prescription drug; wherein the current pattern or the anticipated pattern are identified using periodic reports generated from the single computer database.

15. The system of claim **14**, wherein one or more controls for distribution of the prescription drug are selected based on the identified pattern.

16. The system of claim **15**, wherein the one or more controls are submitted to an approval body for approval of distribution of the prescription drug.

17. The system of claim **1**, wherein additional controls for distribution are selected in a negotiation with an approval body to garner the approval of distribution.

18. The system of claim **17**, wherein the data processor is used to add further controls until approval is obtained.

19. The system of claim **18**, wherein the approval body is the Food and Drug Administration (FDA) or the Drug Enforcement Agency (DEA).

20. The system of claim **1**, wherein current inventory is cycle counted and reconciled with database quantities before shipments for a day or other time period are sent.

21. The system of claim **1**, wherein the single computer database comprises an exclusive computer database of the company that obtained approval for distribution of the prescription drug, wherein all prescriptions for the company's prescription drug are stored only in the exclusive computer database of the company, and wherein the company's prescription drug is sold or distributed by the company using only the exclusive computer database of the company.

22. The system of claim **1**, wherein the single computer database comprises a single computer database of the company that obtained approval for distribution of the prescription drug, wherein the prescription fields store all prescription requests, for all patients being prescribed the company's prescription drug, only in the single computer database of the company, from all physicians or other prescribers allowed to prescribe the company's prescription drug, such that all prescriptions for the company's prescription drug are processed using only the single computer database of the company.

23. A computer-implemented system for treatment of a narcoleptic patient with a prescription drug that has a potential for misuse, abuse or diversion, comprising:

one or more computer memories for storing a single computer database having a database schema that contains and interrelates prescription fields, patient fields, and prescriber fields;

said prescription fields, contained within the database schema, storing prescriptions for the prescription drug with the potential for abuse, misuse or diversion, wherein the prescription drug is sold or distributed by a company that obtained approval for distribution of the prescription drug;

said patient fields, contained within the database schema, storing information sufficient to identify the narcoleptic patient for whom the company's prescription drug is prescribed;

said prescriber fields, contained within the database schema, storing information sufficient to identify a physician or other prescriber of the company's prescription drug and information to show that the physician or other prescriber is authorized to prescribe the company's prescription drug;

a data processor for processing a database query that operates over all data related to the prescription fields, prescriber fields, and patient fields for the prescription drug;

said database query identifying information in the prescription fields and patient fields for reconciling inventory of the prescription drug before the shipments for a day or other time period are sent, wherein an inventory reconciliation is performed where current inventory is counted and reconciled with database quantities before shipments for a day or other time period are sent, and wherein the data processor is configured to selectively block shipment of the prescription drug based on the inventory reconciliation;

wherein the data processor is configured to process a second database query that identifies that the narcoleptic patient is a cash payer and a physician that is interrelated with the narcoleptic patient through the schema of the single computer database;

said identifying that the narcoleptic patient is a cash payer by said second database query being an indicator of a potential misuse, abuse or diversion by the narcoleptic patient and being used to notify the physician that is interrelated with the narcoleptic patient through the schema of the single computer database.

24. A computer-implemented system for treatment of a narcoleptic patient with a prescription drug that has a potential for misuse, abuse or diversion, wherein the prescription drug is sold or distributed by a company that obtained approval for distribution of the prescription drug, comprising:

one or more computer memories for storing a central computer database of the company that obtained approval for distribution of the prescription drug, for receiving prescriptions from any and all patients being prescribed the company's prescription drug, said central computer database having a database schema that contains and interrelates prescription fields, patient fields, and prescriber fields;

said central computer database being distributed over multiple computers;

said prescription fields, contained within the database schema, storing prescriptions for the prescription drug with the potential for abuse, misuse or diversion;

said patient fields, contained within the database schema, storing information sufficient to identify the narcoleptic patient for whom the company's prescription drug is prescribed;

said prescriber fields, contained within the database schema, storing information sufficient to identify any and all physicians or other prescribers of the company's prescription drug and information to show that the physicians or other prescribers are authorized to prescribe the company's prescription drug;

one or more data processors for processing one or more database queries that operate over data related to the prescription fields, prescriber fields, and patient fields for the prescription drug;

said one or more database queries checking for abuse within the central computer database, wherein the filling of the prescriptions is authorized for the company's prescription drug only if there is no record of incidents that indicate abuse, misuse, or diversion by the narcoleptic patient and prescriber and if there is a record of such incidents, the central computer database indicates that such incidents have been investigated, and the central computer database indicates that such incidents do not involve abuse, misuse or diversion.

25. The system of claim **24**, wherein the one or more database queries are processed by the one or more data processors for identifying: that the narcoleptic patient is a cash payer and a physician that is interrelated with the narcoleptic patient through the schema of the single computer database;

said identifying that the narcoleptic patient is a cash payer by said second database query being an indicator of a potential misuse, abuse or diversion by the narcoleptic patient and being used to notify the physician that is interrelated with the narcoleptic patient through the schema of the single computer database.

26. The system of claim **24**, where the central computer database is distributed among multiple computers, and where the one or more database queries operate over all data relating to said prescription fields, prescriber fields, and patient fields for the prescription drug.

27. The system of claim **24**, wherein the central computer database is used to identify a current pattern or an anticipated pattern of abuse of the prescription drug;

wherein the current pattern or the anticipated pattern are identified using periodic reports generated from the single computer database.

28. The system of claim **24**, wherein current inventory is cycle counted and reconciled with database quantities before shipments for a day or other time period are sent.

* * * * *

EXHIBIT H

US008772306B1

(12) **United States Patent**
Eller

(10) **Patent No.: US 8,772,306 B1**
(45) **Date of Patent: *Jul. 8, 2014**

(54) **METHOD OF ADMINISTRATION OF GAMMA HYDROXYBUTYRATE WITH MONOCARBOXYLATE TRANSPORTERS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/872,997**

(22) Filed: **Apr. 29, 2013**

Related U.S. Application Data

(63) Continuation of application No. 13/837,714, filed on Mar. 15, 2013.

(60) Provisional application No. 61/771,557, filed on Mar. 1, 2013, provisional application No. 61/777,873, filed on Mar. 12, 2013.

(51) **Int. Cl.**

A61K 31/505	(2006.01)
A61K 31/33	(2006.01)
A61K 31/55	(2006.01)

(52) **U.S. Cl.**
USPC **514/275**; 514/183; 514/214.03

(58) **Field of Classification Search**
USPC 514/275, 183, 214.03
See application file for complete search history.

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(57) **ABSTRACT**

One embodiment of the present invention is to improve the safety and efficacy of the administration of GHB or a salt thereof to a patient. It has been discovered that the concomitant administration of an MCT inhibitor, such as diclofenac, valproate, or ibuprofen, will affect GHB administration. For example, it has been discovered that diclofenac lowers the effect of GHB in the body, thereby potentially causing an unsafe condition. Furthermore, it has been discovered that valproate increases the effect of GHB on the body, thereby potentially causing an unsafe condition.

34 Claims, 10 Drawing Sheets

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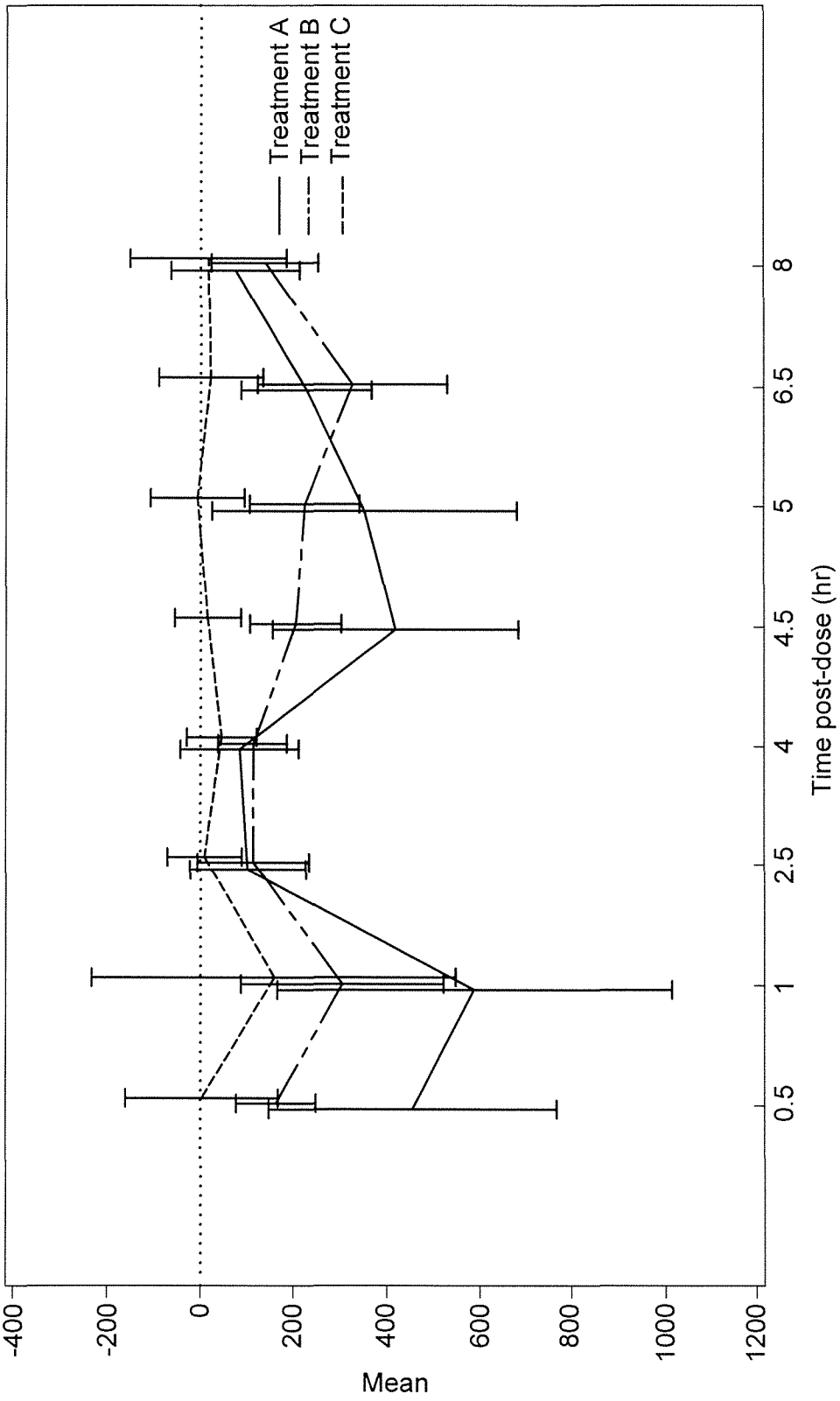
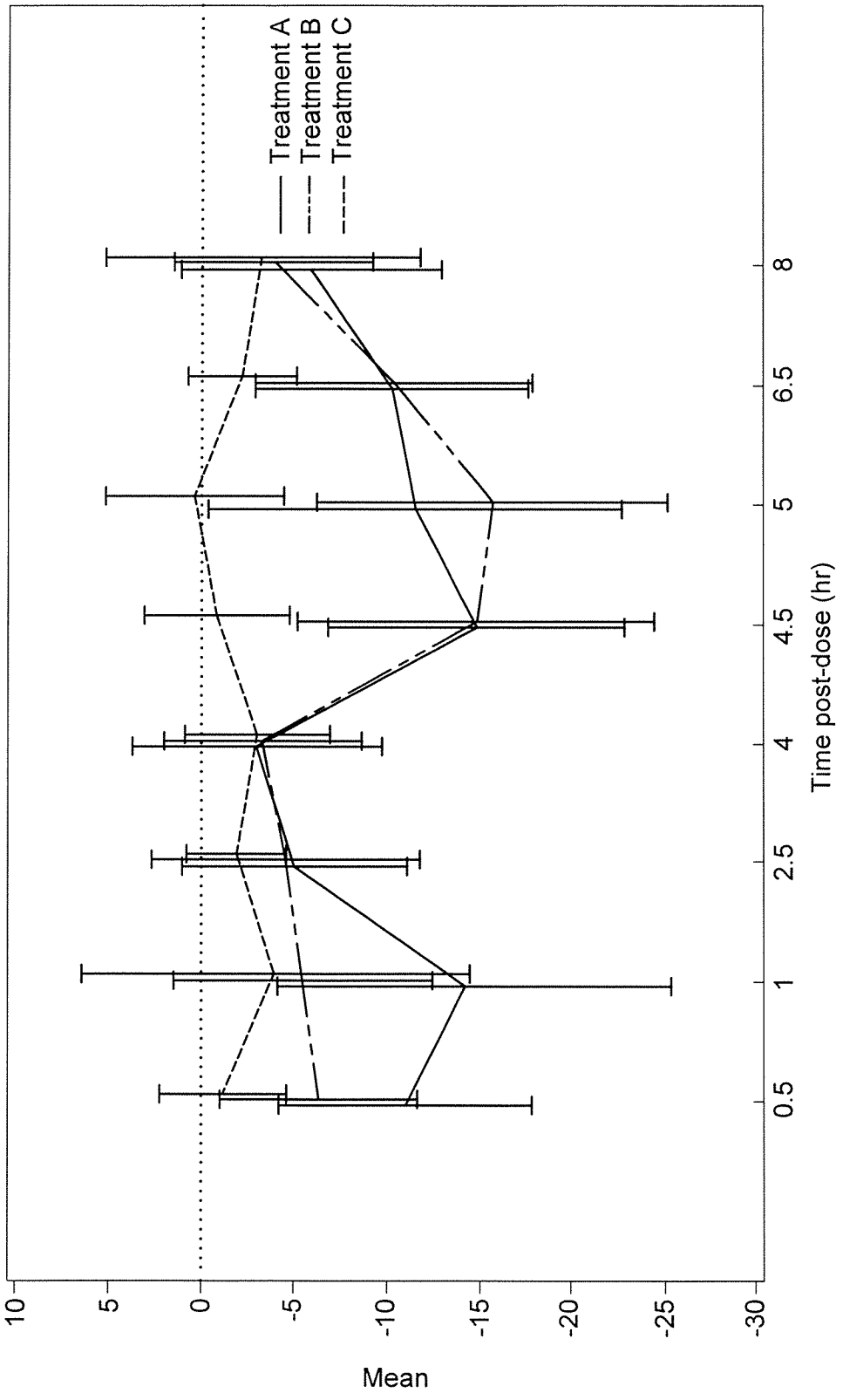

Treatment A
Treatment B
Treatment C
Mean
-400
-200
0
200
400
600
800
1000
1200
Time post-dose (hr)
0.5
1
2.5
4
4.5
5
6.5
8

FIG. 1


Treatment A
Treatment B
Treatment C
Mean
10
5
0
-5
-10
-15
-20
-25
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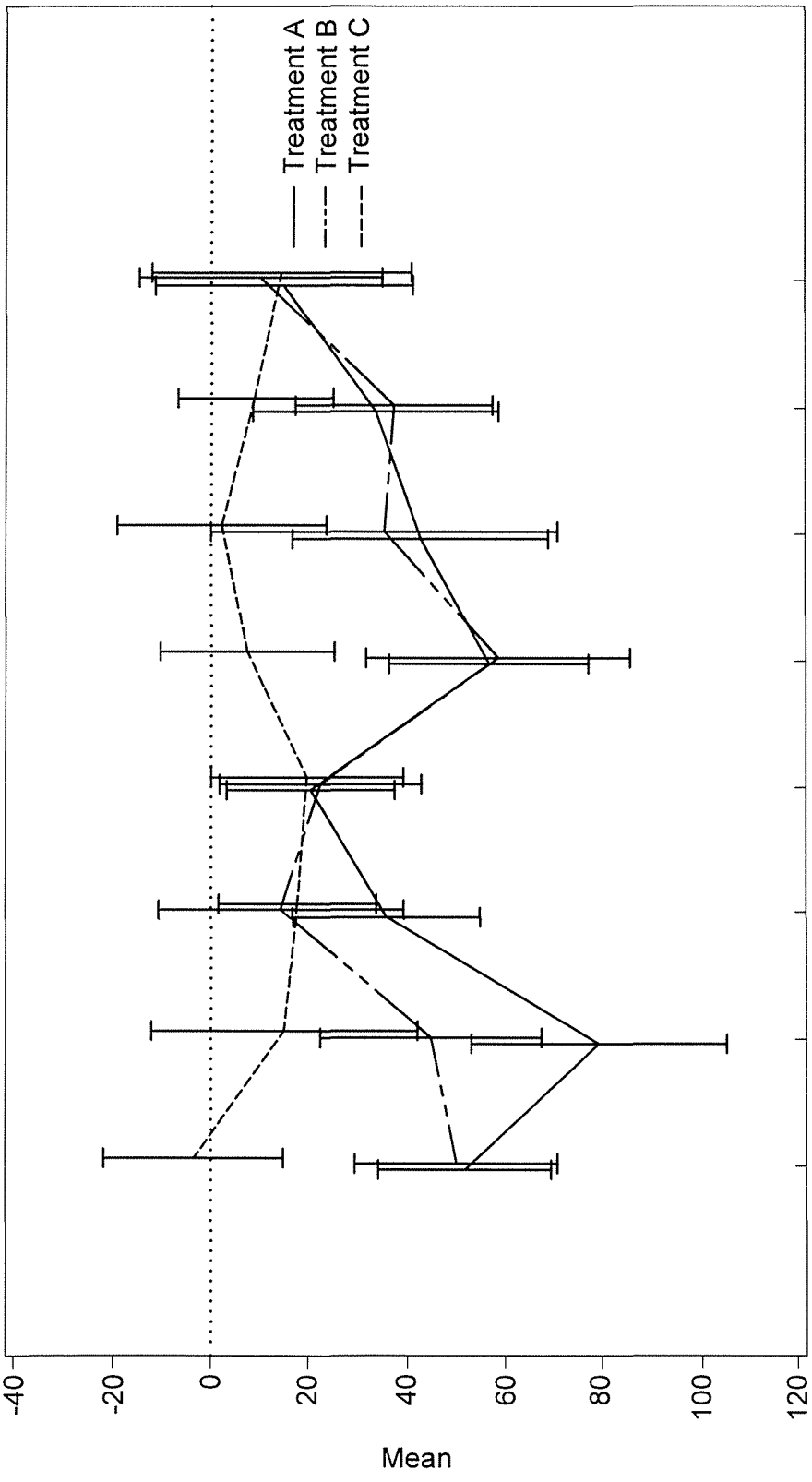
Time post-dose (hr)
0.5
1
2.5
4
4.5
5
6.5
8

FIG. 2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Treatment B
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Mean
-40
-20
0
20
40
60
80
100
120
Time post-dose (hr)
0.5
1
2.5
4
4.5
5
6.5
8

FIG. 3

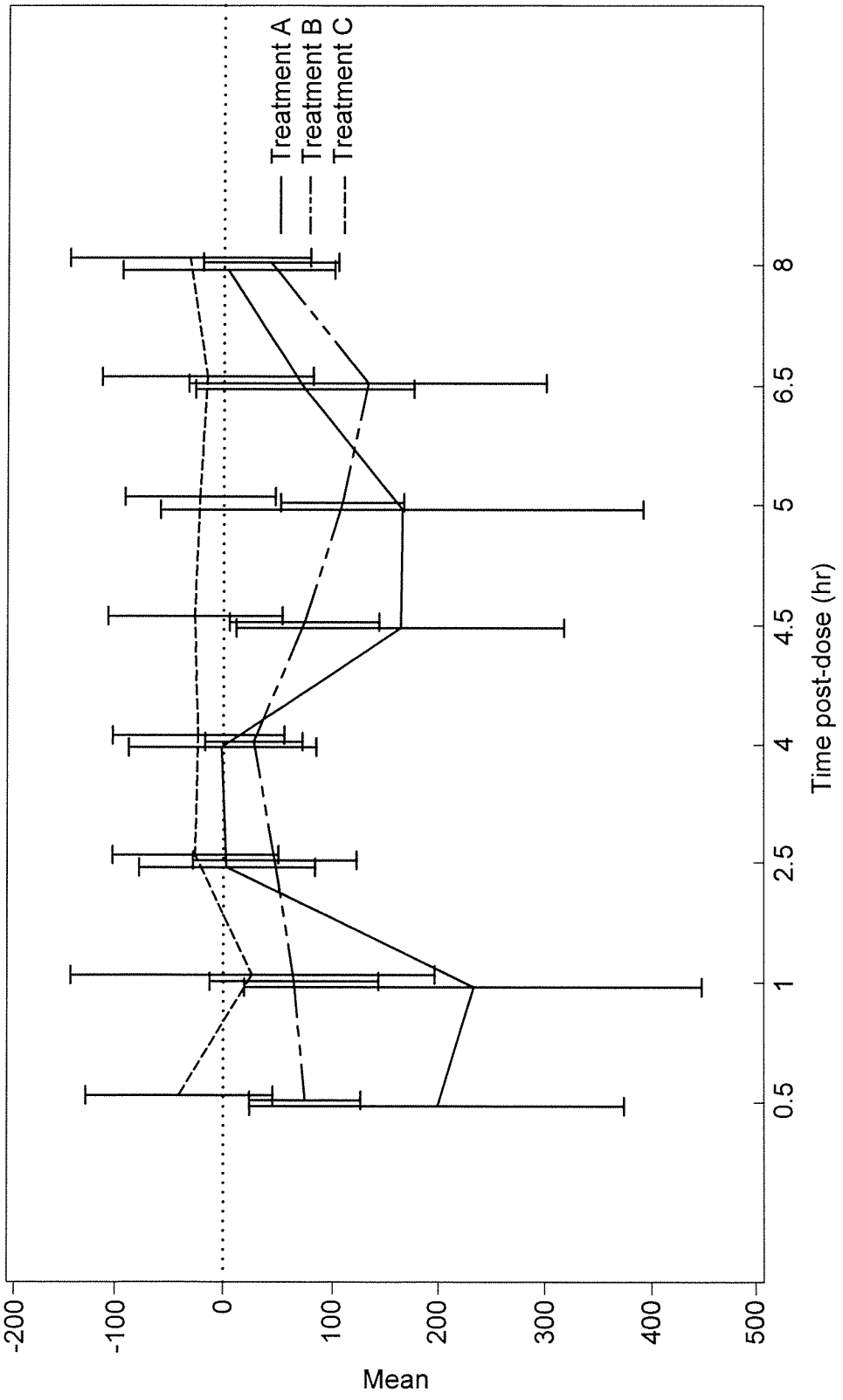
Treatment A
Treatment B
Treatment C
-200
-100
0
100
200
300
400
500
Mean
0.5
1
2.5
4
4.5
5
6.5
8
Time post-dose (hr)

FIG. 4

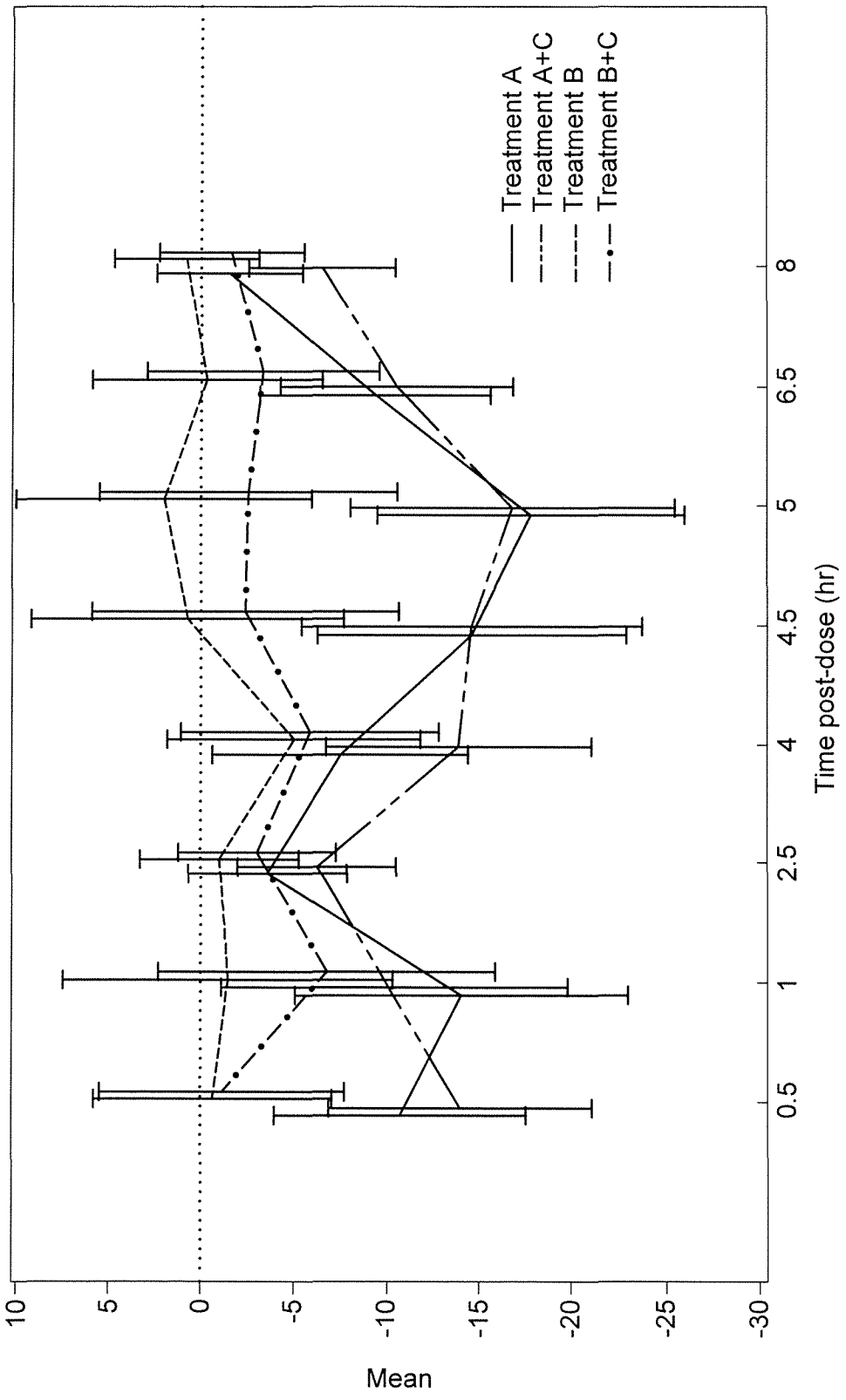
Treatment A
Treatment A+C
Treatment B
Treatment B+C
Time post-dose (hr)
0.5
1
2.5
4
4.5
5
6.5
8
Mean
10
5
0
-5
-10
-15
-20
-25
-30

FIG. 5

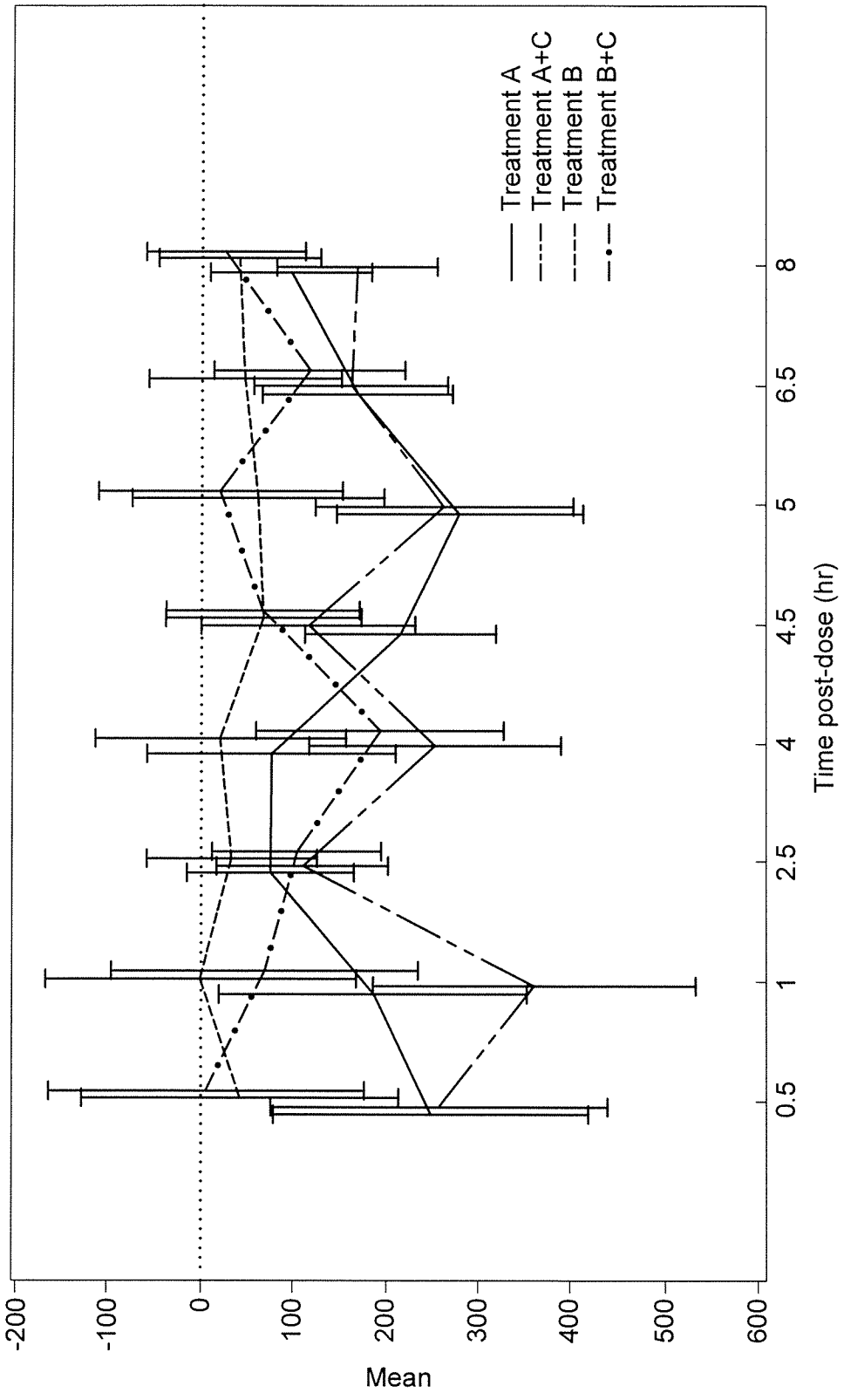
Treatment A
Treatment A+C
Treatment B
Treatment B+C
Time post-dose (hr)
0.5
1
2.5
4
4.5
5
6.5
8
Mean
-200
-100
0
100
200
300
400
500
600

FIG. 6

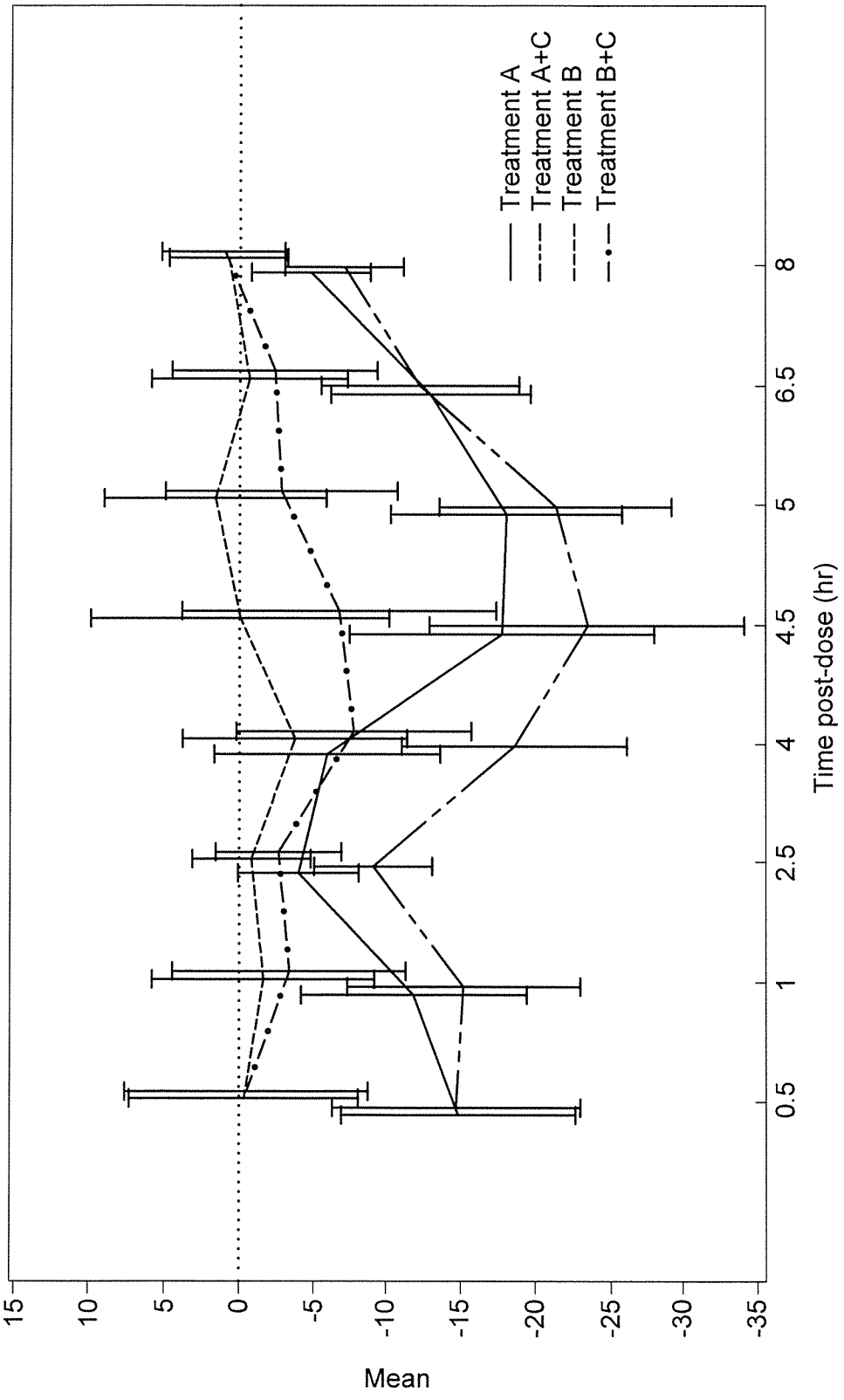
Treatment A
Treatment A+C
Treatment B
Treatment B+C
Time post-dose (hr)
0.5
1
2.5
4
4.5
5
6.5
8
Mean
15
10
5
0
-5
-10
-15
-20
-25
-30
-35

FIG. 7

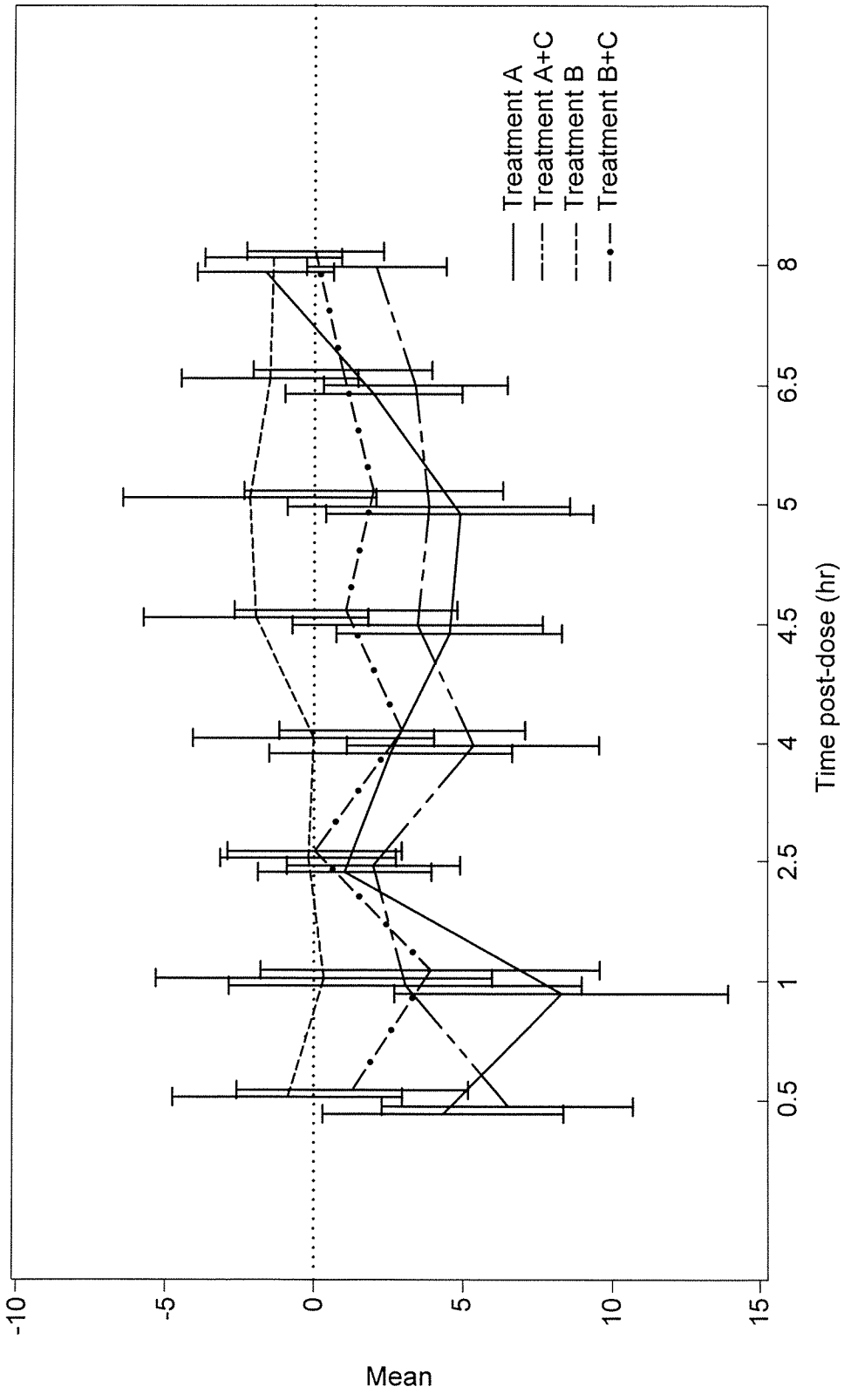
Treatment A
Treatment A+C
Treatment B
Treatment B+C
Time post-dose (hr)
0.5
1
2.5
4
4.5
5
6.5
8
Mean
-10
-5
0
5
10
15

FIG. 8

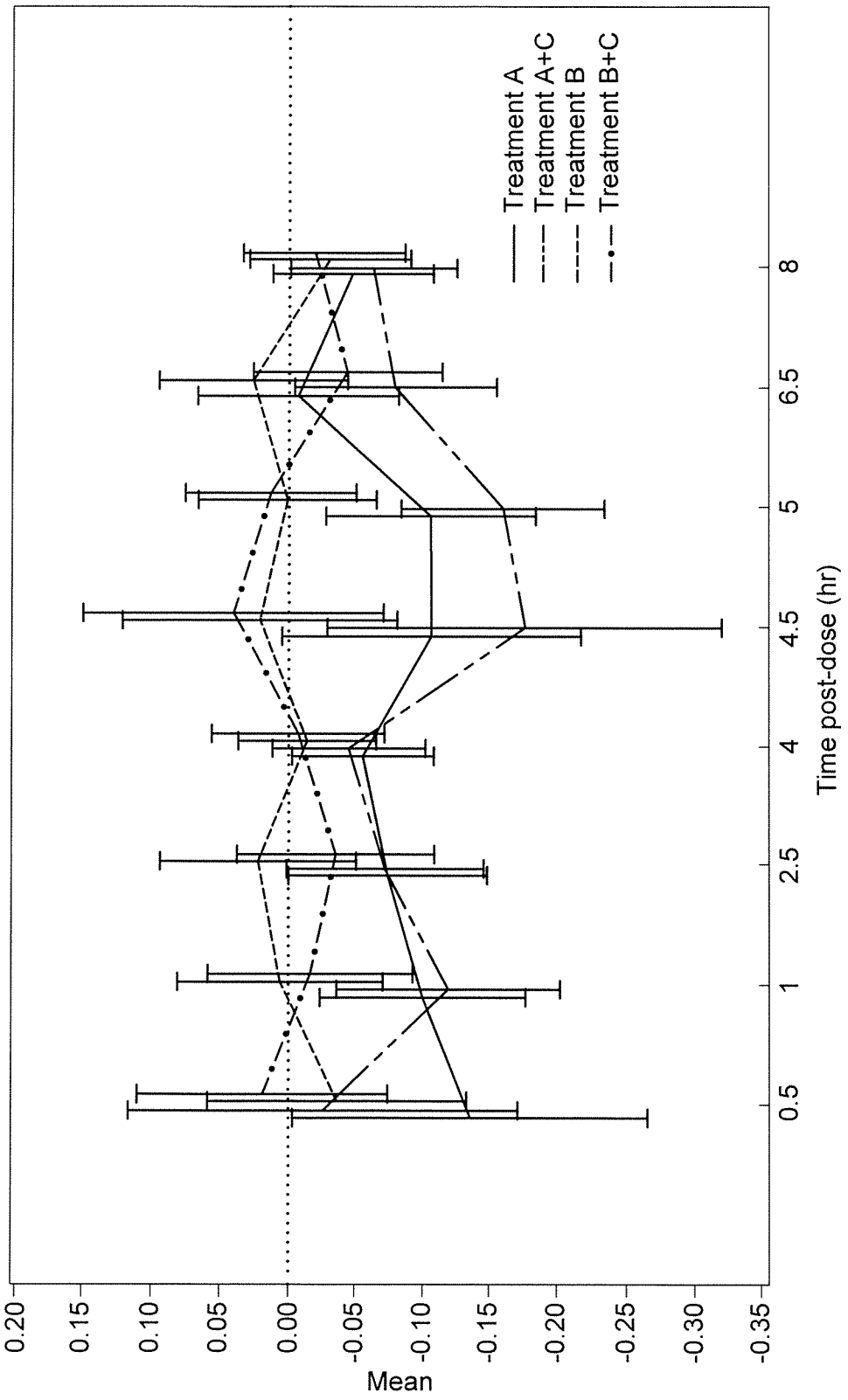
Treatment A
Treatment A+C
Treatment B
Treatment B+C
0.20
0.15
0.10
0.05
0.00
-0.05
-0.10
-0.15
-0.20
-0.25
-0.30
-0.35
Mean
0.5
1
2.5
4
4.5
5
6.5
8
Time post-dose (hr)

FIG. 9

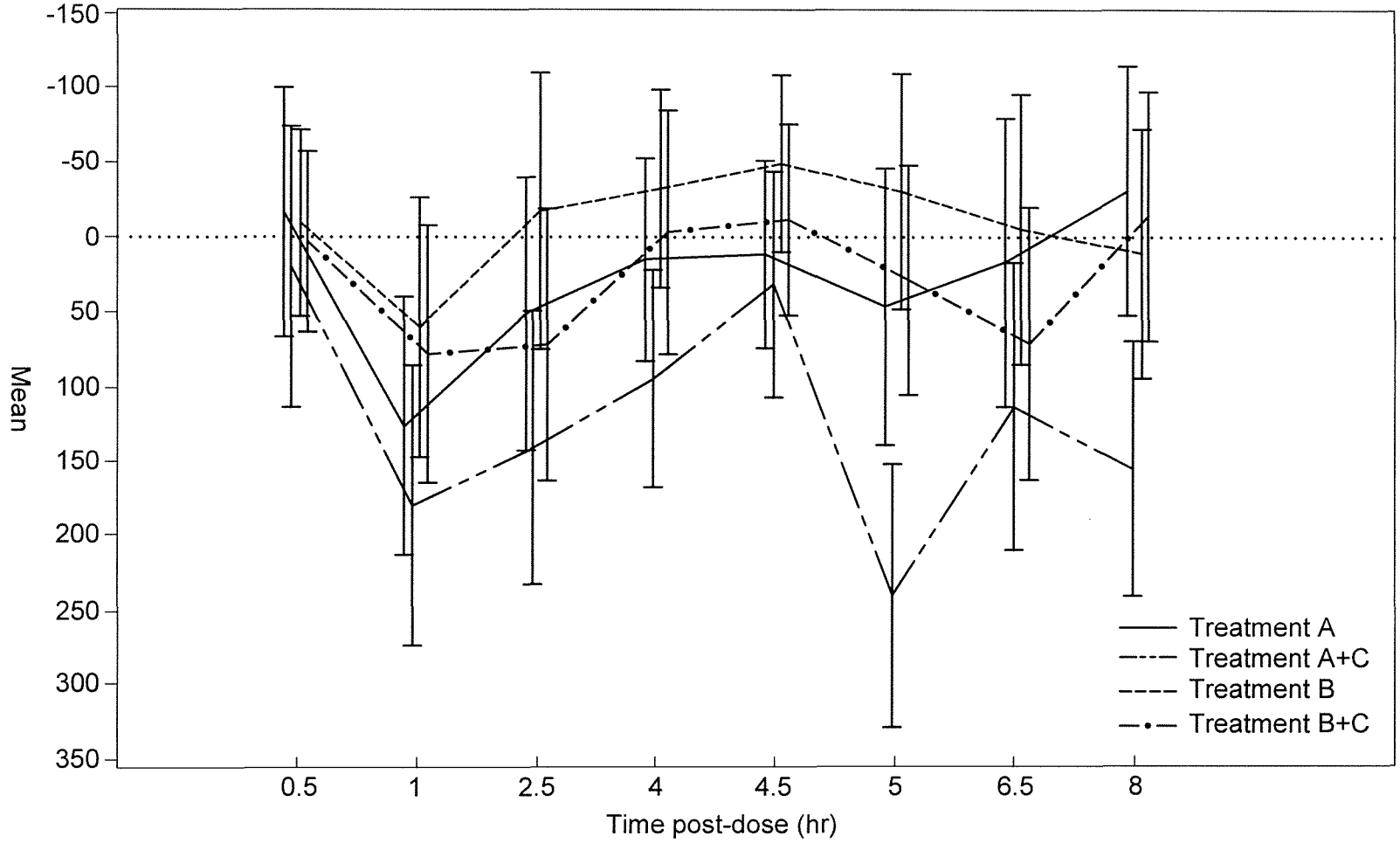
-150
-100
-50
0
50
100
150
200
250
300
350
Mean
0.5
1
2.5
4
4.5
5
6.5
8
Time post-dose (hr)
Treatment A
Treatment A+C
Treatment B
Treatment B+C

FIG. 10

METHOD OF ADMINISTRATION OF GAMMA HYDROXYBUTYRATE WITH MONOCARBOXYLATE TRANSPORTERS

This application is a continuation application of U.S. patent application Ser. No. 13/837,714, filed Mar. 15, 2013, which claims the benefit of U.S. Provisional Application No. 61/771,557, filed Mar. 1, 2013, and U.S. Provisional Application No. 61/777,873, filed Mar. 12, 2013, all of which applications are hereby incorporated by reference in their entireties.

BACKGROUND

This application relates to methods for safely administering gamma hydroxybutyrate (GHB) together with one or more other monocarboxylate transporter (MCT) inhibitors for therapeutic purposes. Example transporter inhibitors are valproate, diclofenac, and ibuprofen and combinations thereof.

SUMMARY OF THE INVENTION

One embodiment of the present invention is a method for treating a patient who is suffering from excessive daytime sleepiness, cataplexy, sleep paralysis, apnea, narcolepsy sleep time disturbances, hypnagogic hallucinations, sleep arousal, insomnia, and nocturnal myoclonus with gamma-hydroxybutyrate (GHB) or a salt thereof, comprising: orally administering to the patient in need of treatment, an adjusted dosage amount of the salt of GHB when the patient is receiving a concomitant administration of valproate. In certain embodiments, the adjusted amount is reduced at least about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% of the normal dose of the salt of GHB normally given to the patient. In certain embodiments, the amount of GHB is reduced at least about 10% and about 30% of the normal administration and the daily administration of the GHB salt is between 1 gram and 10 grams. In certain embodiments, the adjusted amount is reduced between the ranges of about 1% to 5%, about 5% to 10%, about 10% to 15%, about 15% to 20%, about 20% to 25%, about 25% to 30%, about 30% to 35%, about 35% to 40%, about 40% to 45%, or about 45% or 50%, relative to the normal dose of the salt of GHB normally given to the patient. In certain embodiments, the adjusted amount is reduced between the range of about 1% to 50%, about 1% to 45%, about 1% to 40%, about 1% to 35%, about 1% to 30%, about 1% to 25%, about 1% to 20%, about 1% to 15%, about 1% to 10%, about 1% to 5%, about 5% to 50%, about 5% to 45%, about 5% to 40%, about 5% to 35%, about 5% to 30%, about 5% to 25%, about 5% to 20%, about 5% to 15%, about 5% to 10%, about 10% to 50%, about 10% to 45%, about 10% to 40%, about 10% to 35%, about 10% to 30%, about 10% to 25%, about 10% to 20%, about 10% to 15%, about 15% to 50%, about 15% to 45%, about 15% to 40%, about 15% to 35%, about 15% to 30%, about 15% to 25%, about 15% to 20%, about 15% to 15%, about 15% to 10%, about 20% to 50%, about 20% to 45%, about 20% to 40%, about 20% to 35%, about 20% to 30%, about 20% to 25%, about 25% to 50%, about 25% to 45%, about 25% to 40%, about 25% to 35%, about 25% to 30%, about 30% to 50%, about 30% to 45%, about 30% to 40%, about 30% to 35%, about 35% to 50%, about 35% to 45%, about 35% to 40%, about 40% to 50%, relative to the normal dose of the salt of GHB normally given to the patient.

Another embodiment of the invention is a method of safely administering GHB a salt thereof for excessive daytime sleepiness, cataplexy, sleep paralysis, apnea, narcolepsy, sleep time disturbances, hypnagogic hallucinations, sleep arousal, insomnia, and nocturnal myoclonus in a human patient, comprising: determining if the patient is has taken, or will take a concomitant dose of valproate; orally administering a reduced amount of the GHB or GHB salt to the patient compared to the normal dose so as to diminish the additive effects of the GHB or GHB salt when administered with valproate. The amount of GHB is reduced at least 10% to 30%, or at least +15% of the normal administration.

One embodiment of the present invention is a method for treating a patient who is suffering from excessive daytime sleepiness, cataplexy, sleep paralysis, apnea, narcolepsy sleep time disturbances, hypnagogic hallucinations, sleep arousal, insomnia, and nocturnal myoclonus with GHB or a salt thereof, comprising: orally administering to the patient in need of treatment, an adjusted dosage amount of the salt of GHB when the patient is receiving a concomitant administration of diclofenac. In certain embodiments, the adjusted amount is at least about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% higher than the normal dose of the salt of GHB normally given to the patient. In certain embodiments, the increased amount of GHB is at least about 15% more than the normal administration and the daily administration of the GHB salt is between 1 gram and 10 grams. In certain embodiments, the adjusted amount is increased between the range of about 1% to 5%, about 5% to 10%, about 10% to 15%, about 15% to 20%, about 20% to 25%, about 25% to 30%, about 30% to 35%, about 35% to 40%, about 40% to 45%, or about 45% or 50%, relative to the normal dose of the salt of GHB normally given to the patient. In certain embodiments, the adjusted amount is increased between the range of about 1% to 50%, about 1% to 45%, about 1% to 40%, about 1% to 35%, about 1% to 30%, about 1% to 25%, about 1% to 20%, about 1% to 15%, about 1% to 10%, about 1% to 5%, about 5% to 50%, about 5% to 45%, about 5% to 40%, about 5% to 35%, about 5% to 30%, about 5% to 25%, about 5% to 20%, about 5% to 15%, about 5% to 10%, about 10% to 50%, about 10% to 45%, about 10% to 40%, about 10% to 35%, about 10% to 30%, about 10% to 25%, about 10% to 20%, about 10% to 15%, about 15% to 50%, about 15% to 45%, about 15% to 40%, about 15% to 35%, about 15% to 30%, about 15% to 25%, about 15% to 20%, about 15% to 15%, about 15% to 10%, about 20% to 50%, about 20% to 45%, about 20% to 40%, about 20% to 35%, about 20% to 30%, about 20% to 25%, about 25% to 50%, about 25% to 45%, about 25% to 40%, about 25% to 35%, about 25% to 30%, about 30% to 50%, about 30% to 45%, about 30% to 40%, about 30% to 35%, about 35% to 50%, about 35% to 45%, about 35% to 40%, about 40% to 50%, relative to the normal dose of the salt of GHB normally given to the patient. See the product insert for normal dose ranges of GHB as sold by Jazz Pharmaceuticals. GHB is commercially known as Xyrem®.

In another embodiment, the invention is a method of safely administering a GHB salt for excessive daytime sleepiness, cataplexy, sleep paralysis, apnea, narcolepsy, sleep time disturbances, hypnagogic hallucinations, sleep arousal, insomnia, and nocturnal myoclonus in a human patient, comprising: determining if the patient has taken, or will take a concomitant dose of diclofenac; orally administering an increased amount of a GHB salt to the patient so as to compensate for the effects of diclofenac on the GHB salt when concomitantly administered.

Another embodiment of the present invention is a method for treating a patient who is suffering from narcolepsy wherein said patient is currently taking or has been prescribed

GHB or a salt thereof, comprising determining if the patient is taking or has also been prescribed valproate or diclofenac; and adjusting the dose of the GHB or GHB salt to compensate for the effect caused by valproate or diclofenac. In certain embodiments, the method additionally comprises administering the adjusted dose to the patient.

Another embodiment of the present invention is a method for treating a patient who is suffering from excessive daytime sleepiness, cataplexy, sleep paralysis, apnea, narcolepsy, sleep time disturbances, hypnagogic hallucinations, sleep arousal, insomnia, and nocturnal myoclonus with a salt of gamma GHB, wherein said patient is also being treated with valproate or diclofenac, comprising: administering to the patient a daily dose of a GHB salt wherein said daily dose is administered at an amount sufficient to reduce or eliminate additive effects.

The embodiments of the present invention can administer the GHB at a level of between 1 and 4.5 grams/day or between 6 and 10 grams/day. The concentration of the formulation can be between 350-750 mg/ml or 450-550 mg/ml and a pH between 6-10 or 6.5-8.

Another embodiment of the present invention is a method for treating a patient who is suffering from narcolepsy, comprising: administering a salt of GHB or a salt thereof to a patient or determining whether the patient is currently on a GHB drug regimen; determining if the patient is also being administered ibuprofen; and advising a patient to cease or ceasing the administration of ibuprofen. In some embodiments, patients benefitting from this directive when the patient has will have a renal impairment.

Another embodiment of the present invention is a method for treating a patient who is suffering from narcolepsy, comprising: administering a therapeutically effective amount of a formulation containing GHB or a salt thereof to a patient at a concentration of between 450 and 550 mg/ml and a pH between 6 and 8, said formulation being administered before bed and 1-2 hours thereafter; determining if the patient is also being administered valproate; warning of a potential drug/drug interaction due to the combination of valproate and GHB; and reducing the dose of the GHB or GHB salt at least 15% to compensate for the effect caused by valproate. Another embodiment of the present invention is a method for treating a patient who is suffering from narcolepsy, comprising: administering a therapeutically effective amount of a formulation containing GHB or a salt thereof to a patient at a concentration of between 450 and 550 mg/ml and a pH between 6 and 8, said formulation being administered before bed and 1-2 hours thereafter; determining if the patient is also being administered diclofenac; warning of a potential drug/drug interaction due to the combination of diclofenac and the GHB salt; and increasing the dose of the GHB salt at least 15% to compensate for the effect caused by diclofenac.

In each of the embodiments of the invention the method includes administering GHB at between 1 and 4.5 grams/day or between 6 and 10 grams/day and at a concentration of between 350-750 or 450-550 mg/ml, and a pH between 6-10 or between 6.5-8. In further embodiments the valproate or diclofenac is administered within three days, one or two weeks (before or after) of GHB administration. In another embodiment, the present invention is a method wherein aspirin is also administered to the patient, especially with valproate.

In a further embodiment the method can include administering GHB as a single salt or a mixture of salts of GHB selected from the group consisting of a sodium salt of hydroxybutyrate (Na.GHB), a potassium salt of gamma-hydroxybutyrate (K.GHB), a magnesium salt of gamma-hydroxybutyrate ($Mg.(GHB)_2$), and a calcium salt of gamma-hydroxybutyrate ($Ca.(GHB)_2$).

In a further embodiment the method can include administering GHB to a patient suffering from excessive daytime sleepiness, comprising: administering a therapeutically effective amount of GHB to the patient; determining if the patient has concomitant administration of an MCT inhibitor; and adjusting the GHB dose or ceasing administering of the MCT inhibitor to maintain the effect of the GHB.

In any of the versions of the invention, the methods optionally further include administering aspirin to the patient.

In a further embodiment the method of administering GHB to a patient in need thereof comprises administering to the patient a therapeutically effective amount of GHB while avoiding concomitant of a diclofenac or valproate.

Another embodiment of the invention comprises a method of administering GHB or a salt thereof (GHB) to a patient with narcolepsy, wherein said patient is also in need of diclofenac, comprising administering to the patient a daily dosage of between 6 g and 10 g GHB or a GHB salt per day while avoiding diclofenac concomitant administration, and any one or more of the following: (a) advising the patient that diclofenac should be avoided or discontinued, (b) advising the patient that concomitant administration of GHB with drugs that are MCT inhibitors can alter the therapeutic effect or adverse reaction profile of GHB, (c) advising the patient that concomitant administration of GHB with diclofenac can alter the therapeutic effect or adverse reaction profile of GHB, (d) advising the patient that use of GHB in patients being treated with diclofenac is contraindicated, (e) advising the patient that concomitant administration of GHB and diclofenac resulted in an decrease in exposure to GHB, or (f) advising the patient MCT inhibitors should be used with caution in patients receiving GHB due to the potential for increased GHB clearance.

Another embodiment of the invention comprises a administering GHB to a patient with narcolepsy, wherein said patient is also in need of valproate, comprising administering to the patient a daily dosage of between 6 g and 10 g GHB per day while avoiding valproate concomitant administration, and any one or more of the following: (a) advising the patient that valproate should be avoided or discontinued, (b) advising the patient that concomitant administration of GHB with drugs that are MCT inhibitors can alter the therapeutic effect or adverse reaction profile of GHB, (c) advising the patient that concomitant administration of GHB with valproate can alter the therapeutic effect or adverse reaction profile of GHB, (d) advising the patient that use of GHB in patients being treated with valproate is contraindicated, (e) advising the patient that concomitant administration of GHB and valproate resulted in an increase in exposure to GHB, or (f) advising the patient that MCT inhibitors should be used with caution in patients receiving GHB due to the potential for increased GHB clearance.

In another embodiment, the present invention is a method for distributing a drug containing GHB or a salt thereof to an approved pharmacy, the method comprising: identifying an approved pharmacy that has an established management system to dispense information concerning the risks associated with ingesting a MCT inhibitor concomitantly to said drug to patients that are prescribed said drug; providing said pharmacy with said information related to the risks; and authorizing distribution of said drug to said pharmacy, wherein said pharmacy dispenses the drug with said information when filling a prescription for said drug. The method may also comprise including an electronic or written alert, which can explain the risks, to employees to dispense said information

with said drug when prescriptions are filled. Also, the information can be dispensed when a subject refills said prescription. The warnings would be as recited above.

The methods of the present invention may include a warning for patients not to operate hazardous machinery, including automobiles or airplanes, until they are reasonably certain that GHB does not affect them adversely and not to engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery or a motor vehicle or flying an airplane, for at least 6, 7, 8 or 9 hours after taking the second nightly dose of GHB. Any information dispensed with said drug advises patients of the potential for enhanced potency of said drug if said patients also take valproate or advises patients of the potential for decreased potency of said drug if said patients also take diclofenac.

Another embodiment of the present invention is a method of administering GHB to a patient in need thereof, comprising administering to the patient a therapeutically effective amount of GHB while avoiding concomitant administration of diclofenac or valproate.

The invention may also comprise a method for reducing the effects of GHB toxicity in a patient in need thereof, comprising administering to said patient an effective amount of diclofenac such that the toxic effects of GHB are reduced. It may also comprise a method for potentiating the beneficial effects of GHB in a patient in need thereof comprising concomitantly administering to said patient an effective amount of valproate such that the beneficial effects of GHB are increased.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows change from baseline figure (LSmean with 95% CI) for Power of Attention (ms) (PD Completer Population). Treatment A=diclofenac placebo+Xyrem®. Treatment B=diclofenac+Xyrem®. Treatment C=diclofenac+ Xyrem® placebo.

FIG. **2** shows change from baseline figure (LSmean with 95% CI) for Digit Vigilance Accuracy (%) (PD Completer Population).

FIG. **3** shows change from baseline figure (LSmean with 95% CI) for Digit Vigilance Mean Reaction Time (ms) (PD Completer Population).

FIG. **4** shows change from baseline figure (LSmean with 95% CI) for Choice Reaction Time Mean (ms) (PD Compleeter Population).

FIG. **5** shows change from baseline figure (LSmean with 95% CI) for Continuity of Attention (#) (PD Population). Treatment A=Xyrem®. Treatment B=Xyrem® placebo. Treatment C=valproate.

FIG. **6** shows change from baseline figure (LSmean with 95% CI) for Simple Reaction Time Mean (ms) (PD Population).

FIG. **7** shows change from baseline figure (LSmean with 95% CI) for Digit Vigilance Accuracy (%) (PD Population).

FIG. **8** shows change from baseline figure (LSmean with 95% CI) for Tracking Distance from Target (mm) (PD Population).

FIG. **9** shows change from baseline figure (LSmean with 95% CI) for Numeric Working Memory Sensitivity Index (#) (PD Population).

FIG. **10** shows change from baseline figure (LSmean with 95% CI) for Numeric Working Memory Mean Reaction Time (ms) (PD Population).

DETAILED DESCRIPTION OF THE INVENTION

The following patents and applications are hereby incorporated by reference in their entireties for all purposes: 6,472,431, 6,780,889, 7,262,219, 7,851,506, 8,263,650, 8,324,275; 7,895,059; 7,797,171; 7,668,730; 7,765,106; 7,765,107; 61/317,212, 13/071,369, 13/739,886, 12/264,709, PCT/US2010/033572, PCT/US2009/061312, 2009/0137565; and 2012/0076865. The following patents are also incorporated by reference: U.S. Pat. No. 5,380,937; U.S. Pat. No. 4,393,236 German Patent DD 237,309 A1; and British Pat. No. 922,029.

Objects, features and advantages of the methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

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Smolders I, De Klippel N, Sarre S, Ebinger G, Michotte Y (1995). "Tonic GABA-ergic modulation of striatal dopamine release studied by in vivo microdialysis in the freely moving rat". Eur. J. Pharmacol. 284 (1-2): 83-91.

In the specification and claims that follow, references will be made to a number of terms which shall be defined to have the following meaning.

The terms "a" and "an" do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced item. The term "or" means "and/or". The terms "comprising", "having", "including", and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to").

"Concomitant" and "concomitantly" as used herein refer to the administration of at least two drugs to a patient either subsequently, simultaneously, or consequently within a time period during which the effects of the first administered drug are still operative in the patient. Thus, if the first drug is, e.g., Xyrem®, or GHB, and the second drug is valproate, the concomitant administration of the second drug occurs within two weeks, preferably within one week or even three days, before or after the administration of the first drug.

"Dosage amount" means an amount of a drug suitable to be taken during a fixed period, usually during one day (i.e., daily).

"Dosage amount adapted for oral administration" means a dosage amount that is of an amount deemed safe and effective for the particular patient under the conditions specified. As used herein and in the claims, this dosage amount is determined by following the recommendations of the drug manufacturer's Prescribing Information as approved by the US Food and Drug Administration.

"Dosing regimen" means the dose of a drug taken at a first time by a patient and the interval (time or symptomatic) and dosage amounts at which any subsequent doses of the drug are taken by the patient. Each dose may be of the same or a different dosage amount.

A "dose" means the measured quantity of a drug to be taken at one time by a patient.

A "patient" means a human in need of medical treatment. In one embodiment medical treatment can include treatment of an existing condition, such as a disease or disorder, prophylactic or preventative treatment, or diagnostic treatment. In another embodiment, medical treatment also includes

administration to treat excessive daytime sleepiness, cataplexy, sleep paralysis, apnea, narcolepsy, sleep time disturbances, hypnagogic hallucinations, sleep arousal, insomnia, and nocturnal myoclonus.

"Providing" means giving, administering, selling, distributing, transferring (for profit or not), manufacturing, compounding, or dispensing.

The terms "therapeutically effective amount," as used herein, refer to an amount of a compound sufficient to treat, ameliorate, or prevent the identified disease or condition, or to exhibit a detectable therapeutic, prophylactic, or inhibitory effect. The effect can be detected by, for example, an improvement in clinical condition, or reduction in symptoms. The precise effective amount for a subject will depend upon the subject's body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Where a drug has been approved by the U.S. Food and Drug Administration (FDA), a "therapeutically effective amount" refers to the dosage approved by the FDA or its counterpart foreign agency for treatment of the identified disease or condition.

"Side effect" means a secondary effect resulting from taking a drug. The secondary effect can be a negative (unfavorable) effect (i.e., an adverse side effect) or a positive (favorable) effect.

Pharmacokinetic parameters referred to herein describe the in vivo characteristics of drug (or a metabolite or a surrogate marker for the drug) over time. These include plasma concentration (C), as well as C_{max}, C_n, C_{24}, T_{max}, and AUC. The term "T_{max}" refers to the time from drug administration until C_{max} is reached. "AUC" is the area under the curve of a graph of the measured plasma concentration of an active agent vs. time, measured from one time point to another time point. For example AUC_{0-t} is the area under the curve of plasma concentration versus time from time 0 to time t, where time 0 is the time of initial administration of the drug. Time t can be the last time point with measurable plasma concentration for an individual formulation. The $AUC_{0-.infin.}$ or AUC_{0-INF} is the calculated area under the curve of plasma concentration versus time from time 0 to time infinity. In steady-state studies, $AUC_{0-.tau.}$ is the area under the curve of plasma concentration over the dosing interval (i.e., from time 0 to time .tau. (tau), where tau is the length of the dosing interval.

It may be advantageous to incorporate a pharmacy management system into the method of the present invention. Pharmacy management systems are computer-based systems that are used by commercial pharmacies to manage prescriptions and to provide pharmacy and medical personnel with warnings and guidance regarding drugs being administered to patients. Such systems typically provide alerts warning either or both of health care providers and patients when a drug that may be harmful to the particular patient is prescribed. For example, such systems can provide alerts warning that a patient has an allergy to a prescribed drug, or is receiving concomitant administration of a drug that can have a dangerous interaction with a prescribed drug. U.S. Pat. Nos. 7,895,059; 7,797,171; 7,668,730; 7,765,106; 7,765,107; 5,758,095, 5,833,599, 5,845,255, 6,014,631, 6,067,524, 6,112,182, 6,317,719, 6,356,873, and U.S. Pat. No. 7,072,840, each of which is incorporated herein by reference, disclose various pharmacy management systems and aspects thereof. Example pharmacy management systems are now commercially available, e.g., CENTRICITY Pharmacy from BDM Information Systems Ltd., General Electric Healthcare, Waukesha, Wis., Rx30 Pharmacy Systems from Transaction Data Systems, Inc., Ocoee, Fla., SPEED SCRIPT from Digital Simplistics, Inc., Lenexa, Kans., and various pharmacy management systems from OPUS-ISM, Hauppauge, N.Y.

In some embodiments, a pharmacy management system may be required or preferred as part of a drug distribution program. For example, the present invention includes a method for distributing a drug containing GHB or a salt thereof to an approved pharmacy, the method comprising: (1) Identifying an approved pharmacy that has an established management system to dispense information concerning the risks associated with ingesting a MCT inhibitors concomitantly to said drug to patients that are prescribed said drug; (2) Providing said pharmacy with said information related to the risks; and (3) Authorizing distribution of said drug to said pharmacy, wherein said pharmacy dispenses the drug with said information when filling a prescription for said drug. The established management system may include an electronic alert to employees to dispense said information with said drug when prescriptions are filled. Such information may be dispensed in written form, for example in a brochure explaining the risks of concomitant ingestion of GHB and an MCT inhibitor such as diclofenac, valproate, or ibuprofen or combinations thereof. For example, the information dispensed with GHB may advise a patient of the potential for enhanced potency of GHB if the patient also takes valproate. Alternatively, or in addition thereto, the information dispensed with GHB may advise a patient of the potential for decreased potency of GHB if the patient also takes diclofenac. Such information may also be dispensed in verbal form. Distributors may maintain a directory of approved pharmacies, for example in a computer readable storage medium, to further ensure that GHB is dispensed only to patients who are advised of the additive effects.

In addition, the system can prevent the dispensing of GHB or salt thereof until proper testing or confirmation is obtained that the patient is not taking or going to take valproate or diclofenac concomitantly with GHB. Alternatively, the patient can be warned of the adverse effect and instructed to modify the dose of GHB to accommodate the increased or reduced effects of GHB due to valproate or diclofenac.

A pharmacy management system of the present invention can be a REMS system as shown in U.S. Pat. Nos. 7,895,059; 7,797,171; and 7,668,730 and also include monitoring for concomitant use of diclofenac, valproate, or ibuprofen, or combinations thereof. Warnings may be administered through the existing pharmacy management system as described in the patents above.

One embodiment of the present invention, without being limited by theory, is the discovery of drug interactions that change either, or both, the efficacy or safety profile of GHB. The three compounds are valproate, diclofenac, and ibuprophen or combinations thereof. To achieve the above benefits, GHB of the present invention can be administered in a reduced amount when a second compound, such as valproate, is concomitantly administered with GHB. It can also be administered in an increased amount to overcome any effects of diclofenac. The compounds can also be avoided or discontinued to prevent unsafe concomitant administration.

In one embodiment of the present invention, concomitant administration of GHB with other agents is monitored and potential changes to the doses of GHB are made, or changes in the administration of other compounds are made. In one embodiment of the present invention, when GHB was concomitantly administered with ibuprofen, there were pharmacokinetic (PK) changes consistent with monocarboxylic transporter (MCT) inhibition and renal excretion of GHB doubled (statistically significant). Plasma levels were about ~5% lower, which was statistically significant. In another

embodiment of the present invention, when GHB and Diclofenac are concomitantly administered, PD effects were significantly reduced. In another embodiment of the present invention, when GHB and divalproate were concomitantly administered, PK showed both MCT and GHB dehydrogenase inhibition, with the latter predominating. MCT inhibition caused renal clearance to be increased 30% (statistically significant). GHB dehydrogenase inhibition caused systemic exposure (plasma AUC) to be increased 26%. Both measures are statistically significant and outside FDA "equivalence window". PD shows more pronounced effects with concomitant administration.

One embodiment is a method of administering a therapeutically effective amount of GHB to a patient in need of treatment, such as with narcolepsy, the invention provides an improvement that comprises avoiding or discontinuing administration of a compound that affects GHB potency and administering a therapeutically effective amount of GHB. The compound can be diclofenac or valproate and they can alter the therapeutic effect or adverse reaction profile of GHB.

Gamma Hydroxybutyrate (GHB)

GHB (also called oxysorbate or oxybate) is approved in the United States (US) for the treatment of excessive daytime sleepiness (EDS) and for the treatment of cataplexy, both in patients with narcolepsy. GHB is commercially sold as Xyrem® sodium oxybate by Jazz Pharmaceuticals. Sodium oxybate is the sodium salt of the endogenous neurotransmitter gamma hydroxybutyrate (GHB), which is found in many tissues of the body. "GHB", oxybate, a GHB salt or Xyrem® will be used to refer to these active forms. It can be used as a sodium, calcium, potassium, or magnesium salt. See U.S. patent application Ser. No. 13/739,886.

GHB is present, for example, in the mammalian brain and other tissues. In the brain, the highest GHB concentration is found in the hypothalamus and basal ganglia and GHB is postulated to function as a neurotransmitter. The neuropharmacologic effects of GHB include increases in brain acetylcholine, increases in brain dopamine, inhibition of GABA-ketoglutarate transaminase and depression of glucose utilization but not oxygen consumption in the brain. GHB is converted to succinate and then metabolized via the Krebs cycle. Clinical trials have shown that GHB increases delta sleep and improves the continuity of sleep (Laborit, 1973; Lapierre et al., 1988; Lapierre et al., 1990; Yamada et al., 1967; Scharf, 1985).

GHB treatment substantially reduces the signs and symptoms of narcolepsy, i.e. excessive daytime sleepiness, cataplexy, sleep paralysis, apnea, narcolepsy, sleep time disturbances, hypnagogic hallucinations, sleep arousal, insomnia, and nocturnal myoclonus. In addition, GHB increases total sleep time and REM sleep, and it decreases REM latency (Mamelak et al, 1973; Yamada et al., 1967; Bedard et al., 1989), reduces sleep apnea (Scrima et al., 1987), and improves general anesthesia (Hasenbos and Gielen, 1985).

GHB has several clinical applications other than narcolepsy and sleep disorders. GHB has been reported to reduce alcohol craving, the number of daily drinks consumed, and the symptoms of alcohol withdrawal in patients (Gallimberti et al., 1989; Gallimberti et al., 1992; Gessa et al., 1992). GHB has been used to decrease the symptoms of opiate withdrawal, including both heroin and methadone withdrawal (Gallimberti et al., 1994; Gallimberti et al., 1993). It has analgesic effects that make it suitable as a pain reliever (U.S. Pat. No. 4,393,236). Intravenous administration of GHB has been reported to reduce intracranial pressure in patients (Strong, A. 1984). Also, administration of GHB was reported to increase growth hormone levels in patients (Gessa et al, 1994).

A good safety profile for GHB consumption, when used long term for treatment of narcolepsy has been reported. Patients have been safely treated for many years with GHB without development of tolerance (Scharf, 1985). Clinical laboratory tests carried out periodically on many patients have not indicated organ or other toxicities (Lammers, 1993; Scrima, 1990; Scharf, 1985; Mamelack, 1977; Mamelak, 1979; Gessa, 1992). The side effects of GHB treatment have been minimal in incidence and degree of severity, though they include sleepwalking, enuresis, headache, nausea and dizziness (Broughton and Mamelak, 1979; Mamelak et al., 1981; Mamelak et al., 1977; Scrima et al., 1989; Scrima et al., 1990; Scharf et al., 1985). Therefore, it is critical to identify adverse drug-drug interactions to maintain the positive safety profile for GHB.

GHB Pharmacology

GHB has at least two distinct binding sites (See Wu, et al., 2004) in the central nervous system. GHB is an agonist at the GHB receptor, which is excitatory, (Cash et al., 2009) and it is a weak agonist at the GABAB receptor, which is inhibitory. GHB acts in a similar fashion to some neurotransmitters in the mammalian brain and is probably synthesized from GABA in GABAergic neurons, and released when the neurons fire. If taken orally, GABA itself does not effectively cross the blood-brain-barrier. (See Kuriyama et al., 2005).

GHB induces the accumulation of either a derivative of tryptophan or tryptophan itself in the extracellular space, possibly by increasing tryptophan transport across the blood-brain barrier. The blood content of certain neutral amino-acids, including tryptophan, is also increased by peripheral GHB administration. GHB-induced stimulation of tissue serotonin turnover may be due to an increase in tryptophan transport to the brain and in its uptake by serotonergic cells. As the serotonergic system may be involved in the regulation of sleep, mood, and anxiety, the stimulation of this system by high doses of GHB may be involved in certain neuropharmacological events induced by GHB administration.

However, at therapeutic doses, GHB reaches much higher concentrations in the brain and activates GABAB receptors, which are primarily responsible for its sedative effects. (See Dimitrijevic et al., 2005). GHB's sedative effects are blocked by GABAB antagonists.

The role of the GHB receptor in the behavioral effects induced by GHB is more complex. GHB receptors are densely expressed in many areas of the brain, including the cortex and hippocampus, and these are the receptors that GHB displays the highest affinity for. There has been somewhat limited research into the GHB receptor; however, there is evidence that activation of the GHB receptor in some brain areas results in the release of glutamate, the principal excitatory neurotransmitter. Drugs that selectively activate the GHB receptor cause absence seizures in high doses, as do GHB and GABA(B) agonists. (See Banerjee et al., 1995.)

Activation of both the GHB receptor and GABA(B) is responsible for the addictive profile of GHB. GHB's effect on dopamine release is biphasic. (See Hechler et al., 1991). Low concentrations stimulate dopamine release via the GHB receptor. (See Maitre et al., 1990). Higher concentrations inhibit dopamine release via GABA(B) receptors as do other GABA(B) agonists such as baclofen and phenibut. (See Smolders et al., 1995). After an initial phase of inhibition, dopamine release is then increased via the GHB receptor. Both the inhibition and increase of dopamine release by GHB are inhibited by opioid antagonists such as naloxone and naltrexone. Dynorphin may play a role in the inhibition of dopamine release via kappa opioid receptors. (See Mamelak 1989).

This may explain the paradoxical mix of sedative and stimulatory properties of GHB, as well as the so-called "rebound" effect, experienced by individuals using GHB as a sleeping agent, wherein they awake suddenly after several hours of GHB-induced deep sleep. That is to say that, over time, the concentration of GHB in the system decreases below the threshold for significant GABAB receptor activation and activates predominantly the GHB receptor, leading to wakefulness. However, one embodiment of the present invention is the unexpected discovery that drugs change the PD profile of GHB to alter its effects and its safety profile. Example drugs are include valproate and diclofenac. It is important for efficacy safety purposes that the effect of GHB be maintained consistently and not subject to variation due to the effects of other drugs.

Both of the metabolic breakdown pathways shown for GHB can run in either direction, depending on the concentrations of the substances involved, so the body can make its own GHB either from GABA or from succinic semialdehyde. Under normal physiological conditions, the concentration of GHB in the body is rather low, and the pathways would run in the reverse direction to what is shown here to produce endogenous GHB. However, when GHB is consumed for recreational or health promotion purposes, its concentration in the body is much higher than normal, which changes the enzyme kinetics so that these pathways operate to metabolize GHB rather than produce it.

The pharmacokinetics of GHB have been investigated in alcohol dependent patients (Ferrara et al., 1992) and in normal healthy males (Palatini et al., 1993) after oral administration. GHB possesses a rapid onset and short pharmacological effect (Ferrara et al., 1992; Palatine et al., 1993; Lettieri and Fung, 1978; Arena and Fung, 1980; Roth and Giarman, 1966; Vickers, 1969; Lee, 1977). In alcohol dependent patients, GHB absorption into and elimination from the systemic circulation were fast processes. Virtually no unchanged drug could be recovered in the urine. There were preliminary indications that the pharmacokinetics of GHB might be non-linear or dose-dependent (Ferrara et al., 1992). In the healthy volunteers study, the pharmacokinetics of three rising GHB doses (12.5, 25, and 50 mg/kg) were investigated. These findings indicate that both the oral absorption and elimination processes of GHB were capacity-limited though the degree of dose dependency was moderate (Palatini et al., 1993).

Methods of making GHB salts are described, for example, in U.S. Pat. No. 4,393,236, and U.S. patent application Ser. No. 13/739,886 which are incorporated herein by reference.

It has been discovered that there are unexpected drug-drug interactions (DDI) between GHB and common drugs frequently prescribed for other ailments. It is one goal of the present invention to warn when those interactions may affect the safety profile of GHB. In one embodiment of the present invention, drugs that may affect GHB administration include valproate, diclofenac, and ibuprofen and combinations thereof.

GHB is a central nervous system (CNS) depressant. Alcohol and sedative hypnotics are contraindicated in patients who are using GHB. The concurrent use of GHB with other CNS depressants, including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death. If use of these CNS depressants in combination with GHB is required, dose reduction or discontinuation of one or more CNS depressants (including GHB) should be considered. In addition, if short-term use of an opioid (e.g. post- or perioperative) is required, interruption of treatment with GHB should be considered. See the package insert for Xyrem®.

GHB may impair respiratory drive, especially with overdoses associated with interactions with other drugs and alcohol. Since valproate may potentiate the effect of GHB, a warning should accompany any use of valproate and GHB as stated herein. The warning should address the use of additional drugs that may further enhance the effect of GHB, such as alcohol or aspirin, for example.

Healthcare providers should caution patients about operating hazardous machinery, including automobiles or airplanes, until they are reasonably certain that GHB does not affect them adversely (e.g., impair judgment, thinking, or motor skills). Patients should not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery or a motor vehicle or flying an airplane, for at least 6, 7, 8 or 9 hours after taking the second nightly dose of GHB. Patients should be queried about potential adverse events, such as excessive daytime sleepiness, CNS depression related events, etc. upon initiation of GHB therapy and periodically thereafter. These queries should include info regarding additional medication such as diclofenac and valproate for example. See the Xyrem® package insert.

In one embodiment described herein, patients are warned that combination of GHB with valproate can increase plasma levels and potentiate the activity of GHB and exacerbate all the effects and adverse event associated with GHB. These effects include the intended effects of drowsiness, sedation, and sleep and typically unintended events such as depressed respiration, CNS depression, excessive drowsiness, hepatic impairment, and depression, among other things.

In another embodiment, diclofenac mitigates and protects against the pharmcodynamic effects the effects of GHB. However, the mixture of GHB and diclofenac does not affect sleepiness and does not make a patient more attentive. Without wishing to be bound by theory, the effects may be due to the interaction between diclofenac and the GHB receptor in lieu of the MCT inhibitor activity.

Typical concentrations of GHB formulations are shown in U.S. Pat. Nos. 8,263,650 and 8,324,275, for example. They include minimum concentrations starting from 150 mg/ml to 450 mg/ml (at 10 mg/ml increments) and increasing to 600 mg/ml to 750 mg/ml (at 10 mg/ml increments) as a maximum. So, a broad range would include 150-750 mg/ml and any range within the broad range using 10 mg/ml increments. One embodiment of the invention is a range of 350-750 mg/ml and another is 450-550 mg/ml GHB. One embodiment of the present invention uses a GHB formulation with a pH range of 6-10, another uses a pH range of between 6.5-8. For example, a minimum concentration includes 350, 360, 370, 380 mg/ml, and so on up to at least 730, 740, and 750 mg/ml and all concentrations (measured in 10 mg/ml increments in between).

pH adjusting agents can include acids, bases and many of the compounds found in U.S. Pat. No. 8,263,650. In some embodiments the pH adjusting agent is an acid selected from the group of: acetic, acetylsalicylic, barbital, barbituric, benzoic, benzyl penicillin, boric, caffeine, carbonic, citric, dichloroacetic, ethylenediaminetetra-acetic acid (EDTA), formic, glycerophosphoric, glycine, lactic, malic, mandelic, monochloroacetic, oxalic, phenobarbital, phenol, picric, propionic, saccharin, salicylic, sodium dihydrogen phosphate, succinic, sulfadiazine, sulfamerazine, sulfapyridine, sulfathiazole, tartaric, trichloroacetic, and the like, or inorganic acids such as hydrochloric, nitric, phosphoric or sulfuric, and the like.

GHB is commercially available as a sodium salt, however, it can also be formulated as a mixture of salts as shown in U.S. Ser. No. 13/739,886, which is incorporated by reference as stated above. For example, the mixture comprises one, two, or three or more salts selected from the group consisting of a sodium salt of hydroxybutyrate (Na.GHB), a potassium salt of gamma-hydroxybutyrate (K.GHB), a magnesium salt of gamma-hydroxybutyrate ($Mg.(GHB)_2$), and a calcium salt of gamma-hydroxybutyrate ($Ca.(GHB)_2$). The different salts may be present in different percentages. For example, in certain embodiments, the pharmaceutical composition comprises Na.GHB, K.GHB, and $Ca.(GHB)_2$. In certain embodiments, the Na.GHB salt is present in a wt/wt % of about 5% to about 40%, the K.GHB salt is present in a wt/wt % of about 10% to about 40%, and the $Ca.(GHB)_2$ salt is present in a wt/wt % of about 20% to about 80%. In certain embodiments, the Na.GHB, K.GHB, and $Ca.(GHB)_2$ salts are present in a wt/wt % ratio of about 11%:39%:50%, respectively.

Valproic Acid

Valproic acid (VPA, also called valproate or divalproex), an acidic chemical compound, has found clinical use as an anticonvulsant and mood-stabilizing drug, primarily in the treatment of epilepsy, bipolar disorder, and, less commonly, major depression. See G. Rosenberg, Cell. Mol. Life. Sci. 64 (2007) 2090-2103. It is also used to treat migraine headaches and schizophrenia. A typical dose of valproate varies by indication. Dosages for seizures are between 10 to 15 mg/kg/day, with potential increases of 5 to 10 mg/kg/day. VPA is a liquid at room temperature, but it can be reacted with a base such as sodium hydroxide to form the salt sodium valproate, which is a solid. The acid, salt, or a mixture of the two (valproate semisodium, divalproate) are marketed under the various brand names Depakote, Depakote ER, Depakene, Depakene Crono (extended release in Spain), Depacon, Depakine, Valparin and Stavzor.

Valproate is believed to affect the function of the neurotransmitter GABA in the human brain, making it an alternative to lithium salts in treatment of bipolar disorder. Its mechanism of action includes enhanced neurotransmission of GABA (by inhibiting GABA transaminase, which breaks down GABA). However, several other mechanisms of action in neuropsychiatric disorders have been proposed for valproic acid in recent years. See Rosenberg G (2007). "The mechanisms of action of valproate in neuropsychiatric disorders: can we see the forest for the trees?". *Cellular and Molecular Life Sciences* 64 (16): 2090-103.

Valproic acid also blocks the voltage-gated sodium channels and T-type calcium channels. These mechanisms make valproic acid a broad-spectrum anticonvulsant drug. Valproic acid is an inhibitor of the enzyme histone deacetylase 1 (HDAC1), hence it is a histone deacetylase inhibitor. Valproic acid may interact with carbamazepine, as valproates inhibit microsomal epoxide hydrolase (mEH), the enzyme responsible for the breakdown of carbamazepine-10,11 epoxide (the main active metabolite of carbamazepine) into inactive metabolites. (See Gonzalez, Frank J.; Robert H. Tukey (2006). "Drug Metabolism". In Laurence Brunton, John Lazo, Keith Parker (eds.). Goodman & Gilman's The Pharmacological Basis of Therapeutics (11th ed.). New York: McGraw-Hill. pp. 79.) By inhibiting mEH, valproic acid causes a buildup of the active metabolite, prolonging the effects of carbamazepine and delaying its excretion. Valproic acid also decreases the clearance of amitriptyline and nortriptyline.

Aspirin may decrease the clearance of valproic acid, leading to higher-than-intended serum levels of the anticonvulsant. Also, combining valproic acid with the benzodiazepine clonazepam can lead to profound sedation and increases the risk of absence seizures in patients susceptible to them.

Valproic acid and sodium valproate reduce the apparent clearance of lamotrigine (lamictal). In most patients, the lamotrigine dosage for coadministration with valproate must be reduced to half the monotherapy dosage.

Valproic acid is contraindicated in pregnancy, as it decreases the intestinal reabsorption of folate (folic acid), which leads to neural tube defects. Because of a decrease in folate, megaloblastic anemia may also result. Phenyloin also decreases folate absorption, which may lead to the same adverse effects as valproic acid.

Valproic acid, 2-propylvaleric acid, is synthesized by the alkylation of cyanoacetic ester with two moles of propylbromide, to give dipropylcyanoacetic ester. Hydrolysis and decarboxylation of the carboethoxy group gives dipropylacetonitrile, • which is hydrolyzed into valproic acid. See U.S. Pat. Nos. 3,325,361 and 4,155,929 and GB Pat. Nos. 980279 and 1522450. See also, T. R. Henry, "The History of Valproate in Clinical Neuroscience." Psychopharmacology bulletin (2003) 37 (Suppl 2):5-16.

Diclofenac

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) taken to reduce inflammation and as an analgesic reducing pain in certain conditions. Diclofenac is used to treat pain, inflammatory disorders, and dysmenorrhea and is a commonly used NSAID. See Auler et al., Brazilian Jour. Med. Bio. Res., (1977) 30:369-374 and Hasan, et al., and Pakistan Jour. Pharmaceutical Sciences, vol. 18, No. 1, January 2005, pp 18-24 both are hereby incorporated by reference in their entireties.

The name is derived from its chemical name: 2-(2,6-dichloranilino) phenylacetic acid, it may be supplied as either the sodium or potassium salt. Diclofenac is available as a generic drug in a number of formulations; including Dichlofenac diethylammonium applied topically to joints. Over-the-counter (OTC) use is approved in some countries for minor aches and pains and fever associated with common infections.

Diclofenac is typically absorbed readily, but absorption is delayed upon administration with food. Its half-life varies from 1 to 3 hours with mean peak plasma levels of about 0.5 ug/ml to 1.0 ug/ml after 2 hours of a single dose of 25 mg. Diclofenac binds to human serum proteins, specifically albumin. See Hasan et al 2005.

Ibuprofen

Ibuprofen (from iso-butyl-propanoic-phenolic acid) is a nonsteroidal anti-inflammatory drug (NSAID) widely prescribed for pain relief, fever reduction, and swelling. Ibuprofen was derived from propanoic acid. Originally marketed as Brufen, ibuprofen is available under a variety of popular trademarks, including Motrin, Nurofen, Advil, and Nuprin. Ibuprofen is used primarily for fever, pain, dysmenorrhea and inflammatory diseases such as rheumatoid arthritis. It is also used for pericarditis and patent ductus arteriosus. It is a commonly used drug commercially available over the counter.

Nonsteroidal anti-inflammatory drugs such as ibuprofen work by inhibiting the enzyme cyclooxygenase (COX), which converts arachidonic acid to prostaglandin H2 (PGH2). PGH2, in turn, is converted by other enzymes to several other prostaglandins (which are mediators of pain, inflammation, and fever) and to thromboxane A2 (which stimulates platelet aggregation, leading to the formation of blood clots).

Like aspirin and indomethacin, ibuprofen is a nonselective COX inhibitor, in that it inhibits two isoforms of cyclooxygenase, COX-1 and COX-2. The analgesic, antipyretic, and

anti-inflammatory activity of NSAIDs appears to operate mainly through inhibition of COX-2, whereas inhibition of COX-1 would be responsible for unwanted effects on the gastrointestinal tract. However, the role of the individual COX isoforms in the analgesic, anti-inflammatory, and gastric damage effects of NSAIDs is uncertain and different compounds cause different degrees of analgesia and gastric damage.

The synthesis of this compound consisted of six steps, started with the Friedel-Crafts acetylation of isobutylbenzene. Reaction with ethyl chloroacetate (Darzens reaction) gave the α,β-epoxy ester, which was hydrolyzed and decarboxylated to the aldehyde. Reaction with hydroxylamine gave the oxime, which was converted to the nitrile, then hydrolyzed to the desired acid. See U.S. Pat. No. 3,385,886.

An improved synthesis by BHC required only three steps. After a similar acetylation, hydrogenation with Raney nickel gave the alcohol, which underwent palladium-catalyzed carbonylation.

Valproate, diclofenac, and ibruprofen are monocarboxylate transporter inhibitors. One embodiment of the present application is a method to improve safety by monitoring the combination of these compounds with GHB.

Monocarboxylate Transporters

Monocarboxylate transporters, or MCTs, constitute a family of proton-linked plasma membrane transporters that carry molecules having one carboxylate group (monocarboxylates), such as lactate and pyruvate, across biological membranes. See Halestrap A P, Meredith D (2004). "The SLC16 gene family-from monocarboxylate transporters (MCTs) to aromatic amino acid transporters and beyond". Pflugers Arch. 447 (5): 619-28.

MCTs are a series of transporters which move chemicals in body tissues, such as kidneys, blood/brain barrier, intestines, etc. They can transport chemical compounds back from urine to create a higher concentration in the blood than the urine. They can be used to treat an overdose or to prevent excretion of a compound. They can also be used to prevent absorption or transport into the brain or gut, or excretion via the urine. Exemplary MCT inhibitors include valproate, diclofenac, and ibubrofen.

Concomitant Administration of GHB and Drug-Drug Interactions

In one embodiment of the present invention the concomitant administration of MCT inhibitors, such as either valproate, diclofenac, or ibuprofen with GHB can effect GHB levels or activity and alter the GHB safety and efficacy profile to create an unsafe condition. For example, valproate can increase or prolong GHB effects and diclofenac can reduce or shorten GHB effects. For example, if the effects are increased, then there could be an increase of adverse events associated with too much GHB. Also, the effect of GHB may be prolonged to cause side effects, such as excessive daytime sleepiness (EDS), to last into the daytime. Prolongation of the effect would counter the purpose for providing the GHB and could create an unsafe situation for patients who wish to be alert and who may be engaged in otherwise dangerous activity. This concomitant administration can transform an otherwise safe dose of GHB into one with safety concerns. It is a health risk to patients and a medical challenge to health care workers.

The drug-drug interaction could also reduce the effects of GHB by altering its blood levels or otherwise. Reduction in the GHB level may also provide an unsafe condition due to excessive daytime sleepiness. In each situation, where GHB is increased, decreased or excessively cleared, those drug-drug interactions need to be identified to a health care worker to adjust the dose of GHB or discontinue the use of the other compound.

As recited on the product insert for Xyrem®, healthcare providers should caution patients about operating hazardous machinery, including automobiles or airplanes, until they are reasonably certain that GHB does not affect them adversely (e.g., impair judgment, thinking, or motor skills). Patients should not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery or a motor vehicle or flying an airplane, for at least 6, 7, 8 or 9 hours after taking the second nightly dose of GHB.

In some embodiments in which diclofenac or valproate is discontinued to avoid an adverse drug interaction, they are discontinued within at least 3 days prior to or after starting GHB therapy. In various embodiments, diclofenac or valproate is discontinued within at least 4 days, or at least 5 days, or at least 6 days, or at least 7 days (or one week), or at least 8 days, or at least 9 days, or at least 10 days, or at least 11 days, or at least 12 days, or at least 13 days, or at least 14 days (or two weeks), or at least 15 days, or at least 16 days, or at least 17 days, or at least 18 days, or at least 19 days, or at least 20 days, or at least 21 days (or three weeks) prior to or after starting GHB therapy. In some embodiments, the diclofenac or valproate is discontinued no later than 2 weeks or 1 week before starting GHB therapy.

In some embodiments, a method of optimizing GHB therapy when valproate is provided comprises titrating the dosage of GHB administered to a patient downward relative to a previously administered dosage in the patient, so the dose does not result in an increased exposure to GHB. In some embodiments, a method of optimizing GHB therapy when diclofenac is provided comprises titrating the dosage of GHB administered to a patient upward relative to a previously administered dosage in the patient, so the dose results in an effective exposure to GHB.

Thus, the present invention includes a method for treating a patient who is suffering from excessive daytime sleepiness, cataplexy, sleep paralysis, apnea, narcolepsy, sleep time disturbances, hypnagogic hallucinations, sleep arousal, insomnia, and nocturnal myoclonus with a salt of gamma-hydroxybutyrate (GHB), wherein said patient is also being treated with valproate or diclofenac, comprising: administering to the patient a daily dose of a GHB salt wherein said daily dose is administered at an amount sufficient to reduce or eliminate such additive effects.

In one embodiment of the present invention, a reduced amount of GHB is administered to a patient when concomitantly administered with valproate. In another embodiment of the present invention, an increased amount of GHB is administered to a patient when concomitantly administered with diclofenac.

When valproate is concomitantly administered with GHB, The amount of GHB can be reduced at least 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% of the normal dose of GHB. For example, if the normal dose is 9 g/day, then a dose that is adjusted to reduce the normal dose by 15% is 7.65 g/day. The GHB dose reduction may be taken for one or multiple GHB dosings. For example, GHB may be administered in two doses per night for narcolepsy. A typical adult range of doses for GHB are between 4.5 or 6 g as a minimum and 8 or 10 g/day as a maximum divided into two doses. The dose recommended on the package insert and approved by the FDA is between 4.5 and 9.0 g/day. Typical exemplary paediatric daily doses of GHB are between 1 g and 6 g/day for pediatric patients aged 0-6 years. Typical exemplary paediat-

ric daily doses of GHB are between 1 g and 9 g/day for pediatric patients aged 7-17 years. However, these ranges are not absolute and can be increased or decreased by 1-2 grams in either direction. One dose is typically administered prior to bed (night time sleep) and another dose administered 1-2 hours later. See the Xyrem® package insert (Xyrem® is a registered trademark of Jazz Pharmaceuticals plc or its subsidiaries.). Either or both of the multiple doses may be reduced to present a safer administration profile. For example, the first dose may be reduced by the numbers referred to above or the second may be reduced by the same percentages, or both. Furthermore, the absolute amount of GHB per dose or per day may be reduced at least 0.5 g, 1 g, 1.5 g, 2.0 g, 2.5 g, 3.0 g, 3.5 g, or 4 g. An exemplary decrease in an adult dose would be to reduce the maximum dose to less than 8.5, 8, 7.5, 7, 6.5, 6, 5.5, 5, 4.5, 4, 3.5, 3 g/day and so on. The minimum dose will be reduced accordingly to 4, 3.5, 3, 2.5, 2, and so on.

In one embodiment of the present invention, diclofenac may dampen or delay the effect of GHB upon a patient during concomitant administration. In one embodiment, it may be useful to increase the amount of GHB that is administered to the patient. For example, GHB may be increased at least 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% of the normal dose of GHB. For example, if the normal dose is 10 g/day, then a dose that is adjusted to increase the normal dose by 15% is 11.5 g/day. The GHB dose increase may be taken for one or multiple GHB dosings. For example, GHB may be administered in two doses per night for narcolepsy. Either, or both, of the multiple doses may be increased to present a safer administration profile. For example, the first dose may be increased by the numbers referred to above or the second may be increased by the same percentages, or both. Furthermore, the absolute amount of GHB per dose or per day may be increased at least 0.5 g, 1 g, 1.5 g, 2.0 g, 2.5 g, 3.0 g, 3.5 g, or 4 g. An exemplary increase in an adult dose would be to increase the minimum dose to 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5 g/day and so on. An increase in the maximum dose would be at least 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14 g/day and so on.

In another aspect, a package or kit is provided comprising GHB, optionally in a container, and a package insert, package label, instructions or other labelling including any one, two, three or more of the following information or recommendations: (a) use of diclofenac or valproate should be avoided or discontinued, (b) concomitant administration of GHB with drugs that are MCT inhibitors, such as diclofenac or valproate can alter the therapeutic effect or adverse reaction profile of GHB, (c) concomitant administration of GHB and valproate resulted in an increase in exposure to GHB, (d) concomitant administration of GHB and diclofenac resulted in a decrease in exposure to GHB, and/or (e) MCT inhibitors should be used with caution in patients receiving GHB due to the potential for increased GHB clearance.

Alternatively, diclofenac can be administered to counteract the effects of GHB toxicity using a reverse of the numerical relationships above. Similarly, valproate can be used to increase the effects of GHB in patients that cannot take higher amounts of GHB. In this regard, the present invention includes methods for reducing the effects of GHB toxicity in a patient in need thereof, comprising administering to said patient an effective amount of diclofenac such that potential toxic effects of GHB are reduced. The present invention also includes methods for potentiating the beneficial effects of GHB in a patient in need thereof comprising concomitantly administering to said patient an effective amount of valproate such that the beneficial effects of GHB are increased.

The examples below, which show drug interaction studies in healthy adults, demonstrated those instances, test conditions or metrics which showed a distinction between GHB and either of the test compounds, diclofenac, valproate, or ibuprofen. Additionally, drug interaction studies in healthy adults demonstrated pharmacokinetic or clinically significant pharmacodynamic interactions between GHB and diclofenac or valproate.

Example 1

This study was designed to compare Pharmacokinetic (PK) and Pharmacodynamic (PD) endpoints of Xyrem® sodium oxysorbate (GHB) with and without concomitant administration of diclofenac. A crossover design was employed to allow within-subject comparisons of the PK and PD of Xyrem® dosed alone and in combination with diclofenac. The PK and PD effects of Xyrem® upon those of diclofenac were also studied.

The PD parameters included a selection of automated tests of attention, information processing, working memory and skilled coordination from the CDR System. (Rapeport et al, 1996ab; Williams et al, 1996). (Wesnes et al, 1997). (Wesnes et al, 2000) (Modi et al, 2007).

Methods

This was a Phase 1, randomized, double-blind, placebo-controlled, three-period, crossover study in healthy subjects. 24 subjects were recruited to ensure that 18 completed the study. Following Screening and Baseline procedures, eligible subjects were entered into the study and received one of the following treatments per period, in randomized order:

Diclofenac placebo administered as one capsule qid (doses separated by 4 hours during the day, eg, approximately 8 am, 12 pm, 4 pm, and 8 pm) for 2 days before concomitant administration day. On concomitant administration day, one diclofenac placebo capsule administered at −1 h and 3 h, and 3 g of Xyrem® administered at 0 h and 4 h.

Diclofenac administered as 50 mg immediate-release (IR) tablet (overencapsulated) qid (doses separated by 4 hours during the day, eg, approximately 8 am, 12 pm, 4 pm, and 8 pm) for 2 days before concomitant administration day. On concomitant administration day, 50 mg diclofenac administered at −1 h and 3 h and 3 g of Xyrem® administered at 0 h and 4 h.

Diclofenac administered as 50 mg IR tablet (overencapsulated) qid (doses separated by 4 hours during the day, eg, approximately 8 am, 12 pm, 4 pm, and 8 pm) for 2 days before concomitant administration day. On concomitant administration day, 50 mg diclofenac administered at −1 h and 3 h and Xyrem® placebo (volume equivalent to 3 g of Xyrem® oral solution) administered at 0 h and 4 h.

Subjects were randomized to one of the above treatments on Day 1, crossed over to another treatment on Day 6, and crossed over again to the remaining treatment on Day 11 (Table 1). Subjects were dosed in groups of up to 12. A 2-day washout period followed each of the treatment periods. The treatments were as follows: A=Diclofenac placebo (qid 4 h apart on the 1st and 2nd day and 2 doses on the 3rd day of the period)+Xyrem® two 3 g doses 4 h apart on the 3rd day of the period. B=Diclofenac (50 mg qid 4 h apart on the 1st and 2nd day and 2 doses on the 3rd day of the period)+Xyrem® two 3 g doses 4 h apart on the 3rd day of the period. C=Diclofenac (50 mg qid 4 h apart on the 1st and 2nd day and 2 doses on the 3rd day of the period)+Xyrem® placebo two doses 4 h apart on the 3rd day of the period. PD parameters include the following: Cognitive Drug Research (CDR) System tasks: Karolinska Sleepiness Scale (KSS), Simple Reaction Time

(SRT), Digit Vigilance (DV), Choice Reaction Time (CRT), Tracking and Numeric Working Memory (NWM).

Results

Power of attention-On this measure of focussed attention and information processing Xyrem® when co-dosed with diclofenac produced significantly less impairment than Xyrem® alone at 0.5 h; while the smaller impairments with the combination narrowly missed significance at 1 and 4.5 h. Xyrem® when co-dosed with diclofenac also resulted in impairments at two timepoints compared to diclofenac alone which at 6.5 h was significant and a trend at 8 h. See FIG. **1** which shows Change from Baseline Figure (LSmean with 95% CI) for Power of Attention (ms) (PD Completer Population).

Digit Vigilance Accuracy-On this measure of focussed attention Xyrem® when co-dosed with diclofenac produced significantly less impairment than Xyrem® alone at 1 and 2.5 h. See FIG. **2** which shows Change from Baseline Figure (LSmean with 95% CI) for Digit Vigilance Accuracy (%) (PD Completer Population).

Digit Vigilance Mean Reaction Time—On this measure of focussed attention Xyrem® when co-dosed with diclofenac produced significantly less impairment than Xyrem® alone at 1 and 2.5 h. See FIG. **3** which shows Change from Baseline Figure (LSmean with 95% CI) for Digit Vigilance Mean Reaction Time (ms) (PD Completer Population).

Choice Reaction Time Mean-Impairments to this measure of attention and information processing were significantly smaller than with Xyrem® alone when co-dosed with diclofenac during the hour following the first dose of Xyrem®. See FIG. **4** which shows Change from Baseline Figure (LSmean with 95% CI) for Choice Reaction Time Mean (ms) (PD Completer Population).

While diclofenac alone had no effect on sleepiness or cognitive function, when co-dosed with Xyrem® it significantly reduced the effects of the compound on Power of Attention and two of the contributing scores, simple and choice reaction time; these effects being seen during the hour after the first dose of Xyrem®. On the other hand, there was no evidence on any measure of greater cognitive impairment or sleepiness when the two compounds were co-dosed.

The extent of the reductions in the impairments to the ability to focus attention and efficiently process information were quite notable, and likely to be of clinical relevance. It is interesting that protective effect of diclofenac was not seen on the subjects ratings of alertness, such a dissociation having been seen previously with haloperidol in healthy elderly volunteers (Beuzan et al, 1991).

In conclusion, evidence of an interaction was seen in this study over the hour following the first dose of Xyrem® on the study days, the impairments being notably smaller when diclofenac was co-dosed with Xyrem®. There was no interaction however on the feelings of sleepiness in the subjects.

Example 2

This study is designed to compare the pharmacokinetic (PK) and pharmacodynamic (PD) endpoints of Xyrem® with and without co-administration of divalproex sodium extended-release tablets. The crossover design allows within-subject comparisons of the PK and PD of Xyrem® dosed alone and in combination with divalproex sodium extended-release tablets. PD parameters include the following: Cognitive Drug Research (CDR) System tasks: Karolinska Sleepiness Scale (KSS), Simple Reaction Time (SRT), Digit Vigilance (DV), Choice Reaction Time (CRT), Tracking and Numeric Working Memory (NWM).

The objectives of this study were to evaluate the PK and PD of Xyrem® co-administered with divalproex sodium extended-release tablets and to evaluate and compare the safety and tolerability of Xyrem® with and without co-administration of divalproex sodium extended-release tablets.

This was a Phase 1, randomized, double-blind, placebo-controlled, five-period, crossover study in healthy male subjects. The study was conducted in approximately 24 healthy subjects to ensure completion of 16 subjects. Following Screening and Baseline procedures, eligible subjects were randomized to receive Xyrem® and Xyrem® placebo in a crossover fashion in Periods 1 and 2; were dosed with divalproex sodium extended-release tablets for 10 consecutive days in Period 3; and while continuing to take divalproex sodium extended-release tablets, were randomized to receive Xyrem® and Xyrem® placebo in a crossover fashion in Periods 4 and 5 (Table 1).

Periods 1 and 2:

Subjects were randomized to receive two 3 g doses of Xyrem® or Xyrem® placebo 4 hours apart in a crossover fashion at approximately 9 AM (first dose) and 1 PM (second dose) on Days 1 and 3. PK and PD parameters were evaluated during the 24 hours postdose.

Blood samples (4 mL) for sodium oxybate concentrations were collected at predose and at specified time-points up to 12 hours after the first dose of Xyrem® or Xyrem® placebo on Days 1 and 3. A PD Battery including the Karolinska Sleepiness Scale, Simple Reaction Time task, Digit Vigilance task, Choice Reaction Time task, Tracking task, and Numeric Working Memory task was administered at planned time-points up to X hours after first dose (X hours after second dose), and safety were monitored at specified timepoints on Days 1 and 3 as well as throughout the periods.

Period 3:

All subjects received divalproex sodium extended-release tablets 1250 mg at approximately 8 AM on Days 5 through 14. Blood samples (4 mL) for valproic acid concentrations were collected before the divalproex sodium dose (to determine trough concentration for assessment of steady state) on Days 13 and 14. Safety was monitored at specified timepoints as well as throughout the period.

Periods 4 and 5:

Subjects continued taking 1250 mg divalproex sodium extended-release tablets at approximately 8 AM on Days 15 through 18. Subjects were also randomized to receive two 3 g doses of Xyrem® or Xyrem® placebo in a crossover fashion at approximately 9 am (first dose) and 1 pm (second dose) on Days 15 and 18. The first dose of Xyrem® or Xyrem® placebo was taken approximately 1 hour after dosing with divalproex sodium extended-release tablets, and the second dose of Xyrem® or Xyrem® placebo was taken 4 hours after the first Xyrem®/Xyrem® placebo dose.

Blood samples (4 mL) to measure plasma sodium oxybate concentrations were collected at pre Xyrem®/Xyrem® placebo dose and at specified timepoints after the first Xyrem® or Xyrem® placebo dose on Days 15 and 18. Blood samples (4 mL) to measure plasma valproic acid concentrations were collected pre divalproex sodium dose and at specified time-points after the dose of divalproex sodium extended-release tablets on Day 15 and 18.

The PD battery was administered on Day 15 and 18, and safety was monitored at specified times on Days 15 and 18 as well as throughout the periods.

The treatments were as follows: A=Xyrem®, two 3 g doses, 4 hours apart at approximately 9 AM (1^{st} dose) and 1

PM (2nd dose); B=Xyrem® placebo, two doses, 4 hours apart; and C=Divalproex sodium 1250 mg, once a day at approximately 8 AM.

Results

The results below show the tests in which GHB administration was affected by concomitant administration of any of three MCT inhibitors, such as valproate, diclofenac, and ibubrofen.

Continuity of Attention

Xyrem® and divalproex sodium together (A+C) when compared to Xyrem® alone (A) showed a slightly delayed recovery for the combination at 4 hours and 8 hours. See FIG. **5** which shows Change from Baseline Figure (LSmean with 95% CI) for Continuity of Attention (#) (PD Population).

Simple Reaction Time Mean

At 1 hour and 4 hours, Xyrem® and divalproex sodium together produced statistically reliably greater impairments than Xyrem® alone. See FIG. **6**, which shows Change from Baseline Figure (LSmean with 95% CI) for Simple Reaction Time Mean (ms) (PD Population).

Digit Vigilance Accuracy

At 2.5 and 4 hours Xyrem® and divalproex sodium together were statistically reliably different greater impairment to Xyrem® alone. See FIG. **7**, which shows Change from Baseline Figure (LSmean with 95% CI) for Digit Vigilance Accuracy (%) (PD Population).

Tracking Distance from Target

Xyrem® and divalproex sodium together (A+C) when compared to Xyrem® alone (A) showed a statistically significant difference by a slightly delayed recovery for the combination at 4 and 8 hours. See FIG. **8** which shows the Change from Baseline Figure (LSmean with 95% CI) for Tracking Distance from Target (mm) (PD Population).

Numeric Working Memory Sensitivity Index

Xyrem® and divalproex sodium together (A+C) when compared to Xyrem® alone (A) showed a difference at 4.5 through 8 hours. See FIG. **9**, which shows the Change from Baseline Figure (LSmean with 95% CI) for Numeric Working Memory Sensitivity Index (#) (PD Population).

Numeric Working Memory Mean Reaction Time

Xyrem® and divalproex sodium together (A+C) when compared to Xyrem® alone (A) showed statistically significant differences at 2.5, 5 and 8 hours when the combination produced greater impairment. See FIG. **10**, which shows the Change from Baseline Figure (LSmean with 95% CI) for Numeric Working Memory Mean Reaction Time (ms) (PD Population).

In addition, it was observed that renal excretion of GHB increase 30% upon co-administration of Valproate.

We also found pk changes which were consistent with the inhibition of GHB dehydrogenase. This effect will increase the exposure of GHB to the subject and increase Cmax and AUC about 15%.

The combination of Xyrem® dosed with divalproex sodium was compared to divalproex sodium alone, more consistent statistically significant impairments over time were seen with the combination, than when Xyrem® was compared to its placebo, indicating that the effects of co-administration, when they appeared, were in the direction of increased impairments.

As has been seen previously, Xyrem® induces sleepiness and produces impairments to attention, working memory and performance on a tracking task in healthy volunteers. Divalproex sodium alone showed no consistent or notable effects on cognitive function or sleepiness. There were occasions when co-administration of Xyrem® and divalproex sodium produced greater deficits than Xyrem® alone. Further the combination also produced more consistent impairments when compared with divalproex sodium alone, than did Xyrem® when compared to its placebo. Thus this study has found evidence that co-administration of Xyrem® and divalproex produces greater impairments to cognitive function and sleepiness than were seen with Xyrem® alone.

Example 3

The effects of Ibuprofen were evaluated when combined with Xyrem® in a manner similar to the above. No differences were seen using the metrics above for Karolinska Sleepiness Scale (KSS), and the following CDR System tasks: Simple Reaction Time, Digit Vigilance, Choice Reaction Time, Tracking and Numeric Working Memory. However, it was observed that renal excretion of Xyrem® doubled upon concomitant administration of Ibuprofen and Xyrem®.

All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those skilled in the art in light of the teachings of the specification that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

What is claimed is:

1. A method for treating a patient who is suffering from excessive daytime sleepiness, cataplexy, sleep paralysis, apnea, narcolepsy, sleep time disturbances, hypnagogic hallucinations, sleep arousal, insomnia, or nocturnal myoclonus with gamma-hydroxybutyrate (GHB) or a salt thereof, said method comprising:

orally administering to the patient in need of treatment at least 5% decrease in an effective dosage amount of the GHB or salt thereof when the patient is receiving a concomitant administration of valproate, an acid, salt, or mixture thereof.

2. The method in accordance with claim **1**, wherein there is at least about a 15% reduction in the effective dosage amount of the GHB or salt thereof given to the patient and wherein the valproate, acid, salt or mixture thereof is divalproex sodium.

3. The method in accordance with claim **2**, wherein the dose of the GHB or salt thereof given to the patient without concomitant administration of valproate, an acid, salt or mixture thereof is from 4.5 to 9 grams per day.

4. The method in accordance with claim **1**, wherein the effective dosage amount is a reduction of about 5% to 10%, about 10% to 15%, about 15% to 20%, about 20% to 25%, about 25% to 30%, about 30% to 35%, about 35% to 40%, about 40% to 45%, or about 45% to 50%, relative to the dose of the GHB or salt thereof normally given to the patient.

5. The method in accordance with claim **1**, wherein the patient is suffering from narcolepsy.

6. The method in accordance with claim **1**, further comprising administering aspirin to the patient.

7. The method in accordance with claim **1**, wherein the effective dosage amount of the GHB or a salt thereof is reduced from a range of 4.5 to 9 grams per day.

8. The method in accordance with claim **1**, wherein the dose of the GHB or salt thereof without concomitant administration of valproate, an acid, salt or mixture thereof is from 4.5 to 9 grams per day.

9. The method in accordance with claim **1**, wherein the effective dosage amount of the GHB or salt thereof is between 3 grams and 7 grams per day.

10. The method in accordance with claim 1, wherein the effective dosage amount of the GHB or salt thereof is between 3.5 grams and 4 grams per day.

11. A method of safely administering GHB or a salt thereof for excessive daytime sleepiness, cataplexy, sleep paralysis, apnea, narcolepsy, sleep time disturbances, hypnagogic hallucinations, sleep arousal, insomnia, or nocturnal myoclonus in a human patient who is being administered GHB, said method comprising:

determining if the patient has taken, or will take, a concomitant dose of valproate, an acid, salt or mixture thereof; and

orally administering a reduced amount of the GHB or salt thereof to the patient wherein the reduction is at least 5% compared to a dose without concomitant administration of valproate, an acid, salt or mixture thereof.

12. The method in accordance with claim 11, wherein the amount of GHB or salt thereof is reduced at least 10% to 30%.

13. The method in accordance with claim 11, wherein the amount of GHB or salt thereof is reduced at least 15% patient and wherein the valproate, acid, salt, or mixture thereof is divalproex sodium.

14. The method in accordance with claim 11, wherein the valproate, acid, salt or mixture thereof is administered within two weeks of administration of the GHB or salt thereof.

15. The method in accordance with claim 11, wherein the valproate, acid, salt or mixture thereof is administered within three days of administration of the GHB or salt thereof.

16. The method in accordance with claim 11, wherein the patient is suffering from narcolepsy.

17. The method in accordance with claim 11, further comprising administering aspirin to the patient.

18. The method in accordance with claim 11, further comprising recommending to decrease the dose of GHB or salt thereof by 20% patient and wherein the valproate, acid, salt, or mixture thereof is divalproex sodium.

19. A method for treating a patient who is suffering from narcolepsy, said method comprising:

administering a therapeutically effective amount of a formulation containing a GHB salt to a patient starting at a concentration of between 350 and 750 mg/ml with a pH of between 6 and 10;

determining if the patient is also being administered valproate, an acid, salt or mixture thereof;

warning of a potential drug/drug interaction due to the combination of valproate, an acid, salt or mixture thereof and the GHB salt; and

recommending reducing the dose of the GHB salt at least 15%.

20. The method in accordance with claim 19, wherein the valproate, acid, salt or mixture thereof is administered within two weeks of administration of the GHB salt.

21. The method in accordance with claim 19, wherein the valproate, acid, salt or mixture thereof is administered within three days of administration of the GHB salt.

22. The method in accordance with claim 19, wherein the GHB salt is administered starting at a concentration of between 450 to 550 mg/ml.

23. The method in accordance with claim 22, further comprising adding water to the GHB salt formulation.

24. The method in accordance with claim 19, wherein the GHB salt formulation has a pH between 6.5 and 8.

25. The method in accordance with claim 19, further comprising administering the reduced dose of the GHB salt to the patient.

26. The method in accordance with claim 19, wherein the GHB salt comprises a single salt or a mixture of salts of GHB selected from the group consisting of a sodium salt of hydroxybutyrate (Na.GHB), a potassium salt of gamma-hydroxybutyrate (K.GHB), a magnesium salt of gamma-hydroxybutyrate ($Mg.(GHB)_2$), and a calcium salt of gamma-hydroxybutyrate ($Ca.(GHB)_2$).

27. The method in accordance with claim 19, further comprising administering aspirin to the patient.

28. The method in accordance with claim 19, comprising recommending reducing a dose of GHB or salt thereof at least 20% patient and wherein the valproate, acid, salt, or mixture thereof is divalproex sodium.

29. The method in accordance with claim 19, further comprising adding water to the GHB salt formulation.

30. A method for treating a patient who is suffering from narcolepsy, said method comprising:

administering a therapeutically effective amount of a formulation containing a GHB salt to a patient;

determining if the patient is also being administered valproate, an acid, salt or mixture thereof;

recommending a 20% decrease in the starting dose of the GHB salt such that a patient starts taking the GHB salt at an adjusted dosage amount between 3.5 grams and 4 grams the GHB salt per night administered orally.

31. The method in accordance with claim 30, wherein the starting adjusted dosage amount of the GHB salt is about 3.6 grams.

32. The method in accordance with claim 30, further comprising optionally diluting the GHB salt formulation from a starting concentration of between 350 and 750 mg/ml with a pH of between 6 and 10.

33. A method for treating a patient who is suffering from narcolepsy, said method comprising:

orally administering a therapeutically effective amount of a formulation containing a GHB salt;

determining if the patient is also being administered valproate, an acid, salt or mixture thereof;

recommending a 20% decrease in the starting dose of the GHB salt such that the amount that the patient is administered is reduced to about 3.6 grams GHB per day.

34. The method in accordance with claim 33, further comprising optionally diluting the GHB salt formulation from a starting concentration of between 350 and 750 mg/ml with a pH of between 6 and 10.

* * * * *

EXHIBIT I

US009050302B2

(12) **United States Patent**
Eller

(10) **Patent No.: US 9,050,302 B2**
(45) **Date of Patent: *Jun. 9, 2015**

(54) **METHOD OF ADMINISTRATION OF GAMMA HYDROXYBUTYRATE WITH MONOCARBOXYLATE TRANSPORTERS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/837,714**

(22) Filed: **Mar. 15, 2013**

(65) **Prior Publication Data**

US 2014/0249115 A1 Sep. 4, 2014

Related U.S. Application Data

(60) Provisional application No. 61/771,557, filed on Mar. 1, 2013, provisional application No. 61/777,873, filed on Mar. 12, 2013.

(51) **Int. Cl.**

A01N 37/36	(2006.01)
A61K 31/19	(2006.01)
A61K 31/616	(2006.01)
A61K 31/20	(2006.01)
A61K 31/33	(2006.01)
A61K 31/505	(2006.01)
A61K 31/55	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/19*** (2013.01); ***A61K 31/616*** (2013.01); ***A61K 31/20*** (2013.01); ***A61K 31/33*** (2013.01); ***A61K 31/505*** (2013.01); ***A61K 31/55*** (2013.01)

(58) **Field of Classification Search**

USPC 514/163, 557

See application file for complete search history.

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(57) **ABSTRACT**

One embodiment of the present invention is to improve the safety and efficacy of the administration of GHB or a salt thereof to a patient. It has been discovered that the concomitant administration of an MCT inhibitor, such as diclofenac, valproate, or ibuprofen, will affect GHB administration. For example, it has been discovered that diclofenac lowers the effect of GHB in the body, thereby potentially causing an unsafe condition. Furthermore, it has been discovered that valproate increases the effect of GHB on the body, thereby potentially causing an unsafe condition.

31 Claims, 10 Drawing Sheets

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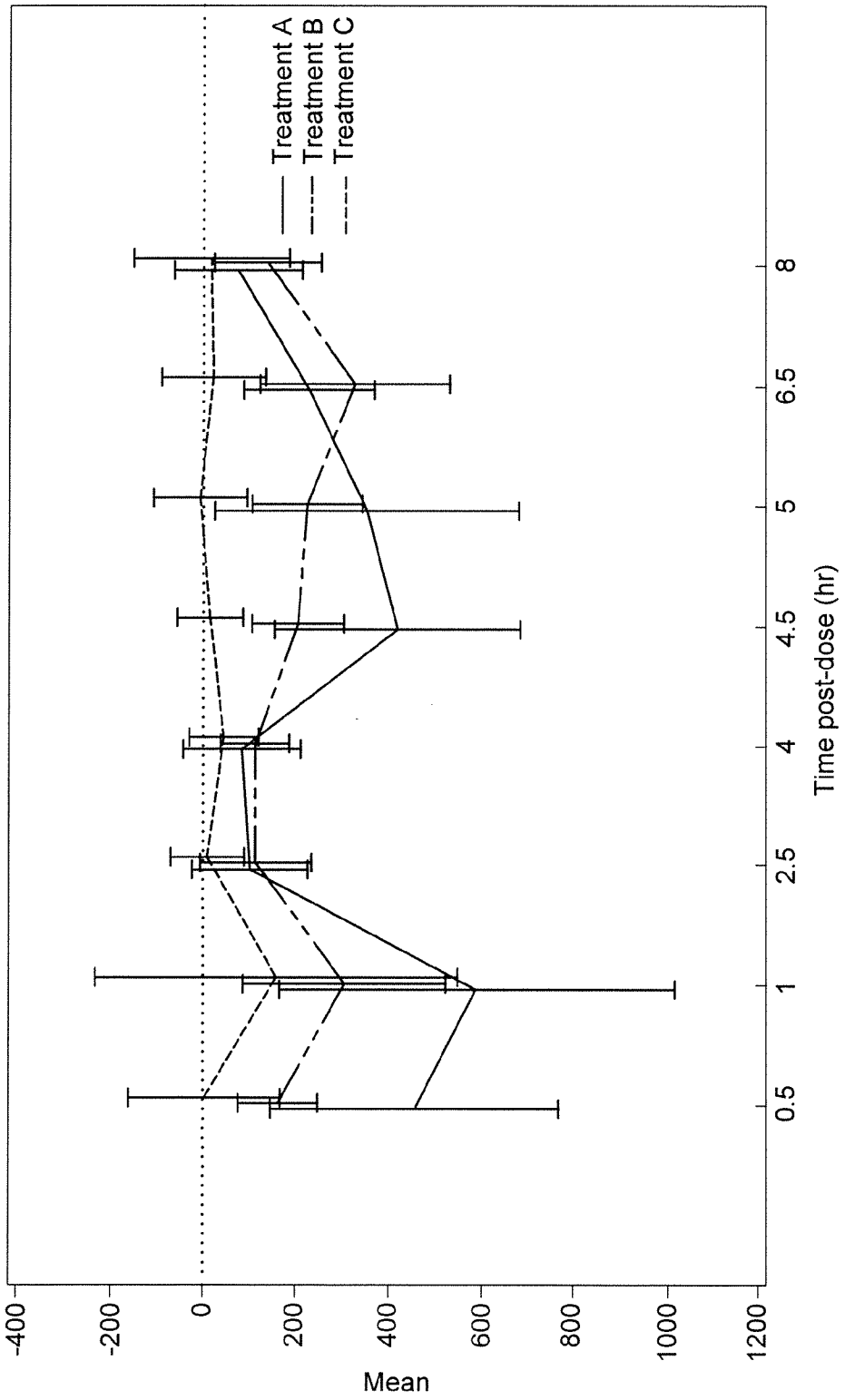
Treatment A
Treatment B
Treatment C
Mean
-400
-200
0
200
400
600
800
1000
1200
Time post-dose (hr)
0.5
1
2.5
4
4.5
5
6.5
8

FIG. 1

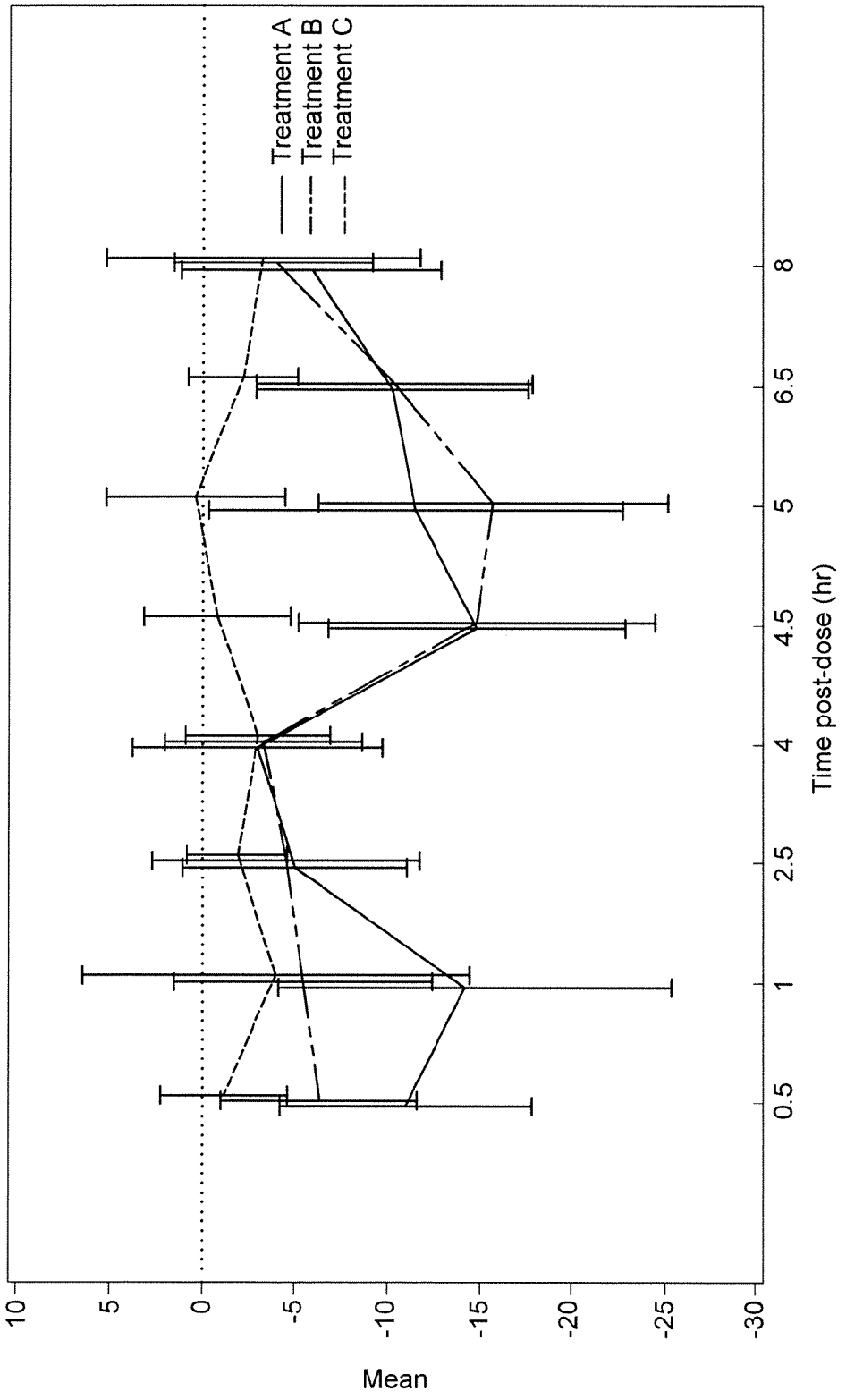
Treatment A
Treatment B
Treatment C
Mean
10
5
0
-5
-10
-15
-20
-25
-30
Time post-dose (hr)
0.5
1
2.5
4
4.5
5
6.5
8

FIG. 2

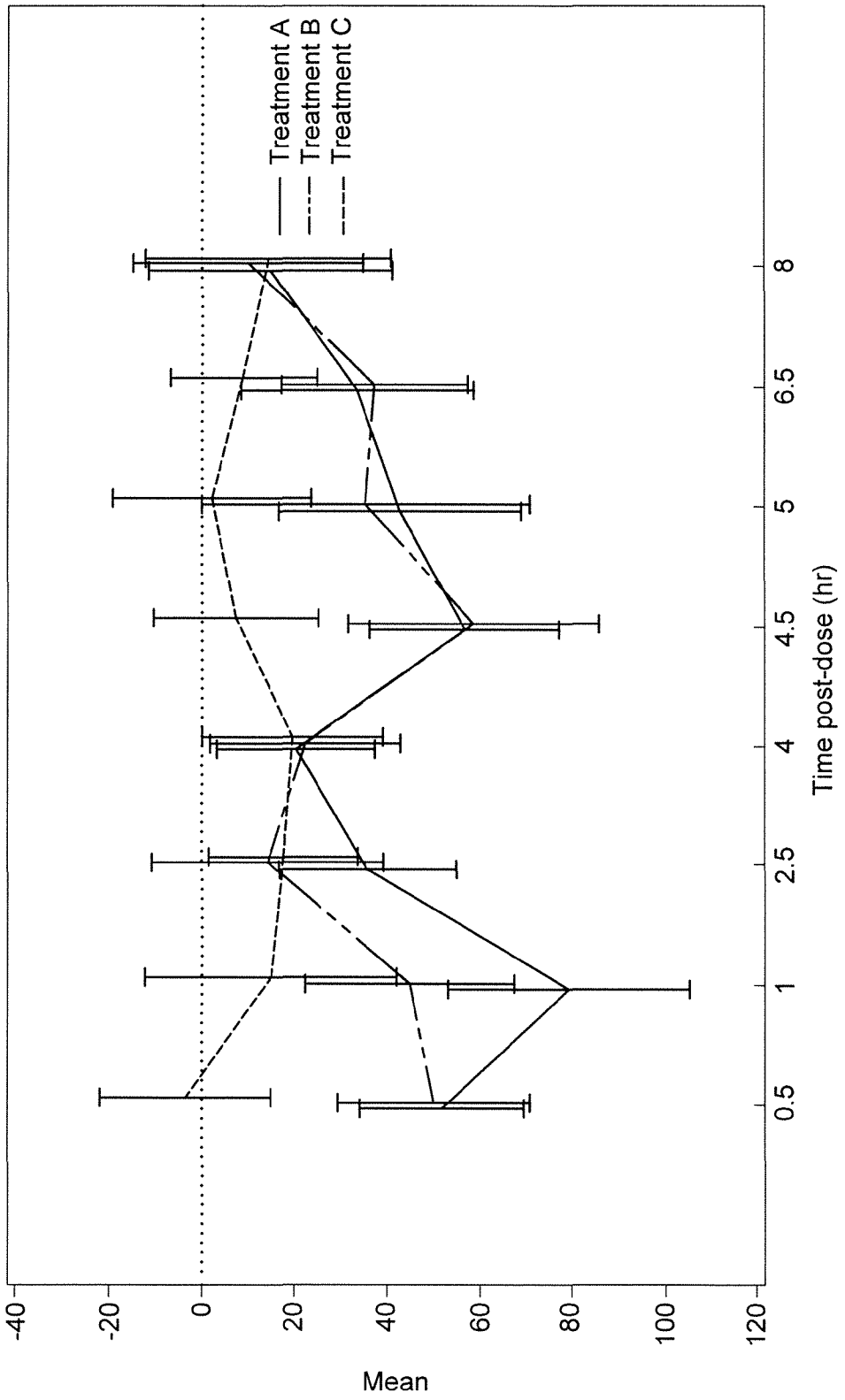
Treatment A
Treatment B
Treatment C
Mean
-40
-20
0
20
40
60
80
100
120
Time post-dose (hr)
0.5
1
2.5
4
4.5
5
6.5
8

FIG. 3

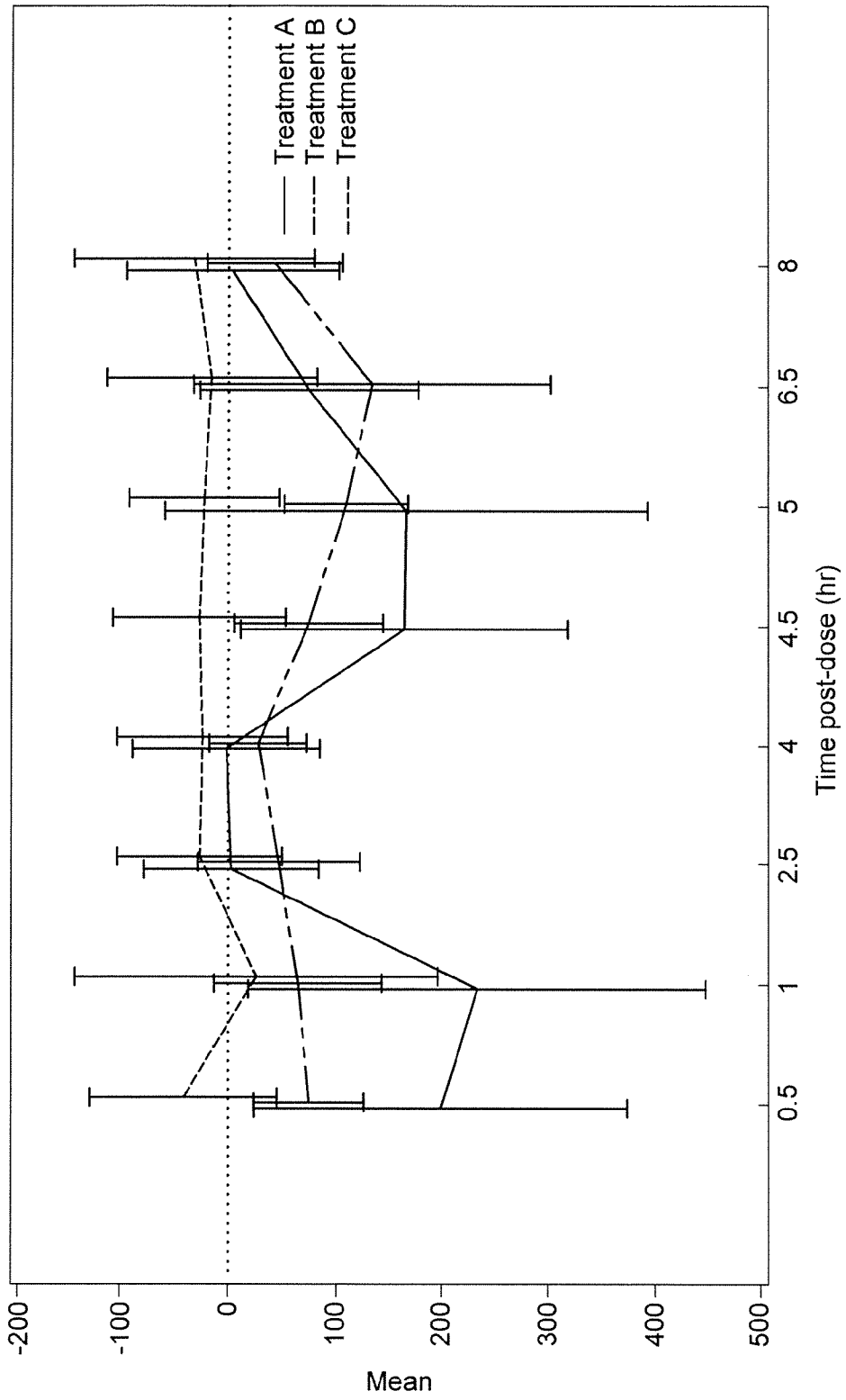
Treatment A
Treatment B
Treatment C
-200
-100
0
100
200
300
400
500
Mean
0.5
1
2.5
4
4.5
5
6.5
8
Time post-dose (hr)

FIG. 4

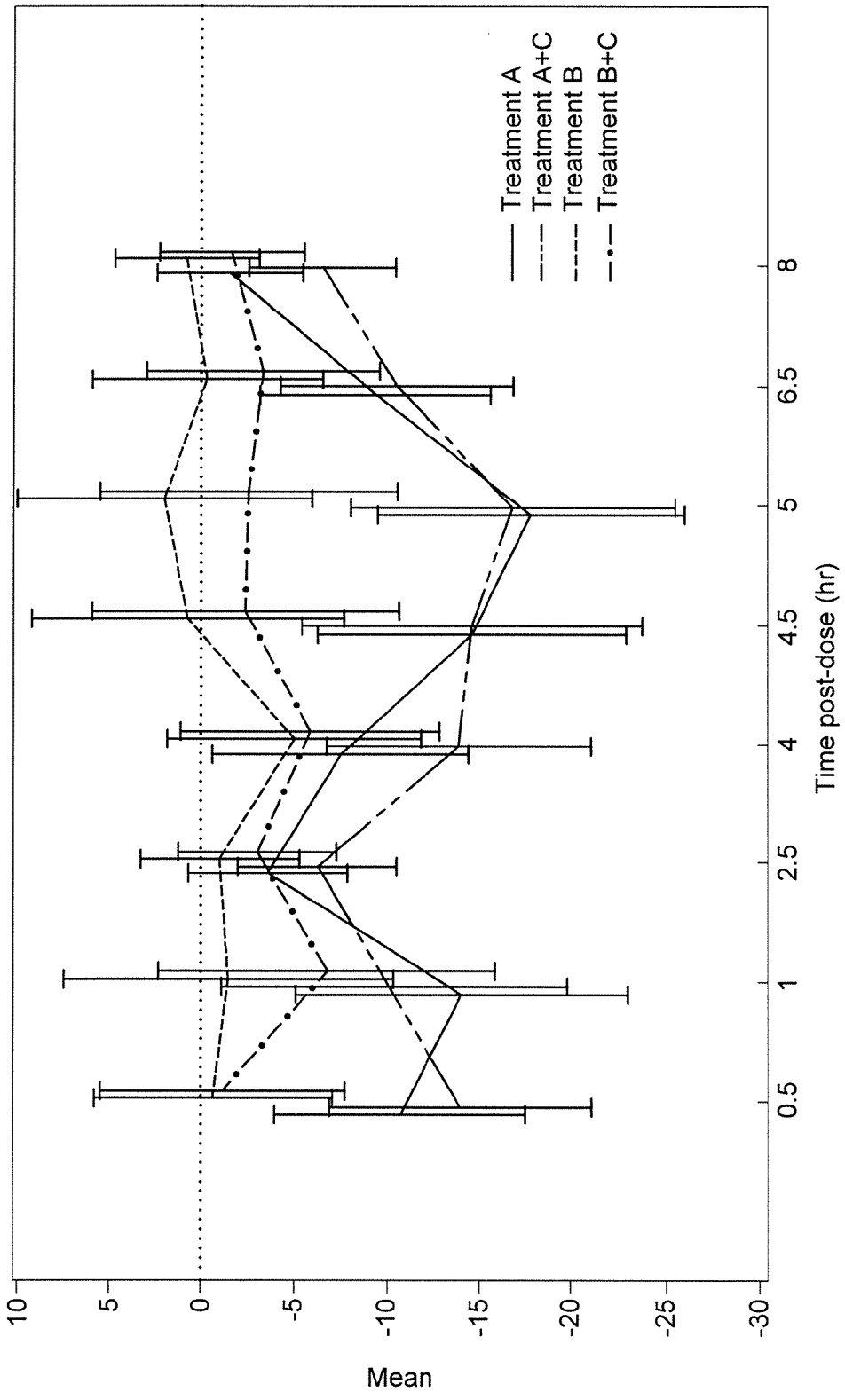
Treatment A
Treatment A+C
Treatment B
Treatment B+C
Time post-dose (hr)
0.5
1
2.5
4
4.5
5
6.5
8
Mean
10
5
0
-5
-10
-15
-20
-25
-30

FIG. 5

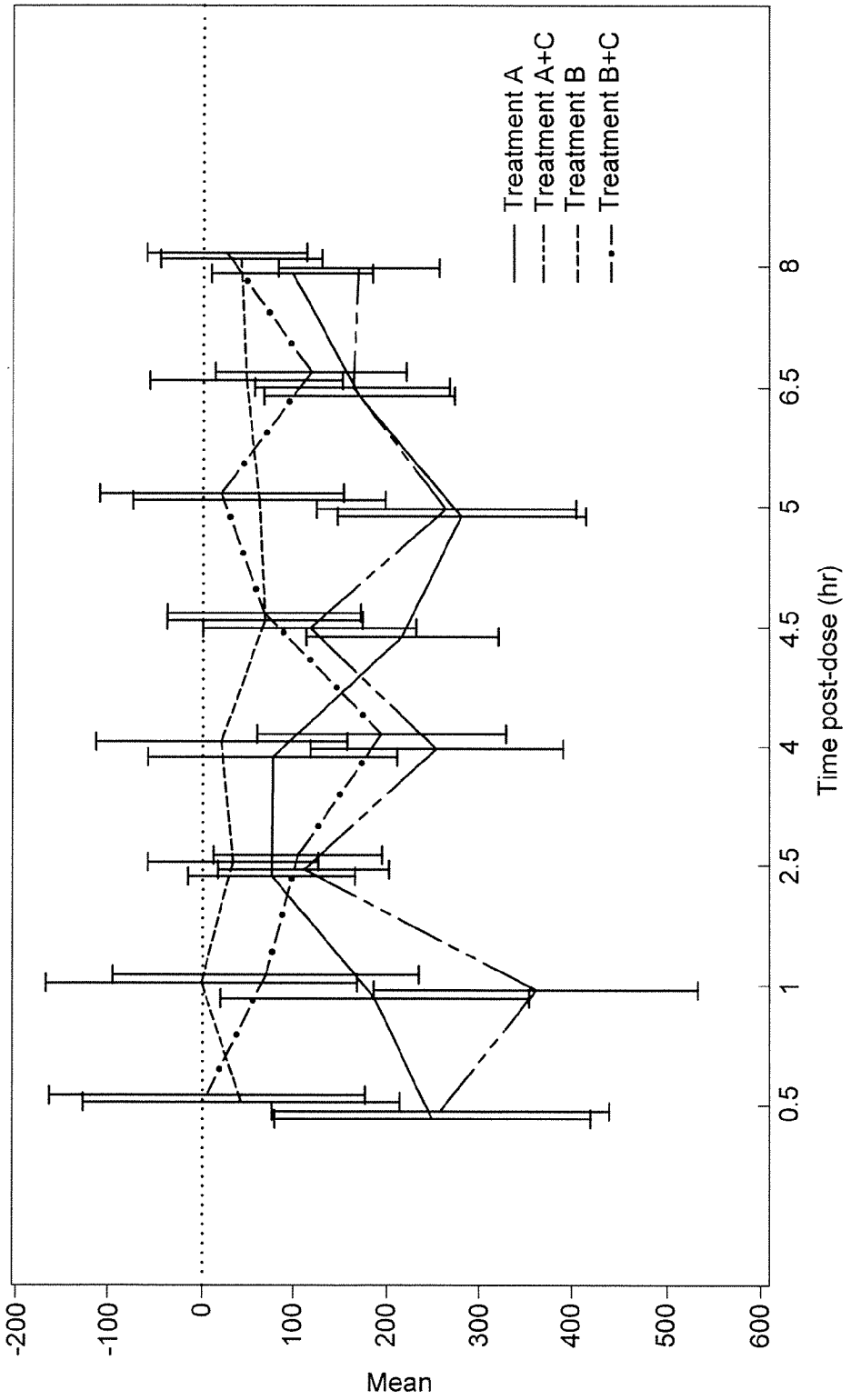
Treatment A
Treatment A+C
Treatment B
Treatment B+C
-200
-100
0
100
200
300
400
500
600
Mean
0.5
1
2.5
4
4.5
5
6.5
8
Time post-dose (hr)

FIG. 6

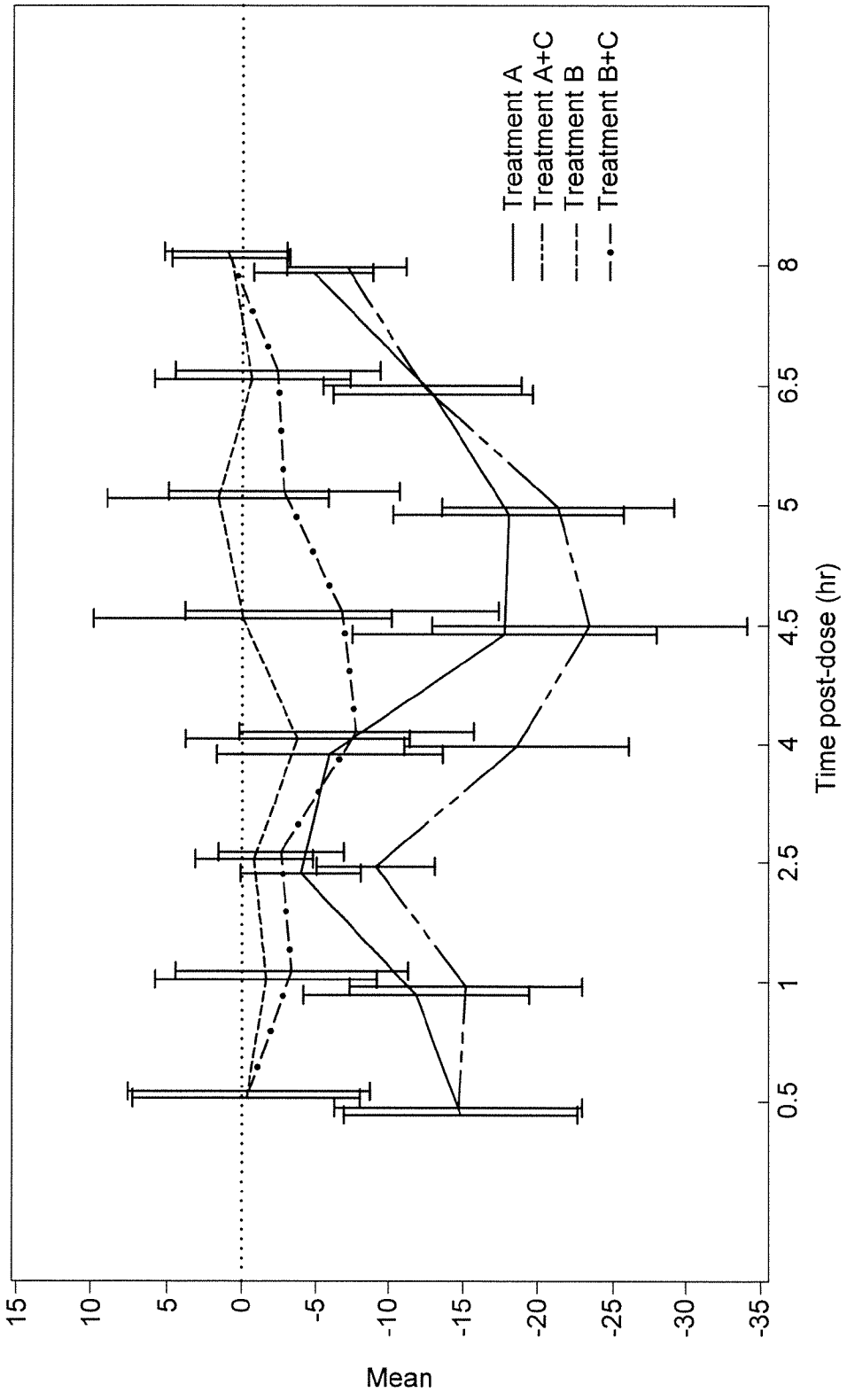
Treatment A
Treatment A+C
Treatment B
Treatment B+C
Time post-dose (hr)
0.5
1
2.5
4
4.5
5
6.5
8
Mean
15
10
5
0
-5
-10
-15
-20
-25
-30
-35

FIG. 7

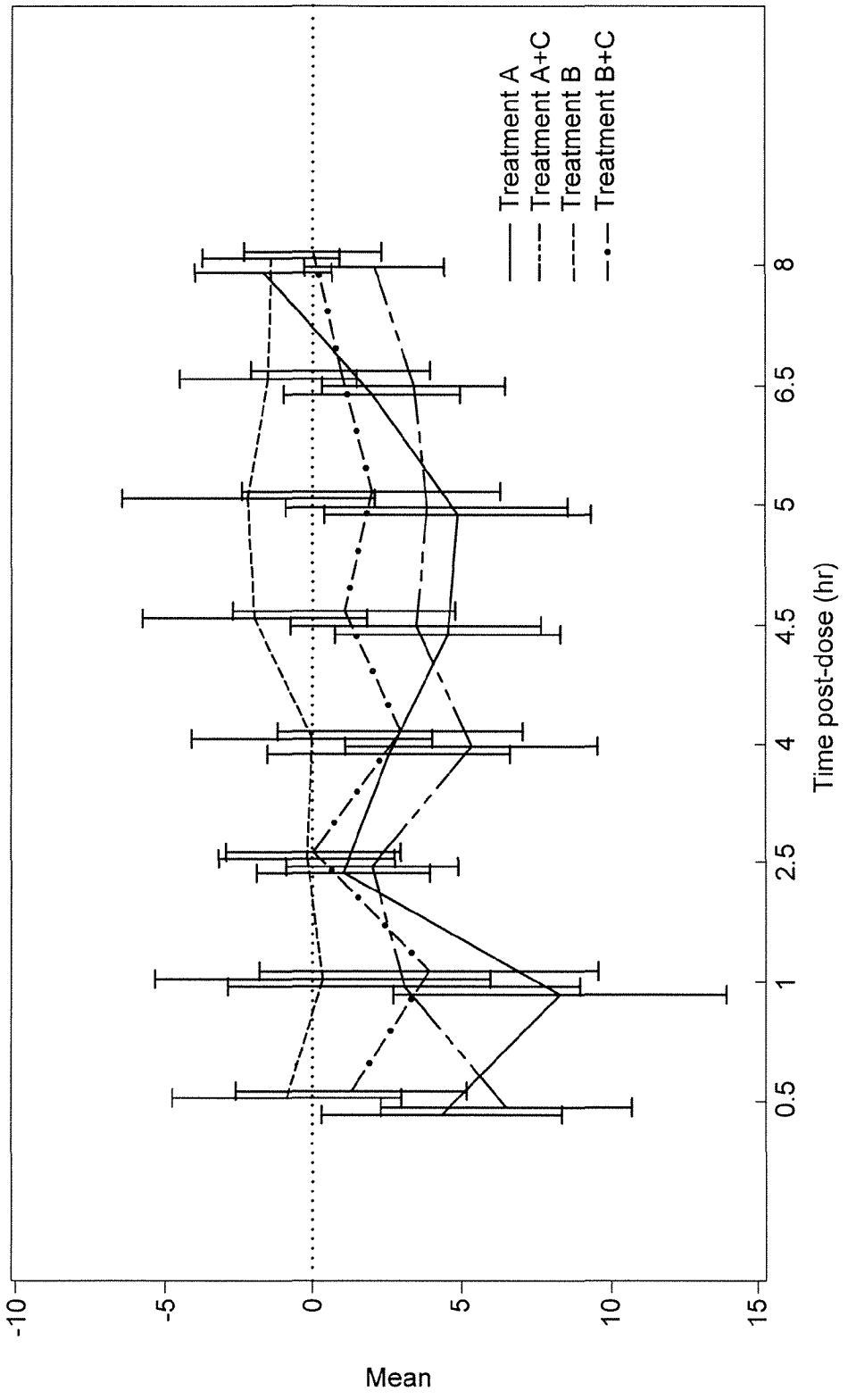
Treatment A
Treatment A+C
Treatment B
Treatment B+C
Time post-dose (hr)
0.5
1
2.5
4
4.5
5
6.5
8
Mean
-10
-5
0
5
10
15

FIG. 8

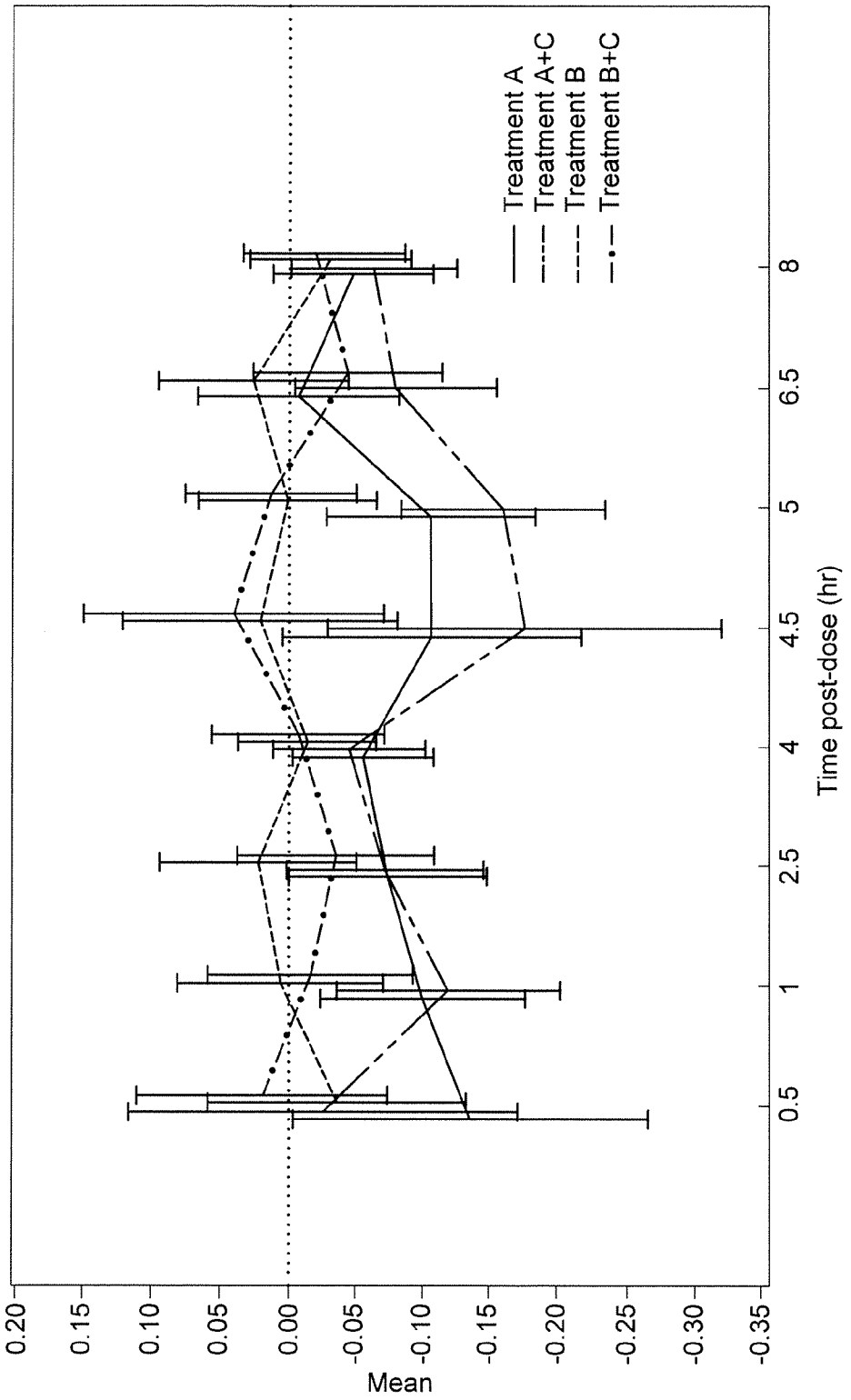
Treatment A
Treatment A+C
Treatment B
Treatment B+C
0.20
0.15
0.10
0.05
0.00
-0.05
-0.10
-0.15
-0.20
-0.25
-0.30
-0.35
Mean
0.5
1
2.5
4
4.5
5
6.5
8
Time post-dose (hr)

FIG. 9

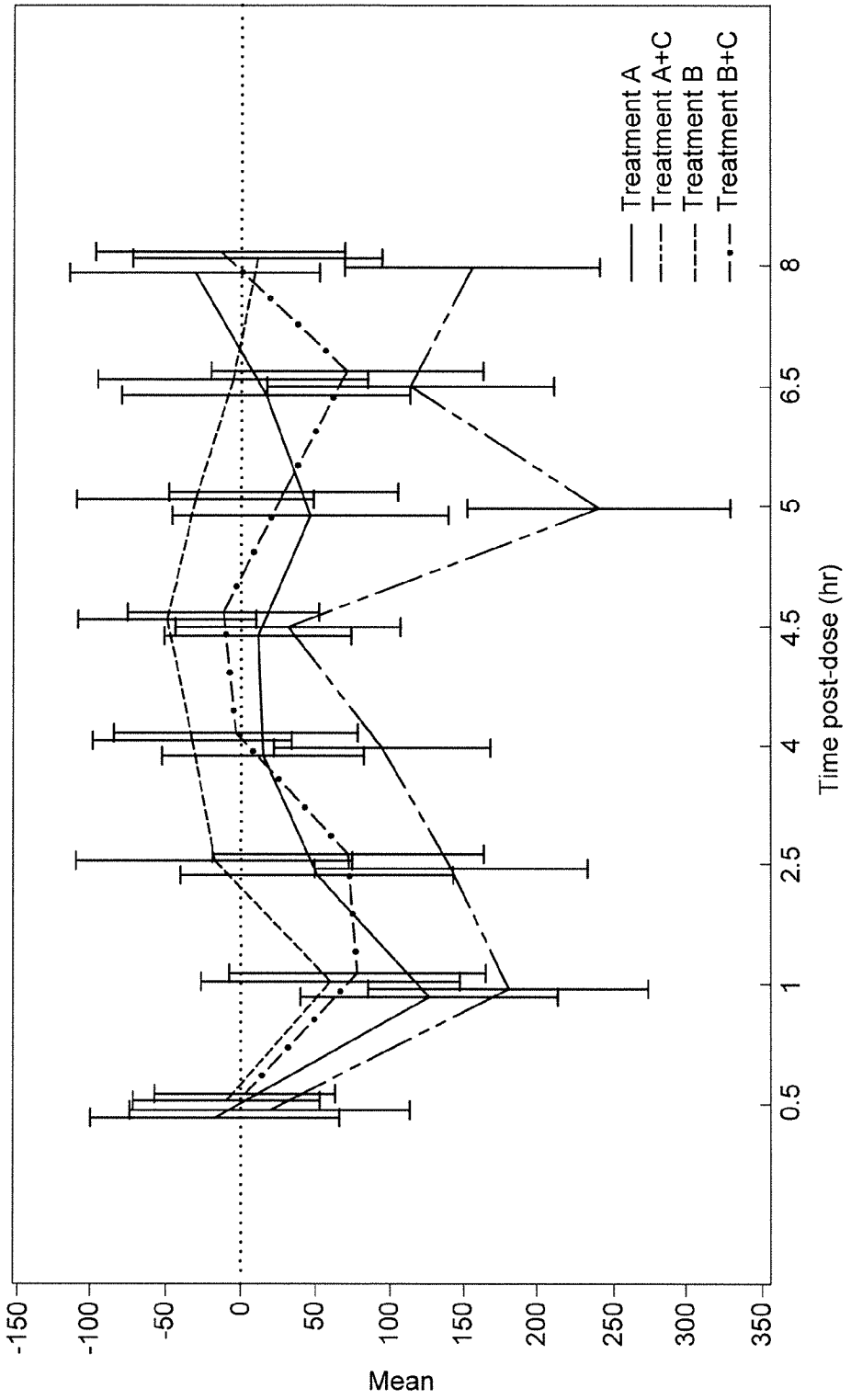
Treatment A
Treatment A+C
Treatment B
Treatment B+C
Time post-dose (hr)
0.5
1
2.5
4
4.5
5
6.5
8
Mean
-150
-100
-50
0
50
100
150
200
250
300
350

FIG. 10

METHOD OF ADMINISTRATION OF GAMMA HYDROXYBUTYRATE WITH MONOCARBOXYLATE TRANSPORTERS

This application claims the benefit of U.S. Provisional Application No. 61/771,557, filed Mar. 1, 2013, and U.S. Provisional Application No. 61/777,873, filed Mar. 12, 2013, each of which is hereby incorporated by reference in its entirety.

BACKGROUND

This application relates to methods for safely administering gamma hydroxybutyrate (GHB) together with one or more other monocarboxylate transporter (MCT) inhibitors for therapeutic purposes. Example transporter inhibitors are valproate, diclofenac, and ibuprofen and combinations thereof.

SUMMARY OF THE INVENTION

One embodiment of the present invention is a method for treating a patient who is suffering from excessive daytime sleepiness, cataplexy, sleep paralysis, apnea, narcolepsy sleep time disturbances, hypnagogic hallucinations, sleep arousal, insomnia, and nocturnal myoclonus with gamma-hydroxybutyrate (GHB) or a salt thereof, comprising: orally administering to the patient in need of treatment, an adjusted dosage amount of the salt of GHB when the patient is receiving a concomitant administration of valproate. In certain embodiments, the adjusted amount is reduced at least about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% of the normal dose of the salt of GHB normally given to the patient. In certain embodiments, the amount of GHB is reduced at least about 10% and about 30% of the normal administration and the daily administration of the GHB salt is between 1 gram and 10 grams. In certain embodiments, the adjusted amount is reduced between the ranges of about 1% to 5%, about 5% to 10%, about 10% to 15%, about 15% to 20%, about 20% to 25%, about 25% to 30%, about 30% to 35%, about 35% to 40%, about 40% to 45%, or about 45% or 50%, relative to the normal dose of the salt of GHB normally given to the patient. In certain embodiments, the adjusted amount is reduced between the range of about 1% to 50%, about 1% to 45%, about 1% to 40%, about 1% to 35%, about 1% to 30%, about 1% to 25%, about 1% to 20%, about 1% to 15%, about 1% to 10%, about 1% to 5%, about 5% to 50%, about 5% to 45%, about 5% to 40%, about 5% to 35%, about 5% to 30%, about 5% to 25%, about 5% to 20%, about 5% to 15%, about 5% to 10%, about 10% to 50%, about 10% to 45%, about 10% to 40%, about 10% to 35%, about 10% to 30%, about 10% to 25%, about 10% to 20%, about 10% to 15%, about 15% to 50%, about 15% to 45%, about 15% to 40%, about 15% to 35%, about 15% to 30%, about 15% to 25%, about 15% to 20%, about 15% to 15%, about 15% to 10%, about 20% to 50%, about 20% to 45%, about 20% to 40%, about 20% to 35%, about 20% to 30%, about 20% to 25%, about 25% to 50%, about 25% to 45%, about 25% to 40%, about 25% to 35%, about 25% to 30%, about 30% to 50%, about 30% to 45%, about 30% to 40%, about 30% to 35%, about 35% to 50%, about 35% to 45%, about 35% to 40%, about 40% to 50%, relative to the normal dose of the salt of GHB normally given to the patient.

Another embodiment of the invention is a method of safely administering GHB a salt thereof for excessive daytime sleepiness, cataplexy, sleep paralysis, apnea, narcolepsy, sleep time disturbances, hypnagogic hallucinations, sleep arousal, insomnia, and nocturnal myoclonus in a human patient, comprising: determining if the patient is has taken, or will take a concomitant dose of valproate; orally administering a reduced amount of the GHB or GHB salt to the patient compared to the normal dose so as to diminish the additive effects of the GHB or GHB salt when administered with valproate. The amount of GHB is reduced at least 10% to 30%, or at least+15% of the normal administration.

One embodiment of the present invention is a method for treating a patient who is suffering from excessive daytime sleepiness, cataplexy, sleep paralysis, apnea, narcolepsy sleep time disturbances, hypnagogic hallucinations, sleep arousal, insomnia, and nocturnal myoclonus with GHB or a salt thereof, comprising: orally administering to the patient in need of treatment, an adjusted dosage amount of the salt of GHB when the patient is receiving a concomitant administration of diclofenac. In certain embodiments, the adjusted amount is at least about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% higher than the normal dose of the salt of GHB normally given to the patient. In certain embodiments, the increased amount of GHB is at least about 15% more than the normal administration and the daily administration of the GHB salt is between 1 gram and 10 grams. In certain embodiments, the adjusted amount is increased between the range of about 1% to 5%, about 5% to 10%, about 10% to 15%, about 15% to 20%, about 20% to 25%, about 25% to 30%, about 30% to 35%, about 35% to 40%, about 40% to 45%, or about 45% or 50%, relative to the normal dose of the salt of GHB normally given to the patient. In certain embodiments, the adjusted amount is increased between the range of about 1% to 50%, about 1% to 45%, about 1% to 40%, about 1% to 35%, about 1% to 30%, about 1% to 25%, about 1% to 20%, about 1% to 15%, about 1% to 10%, about 1% to 5%, about 5% to 50%, about 5% to 45%, about 5% to 40%, about 5% to 35%, about 5% to 30%, about 5% to 25%, about 5% to 20%, about 5% to 15%, about 5% to 10%, about 10% to 50%, about 10% to 45%, about 10% to 40%, about 10% to 35%, about 10% to 30%, about 10% to 25%, about 10% to 20%, about 10% to 15%, about 15% to 50%, about 15% to 45%, about 15% to 40%, about 15% to 35%, about 15% to 30%, about 15% to 25%, about 15% to 20%, about 15% to 15%, about 15% to 10%, about 20% to 50%, about 20% to 45%, about 20% to 40%, about 20% to 35%, about 20% to 30%, about 20% to 25%, about 25% to 50%, about 25% to 45%, about 25% to 40%, about 25% to 35%, about 25% to 30%, about 30% to 50%, about 30% to 45%, about 30% to 40%, about 30% to 35%, about 35% to 50%, about 35% to 45%, about 35% to 40%, about 40% to 50%, relative to the normal dose of the salt of GHB normally given to the patient. See the product insert for normal dose ranges of GHB as sold by Jazz Pharmaceuticals. GHB is commercially known as Xyrem®.

In another embodiment, the invention is a method of safely administering a GHB salt for excessive daytime sleepiness, cataplexy, sleep paralysis, apnea, narcolepsy, sleep time disturbances, hypnagogic hallucinations, sleep arousal, insomnia, and nocturnal myoclonus in a human patient, comprising: determining if the patient has taken, or will take a concomitant dose of diclofenac; orally administering an increased amount of a GHB salt to the patient so as to compensate for the effects of diclofenac on the GHB salt when concomitantly administered.

Another embodiment of the present invention is a method for treating a patient who is suffering from narcolepsy wherein said patient is currently taking or has been prescribed GHB or a salt thereof, comprising determining if the patient is taking or has also been prescribed valproate or diclofenac;

and adjusting the dose of the GHB or GHB salt to compensate for the effect caused by valproate or diclofenac. In certain embodiments, the method additionally comprises administering the adjusted dose to the patient.

Another embodiment of the present invention is a method for treating a patient who is suffering from excessive daytime sleepiness, cataplexy, sleep paralysis, apnea, narcolepsy, sleep time disturbances, hypnagogic hallucinations, sleep arousal, insomnia, and nocturnal myoclonus with a salt of gamma GHB, wherein said patient is also being treated with valproate or diclofenac, comprising: administering to the patient a daily dose of a GHB salt wherein said daily dose is administered at an amount sufficient to reduce or eliminate additive effects.

The embodiments of the present invention can administer the GHB at a level of between 1 and 4.5 grams/day or between 6 and 10 grams/day. The concentration of the formulation can be between 350-750 mg/ml or 450-550 mg/ml and a pH between 6-10 or 6.5-8.

Another embodiment of the present invention is a method for treating a patient who is suffering from narcolepsy, comprising: administering a salt of GHB or a salt thereof to a patient or determining whether the patient is currently on a GHB drug regimen; determining if the patient is also being administered ibuprofen; and advising a patient to cease or ceasing the administration of ibuprofen. In some embodiments, patients benefiting from this directive when the patient has will have a renal impairment.

Another embodiment of the present invention is a method for treating a patient who is suffering from narcolepsy, comprising: administering a therapeutically effective amount of a formulation containing GHB or a salt thereof to a patient at a concentration of between 450 and 550 mg/ml and a pH between 6 and 8, said formulation being administered before bed and 1-2 hours thereafter; determining if the patient is also being administered valproate; warning of a potential drug/drug interaction due to the combination of valproate and GHB; and reducing the dose of the GHB or GHB salt at least 15% to compensate for the effect caused by valproate. Another embodiment of the present invention is a method for treating a patient who is suffering from narcolepsy, comprising: administering a therapeutically effective amount of a formulation containing GHB or a salt thereof to a patient at a concentration of between 450 and 550 mg/ml and a pH between 6 and 8, said formulation being administered before bed and 1-2 hours thereafter; determining if the patient is also being administered diclofenac; warning of a potential drug/drug interaction due to the combination of diclofenac and the GHB salt; and increasing the dose of the GHB salt at least 15% to compensate for the effect caused by diclofenac.

In each of the embodiments of the invention the method includes administering GHB at between 1 and 4.5 grams/day or between 6 and 10 grams/day and at a concentration of between 350-750 or 450-550 mg/ml, and a pH between 6-10 or between 6.5-8. In further embodiments the valproate or diclofenac is administered within three days, one or two weeks (before or after) of GHB administration. In another embodiment, the present invention is a method wherein aspirin is also administered to the patient, especially with valproate.

In a further embodiment the method can include administering GHB as a single salt or a mixture of salts of GHB selected from the group consisting of a sodium salt of hydroxybutyrate (Na.GHB), a potassium salt of gamma-hydroxybutyrate (K.GHB), a magnesium salt of gamma-hydroxybutyrate ($Mg.(GHB)_2$), and a calcium salt of gamma-hydroxybutyrate ($Ca.(GHB)_2$).

In a further embodiment the method can include administering GHB to a patient suffering from excessive daytime sleepiness, comprising: administering a therapeutically effective amount of GHB to the patient; determining if the patient has concomitant administration of an MCT inhibitor; and adjusting the GHB dose or ceasing administering of the MCT inhibitor to maintain the effect of the GHB.

In any of the versions of the invention, the methods optionally further include administering aspirin to the patient.

In a further embodiment the method of administering GHB to a patient in need thereof comprises administering to the patient a therapeutically effective amount of GHB while avoiding concomitant of a diclofenac or valproate.

Another embodiment of the invention comprises a method of administering GHB or a salt thereof (GHB) to a patient with narcolepsy, wherein said patient is also in need of diclofenac, comprising administering to the patient a daily dosage of between 6 g and 10 g GHB or a GHB salt per day while avoiding diclofenac concomitant administration, and any one or more of the following: (a) advising the patient that diclofenac should be avoided or discontinued, (b) advising the patient that concomitant administration of GHB with drugs that are MCT inhibitors can alter the therapeutic effect or adverse reaction profile of GHB, (c) advising the patient that concomitant administration of GHB with diclofenac can alter the therapeutic effect or adverse reaction profile of GHB, (d) advising the patient that use of GHB in patients being treated with diclofenac is contraindicated, (e) advising the patient that concomitant administration of GHB and diclofenac resulted in an decrease in exposure to GHB, or (f) advising the patient MCT inhibitors should be used with caution in patients receiving GHB due to the potential for increased GHB clearance.

Another embodiment of the invention comprises a administering GHB to a patient with narcolepsy, wherein said patient is also in need of valproate, comprising administering to the patient a daily dosage of between 6 g and 10 g GHB per day while avoiding valproate concomitant administration, and any one or more of the following: (a) advising the patient that valproate should be avoided or discontinued, (b) advising the patient that concomitant administration of GHB with drugs that are MCT inhibitors can alter the therapeutic effect or adverse reaction profile of GHB, (c) advising the patient that concomitant administration of GHB with valproate can alter the therapeutic effect or adverse reaction profile of GHB, (d) advising the patient that use of GHB in patients being treated with valproate is contraindicated, (e) advising the patient that concomitant administration of GHB and valproate resulted in an increase in exposure to GHB, or (f) advising the patient that MCT inhibitors should be used with caution in patients receiving GHB due to the potential for increased GHB clearance.

In another embodiment, the present invention is a method for distributing a drug containing GHB or a salt thereof to an approved pharmacy, the method comprising: identifying an approved pharmacy that has an established management system to dispense information concerning the risks associated with ingesting a MCT inhibitor concomitantly to said drug to patients that are prescribed said drug; providing said pharmacy with said information related to the risks; and authorizing distribution of said drug to said pharmacy, wherein said pharmacy dispenses the drug with said information when filling a prescription for said drug. The method may also comprise including an electronic or written alert, which can explain the risks, to employees to dispense said information with said drug when prescriptions are filled. Also, the infor-

mation can be dispensed when a subject refills said prescription. The warnings would be as recited above.

The methods of the present invention may include a warning for patients not to operate hazardous machinery, including automobiles or airplanes, until they are reasonably certain that GHB does not affect them adversely and not to engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery or a motor vehicle or flying an airplane, for at least 6, 7, 8 or 9 hours after taking the second nightly dose of GHB. Any information dispensed with said drug advises patients of the potential for enhanced potency of said drug if said patients also take valproate or advises patients of the potential for decreased potency of said drug if said patients also take diclofenac.

Another embodiment of the present invention is a method of administering GHB to a patient in need thereof, comprising administering to the patient a therapeutically effective amount of GHB while avoiding concomitant administration of diclofenac or valproate.

The invention may also comprise a method for reducing the effects of GHB toxicity in a patient in need thereof, comprising administering to said patient an effective amount of diclofenac such that the toxic effects of GHB are reduced. It may also comprise a method for potentiating the beneficial effects of GHB in a patient in need thereof comprising concomitantly administering to said patient an effective amount of valproate such that the beneficial effects of GHB are increased.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows change from baseline figure (LSmean with 95% CI) for Power of Attention (ms) (PD Completer Population). Treatment A=diclofenac placebo+Xyrem®. Treatment B=diclofenac+Xyrem®. Treatment C=diclofenac+Xyrem® placebo.

FIG. **2** shows change from baseline figure (LSmean with 95% CI) for Digit Vigilance Accuracy (%) (PD Completer Population).

FIG. **3** shows change from baseline figure (LSmean with 95% CI) for Digit Vigilance Mean Reaction Time (ms) (PD Completer Population).

FIG. **4** shows change from baseline figure (LSmean with 95% CI) for Choice Reaction Time Mean (ms) (PD Completer Population).

FIG. **5** shows change from baseline figure (LSmean with 95% CI) for Continuity of Attention (#) (PD Population). Treatment A=Xyrem®. Treatment B=Xyrem® placebo. Treatment C=valproate.

FIG. **6** shows change from baseline figure (LSmean with 95% CI) for Simple Reaction Time Mean (ms) (PD Population).

FIG. **7** shows change from baseline figure (LSmean with 95% CI) for Digit Vigilance Accuracy (%) (PD Population).

FIG. **8** shows change from baseline figure (LSmean with 95% CI) for Tracking Distance from Target (mm) (PD Population).

FIG. **9** shows change from baseline figure (LSmean with 95% CI) for Numeric Working Memory Sensitivity Index (#) (PD Population).

FIG. **10** shows change from baseline figure (LSmean with 95% CI) for Numeric Working Memory Mean Reaction Time (ms) (PD Population).

DETAILED DESCRIPTION OF THE INVENTION

The following patents and applications are hereby incorporated by reference in their entireties for all purposes: U.S. Pat. Nos. 6,472,431, 6,780,889, 7,262,219, 7,851,506, 8,263,650, 8,324,275; 7,895,059; 7,797,171; 7,668,730; 7,765,106; 7,765,107; Ser. Nos. 61/317,212, 13/071,369, 13/739,886, 12/264,709, PCT/US2010/033572, PCT/US2009/061312, 2009/0137565; and 2012/0076865. The following patents are also incorporated by reference: U.S. Pat. No. 5,380,937; U.S. Pat. No. 4,393,236 German Patent DD 237,309 A1; and British Pat. No. 922,029.

Objects, features and advantages of the methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

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In the specification and claims that follow, references will be made to a number of terms which shall be defined to have the following meaning.

The terms "a" and "an" do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced item. The term "or" means "and/or". The terms "comprising", "having", "including", and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to").

"Concomitant" and "concomitantly" as used herein refer to the administration of at least two drugs to a patient either subsequently, simultaneously, or consequently within a time period during which the effects of the first administered drug are still operative in the patient. Thus, if the first drug is, e.g., Xyrem®, or GHB, and the second drug is valproate, the concomitant administration of the second drug occurs within two weeks, preferably within one week or even three days, before or after the administration of the first drug.

"Dosage amount" means an amount of a drug suitable to be taken during a fixed period, usually during one day (i.e., daily).

"Dosage amount adapted for oral administration" means a dosage amount that is of an amount deemed safe and effective for the particular patient under the conditions specified. As used herein and in the claims, this dosage amount is determined by following the recommendations of the drug manufacturer's Prescribing Information as approved by the US Food and Drug Administration.

"Dosing regimen" means the dose of a drug taken at a first time by a patient and the interval (time or symptomatic) and dosage amounts at which any subsequent doses of the drug are taken by the patient. Each dose may be of the same or a different dosage amount.

A "dose" means the measured quantity of a drug to be taken at one time by a patient.

A "patient" means a human in need of medical treatment. In one embodiment medical treatment can include treatment of an existing condition, such as a disease or disorder, prophylactic or preventative treatment, or diagnostic treatment. In another embodiment, medical treatment also includes

administration to treat excessive daytime sleepiness, cataplexy, sleep paralysis, apnea, narcolepsy, sleep time disturbances, hypnagogic hallucinations, sleep arousal, insomnia, and nocturnal myoclonus.

"Providing" means giving, administering, selling, distributing, transferring (for profit or not), manufacturing, compounding, or dispensing.

The terms "therapeutically effective amount," as used herein, refer to an amount of a compound sufficient to treat, ameliorate, or prevent the identified disease or condition, or to exhibit a detectable therapeutic, prophylactic, or inhibitory effect. The effect can be detected by, for example, an improvement in clinical condition, or reduction in symptoms. The precise effective amount for a subject will depend upon the subject's body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Where a drug has been approved by the U.S. Food and Drug Administration (FDA), a "therapeutically effective amount" refers to the dosage approved by the FDA or its counterpart foreign agency for treatment of the identified disease or condition.

"Side effect" means a secondary effect resulting from taking a drug. The secondary effect can be a negative (unfavorable) effect (i.e., an adverse side effect) or a positive (favorable) effect.

Pharmacokinetic parameters referred to herein describe the in vivo characteristics of drug (or a metabolite or a surrogate marker for the drug) over time. These include plasma concentration (C), as well as C_{max}, C_n, C_{24}, T_{max}, and AUC. The term "T_{max}" refers to the time from drug administration until C_{max} is reached. "AUC" is the area under the curve of a graph of the measured plasma concentration of an active agent vs. time, measured from one time point to another time point. For example AUC_{0-t} is the area under the curve of plasma concentration versus time from time 0 to time t, where time 0 is the time of initial administration of the drug. Time t can be the last time point with measurable plasma concentration for an individual formulation. The $AUC_{0-.infin.}$ or AUC_{0-INF} is the calculated area under the curve of plasma concentration versus time from time 0 to time infinity. In steady-state studies, $AUC_{0-.tau.}$ is the area under the curve of plasma concentration over the dosing interval (i.e., from time 0 to time .tau. (tau), where tau is the length of the dosing interval.

It may be advantageous to incorporate a pharmacy management system into the method of the present invention. Pharmacy management systems are computer-based systems that are used by commercial pharmacies to manage prescriptions and to provide pharmacy and medical personnel with warnings and guidance regarding drugs being administered to patients. Such systems typically provide alerts warning either or both of health care providers and patients when a drug that may be harmful to the particular patient is prescribed. For example, such systems can provide alerts warning that a patient has an allergy to a prescribed drug, or is receiving concomitant administration of a drug that can have a dangerous interaction with a prescribed drug. U.S. Pat. Nos. 7,895,059; 7,797,171; 7,668,730; 7,765,106; 7,765,107; 5,758,095, 5,833,599, 5,845,255, 6,014,631, 6,067,524, 6,112,182, 6,317,719, 6,356,873, and 7,072,840, each of which is incorporated herein by reference, disclose various pharmacy management systems and aspects thereof. Example pharmacy management systems are now commercially available, e.g., CENTRICITY Pharmacy from BDM Information Systems Ltd., General Electric Healthcare, Waukesha, Wis., Rx30 Pharmacy Systems from Transaction Data Systems, Inc., Ocoee, Fla., SPEED SCRIPT from Digital Simplistics, Inc., Lenexa, Kans., and various pharmacy management systems from OPUS-ISM, Hauppauge, N.Y.

In some embodiments, a pharmacy management system may be required or preferred as part of a drug distribution program. For example, the present invention includes a method for distributing a drug containing GHB or a salt thereof to an approved pharmacy, the method comprising: (1) Identifying an approved pharmacy that has an established management system to dispense information concerning the risks associated with ingesting a MCT inhibitors concomitantly to said drug to patients that are prescribed said drug; (2) Providing said pharmacy with said information related to the risks; and (3) Authorizing distribution of said drug to said pharmacy, wherein said pharmacy dispenses the drug with said information when filling a prescription for said drug. The established management system may include an electronic alert to employees to dispense said information with said drug when prescriptions are filled. Such information may be dispensed in written form, for example in a brochure explaining the risks of concomitant ingestion of GHB and an MCT inhibitor such as diclofenac, valproate, or ibuprofen or combinations thereof. For example, the information dispensed with GHB may advise a patient of the potential for enhanced potency of GHB if the patient also takes valproate. Alternatively, or in addition thereto, the information dispensed with GHB may advise a patient of the potential for decreased potency of GHB if the patient also takes diclofenac. Such information may also be dispensed in verbal form. Distributors may maintain a directory of approved pharmacies, for example in a computer readable storage medium, to further ensure that GHB is dispensed only to patients who are advised of the additive effects.

In addition, the system can prevent the dispensing of GHB or salt thereof until proper testing or confirmation is obtained that the patient is not taking or going to take valproate or diclofenac concomitantly with GHB. Alternatively, the patient can be warned of the adverse effect and instructed to modify the dose of GHB to accommodate the increased or reduced effects of GHB due to valproate or diclofenac.

A pharmacy management system of the present invention can be a REMS system as shown in U.S. Pat. Nos. 7,895,059; 7,797,171; and 7,668,730 and also include monitoring for concomitant use of diclofenac, valproate, or ibuprofen, or combinations thereof. Warnings may be administered through the existing pharmacy management system as described in the patents above.

One embodiment of the present invention, without being limited by theory, is the discovery of drug interactions that change either, or both, the efficacy or safety profile of GHB. The three compounds are valproate, diclofenac, and ibuprophen or combinations thereof. To achieve the above benefits, GHB of the present invention can be administered in a reduced amount when a second compound, such as valproate, is concomitantly administered with GHB. It can also be administered in an increased amount to overcome any effects of diclofenac. The compounds can also be avoided or discontinued to prevent unsafe concomitant administration.

In one embodiment of the present invention, concomitant administration of GHB with other agents is monitored and potential changes to the doses of GHB are made, or changes in the administration of other compounds are made. In one embodiment of the present invention, when GHB was concomitantly administered with ibuprofen, there were pharmacokinetic (PK) changes consistent with monocarboxylic transporter (MCT) inhibition and renal excretion of GHB doubled (statistically significant). Plasma levels were about ~5% lower, which was statistically significant. In another

embodiment of the present invention, when GHB and Diclofenac are concomitantly administered, PD effects were significantly reduced. In another embodiment of the present invention, when GHB and divalproate were concomitantly administered, PK showed both MCT and GHB dehydrogenase inhibition, with the latter predominating. MCT inhibition caused renal clearance to be increased 30% (statistically significant). GHB dehydrogenase inhibition caused systemic exposure (plasma AUC) to be increased 26%. Both measures are statistically significant and outside FDA "equivalence window". PD shows more pronounced effects with concomitant administration.

One embodiment is a method of administering a therapeutically effective amount of GHB to a patient in need of treatment, such as with narcolepsy, the invention provides an improvement that comprises avoiding or discontinuing administration of a compound that affects GHB potency and administering a therapeutically effective amount of GHB. The compound can be diclofenac or valproate and they can alter the therapeutic effect or adverse reaction profile of GHB.

Gamma Hydroxybutyrate (GHB)

GHB (also called oxysorbate or oxybate) is approved in the United States (US) for the treatment of excessive daytime sleepiness (EDS) and for the treatment of cataplexy, both in patients with narcolepsy. GHB is commercially sold as Xyrem® sodium oxybate by Jazz Pharmaceuticals. Sodium oxybate is the sodium salt of the endogenous neurotransmitter gamma hydroxybutyrate (GHB), which is found in many tissues of the body. "GHB", oxybate, a GHB salt or Xyrem® will be used to refer to these active forms. It can be used as a sodium, calcium, potassium, or magnesium salt. See U.S. patent application Ser. No. 13/739,886.

GHB is present, for example, in the mammalian brain and other tissues. In the brain, the highest GHB concentration is found in the hypothalamus and basal ganglia and GHB is postulated to function as a neurotransmitter. The neuropharmacologic effects of GHB include increases in brain acetylcholine, increases in brain dopamine, inhibition of GABA-ketoglutarate transaminase and depression of glucose utilization but not oxygen consumption in the brain. GHB is converted to succinate and then metabolized via the Krebs cycle. Clinical trials have shown that GHB increases delta sleep and improves the continuity of sleep (Laborit, 1973; Lapierre et al., 1988; Lapierre et al., 1990; Yamada et al., 1967; Scharf, 1985).

GHB treatment substantially reduces the signs and symptoms of narcolepsy, i.e. excessive daytime sleepiness, cataplexy, sleep paralysis, apnea, narcolepsy, sleep time disturbances, hypnagogic hallucinations, sleep arousal, insomnia, and nocturnal myoclonus. In addition, GHB increases total sleep time and REM sleep, and it decreases REM latency (Mamelak et al, 1973; Yamada et al., 1967; Bedard et al., 1989), reduces sleep apnea (Scrima et al., 1987), and improves general anesthesia (Hasenbos and Gielen, 1985).

GHB has several clinical applications other than narcolepsy and sleep disorders. GHB has been reported to reduce alcohol craving, the number of daily drinks consumed, and the symptoms of alcohol withdrawal in patients (Gallimberti et al., 1989; Gallimberti et al., 1992; Gessa et al., 1992). GHB has been used to decrease the symptoms of opiate withdrawal, including both heroin and methadone withdrawal (Gallimberti et al., 1994; Gallimberti et al., 1993). It has analgesic effects that make it suitable as a pain reliever (U.S. Pat. No. 4,393,236). Intravenous administration of GHB has been reported to reduce intracranial pressure in patients (Strong, A. 1984). Also, administration of GHB was reported to increase growth hormone levels in patients (Gessa et al, 1994).

A good safety profile for GHB consumption, when used long term for treatment of narcolepsy has been reported. Patients have been safely treated for many years with GHB without development of tolerance (Scharf, 1985). Clinical laboratory tests carried out periodically on many patients have not indicated organ or other toxicities (Lammers, 1993; Scrima, 1990; Scharf, 1985; Mamelack, 1977; Mamelak, 1979; Gessa, 1992). The side effects of GHB treatment have been minimal in incidence and degree of severity, though they include sleepwalking, enuresis, headache, nausea and dizziness (Broughton and Mamelak, 1979; Mamelak et al., 1981; Mamelak et al., 1977; Scrima et al., 1989; Scrima et al., 1990; Scharf et al., 1985). Therefore, it is critical to identify adverse drug-drug interactions to maintain the positive safety profile for GHB.

GHB Pharmacology

GHB has at least two distinct binding sites (See Wu, et al., 2004) in the central nervous system. GHB is an agonist at the GHB receptor, which is excitatory, (Cash et al., 2009) and it is a weak agonist at the GABAB receptor, which is inhibitory. GHB acts in a similar fashion to some neurotransmitters in the mammalian brain and is probably synthesized from GABA in GABAergic neurons, and released when the neurons fire. If taken orally, GABA itself does not effectively cross the blood-brain-barrier. (See Kuriyama et al., 2005).

GHB induces the accumulation of either a derivative of tryptophan or tryptophan itself in the extracellular space, possibly by increasing tryptophan transport across the blood-brain barrier. The blood content of certain neutral amino-acids, including tryptophan, is also increased by peripheral GHB administration. GHB-induced stimulation of tissue serotonin turnover may be due to an increase in tryptophan transport to the brain and in its uptake by serotonergic cells. As the serotonergic system may be involved in the regulation of sleep, mood, and anxiety, the stimulation of this system by high doses of GHB may be involved in certain neuropharmacological events induced by GHB administration.

However, at therapeutic doses, GHB reaches much higher concentrations in the brain and activates GABAB receptors, which are primarily responsible for its sedative effects. (See Dimitrijevic et al., 2005). GHB's sedative effects are blocked by GABAB antagonists.

The role of the GHB receptor in the behavioral effects induced by GHB is more complex. GHB receptors are densely expressed in many areas of the brain, including the cortex and hippocampus, and these are the receptors that GHB displays the highest affinity for. There has been somewhat limited research into the GHB receptor; however, there is evidence that activation of the GHB receptor in some brain areas results in the release of glutamate, the principal excitatory neurotransmitter. Drugs that selectively activate the GHB receptor cause absence seizures in high doses, as do GHB and GABA(B) agonists. (See Banerjee et al., 1995.)

Activation of both the GHB receptor and GABA(B) is responsible for the addictive profile of GHB. GHB's effect on dopamine release is biphasic. (See Hechler et al., 1991). Low concentrations stimulate dopamine release via the GHB receptor. (See Maitre et al., 1990). Higher concentrations inhibit dopamine release via GABA(B) receptors as do other GABA(B) agonists such as baclofen and phenibut. (See Smolders et al., 1995). After an initial phase of inhibition, dopamine release is then increased via the GHB receptor. Both the inhibition and increase of dopamine release by GHB are inhibited by opioid antagonists such as naloxone and naltrexone. Dynorphin may play a role in the inhibition of dopamine release via kappa opioid receptors. (See Mamelak 1989).

This may explain the paradoxical mix of sedative and stimulatory properties of GHB, as well as the so-called "rebound" effect, experienced by individuals using GHB as a sleeping agent, wherein they awake suddenly after several hours of GHB-induced deep sleep. That is to say that, over time, the concentration of GHB in the system decreases below the threshold for significant GABAB receptor activation and activates predominantly the GHB receptor, leading to wakefulness. However, one embodiment of the present invention is the unexpected discovery that drugs change the PD profile of GHB to alter its effects and its safety profile. Example drugs are include valproate and diclofenac. It is important for efficacy safety purposes that the effect of GHB be maintained consistently and not subject to variation due to the effects of other drugs.

Both of the metabolic breakdown pathways shown for GHB can run in either direction, depending on the concentrations of the substances involved, so the body can make its own GHB either from GABA or from succinic semialdehyde. Under normal physiological conditions, the concentration of GHB in the body is rather low, and the pathways would run in the reverse direction to what is shown here to produce endogenous GHB. However, when GHB is consumed for recreational or health promotion purposes, its concentration in the body is much higher than normal, which changes the enzyme kinetics so that these pathways operate to metabolize GHB rather than produce it.

The pharmacokinetics of GHB have been investigated in alcohol dependent patients (Ferrara et al., 1992) and in normal healthy males (Palatini et al., 1993) after oral administration. GHB possesses a rapid onset and short pharmacological effect (Ferrara et al., 1992; Palatine et al., 1993; Lettieri and Fung, 1978; Arena and Fung, 1980; Roth and Giarman, 1966; Vickers, 1969; Lee, 1977). In alcohol dependent patients, GHB absorption into and elimination from the systemic circulation were fast processes. Virtually no unchanged drug could be recovered in the urine. There were preliminary indications that the pharmacokinetics of GHB might be non-linear or dose-dependent (Ferrara et al., 1992). In the healthy volunteers study, the pharmacokinetics of three rising GHB doses (12.5, 25, and 50 mg/kg) were investigated. These findings indicate that both the oral absorption and elimination processes of GHB were capacity-limited though the degree of dose dependency was moderate (Palatini et al., 1993).

Methods of making GHB salts are described, for example, in U.S. Pat. No. 4,393,236, and U.S. patent application Ser. No. 13/739,886 which are incorporated herein by reference.

It has been discovered that there are unexpected drug-drug interactions (DDI) between GHB and common drugs frequently prescribed for other ailments. It is one goal of the present invention to warn when those interactions may affect the safety profile of GHB. In one embodiment of the present invention, drugs that may affect GHB administration include valproate, diclofenac, and ibuprofen and combinations thereof.

GHB is a central nervous system (CNS) depressant. Alcohol and sedative hypnotics are contraindicated in patients who are using GHB. The concurrent use of GHB with other CNS depressants, including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death. If use of these CNS depressants in combination with GHB is required, dose reduction or discontinuation of one or more CNS depressants (including GHB) should be considered. In addition, if short-term use of an opioid (e.g. post- or perioperative) is required, interruption of treatment with GHB should be considered. See the package insert for Xyrem®.

GHB may impair respiratory drive, especially with overdoses associated with interactions with other drugs and alcohol. Since valproate may potentiate the effect of GHB, a warning should accompany any use of valproate and GHB as stated herein. The warning should address the use of additional drugs that may further enhance the effect of GHB, such as alcohol or aspirin, for example.

Healthcare providers should caution patients about operating hazardous machinery, including automobiles or airplanes, until they are reasonably certain that GHB does not affect them adversely (e.g., impair judgment, thinking, or motor skills). Patients should not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery or a motor vehicle or flying an airplane, for at least 6, 7, 8 or 9 hours after taking the second nightly dose of GHB. Patients should be queried about potential adverse events, such as excessive daytime sleepiness, CNS depression related events, etc. upon initiation of GHB therapy and periodically thereafter. These queries should include info regarding additional medication such as diclofenac and valproate for example. See the Xyrem® package insert.

In one embodiment described herein, patients are warned that combination of GHB with valproate can increase plasma levels and potentiate the activity of GHB and exacerbate all the effects and adverse event associated with GHB. These effects include the intended effects of drowsiness, sedation, and sleep and typically unintended events such as depressed respiration, CNS depression, excessive drowsiness, hepatic impairment, and depression, among other things.

In another embodiment, diclofenac mitigates and protects against the pharmcodynamic effects the effects of GHB. However, the mixture of GHB and diclofenac does not affect sleepiness and does not make a patient more attentive. Without wishing to be bound by theory, the effects may be due to the interaction between diclofenac and the GHB receptor in lieu of the MCT inhibitor activity.

Typical concentrations of GHB formulations are shown in U.S. Pat. Nos. 8,263,650 and 8,324,275, for example. They include minimum concentrations starting from 150 mg/ml to 450 mg/ml (at 10 mg/ml increments) and increasing to 600 mg/ml to 750 mg/ml (at 10 mg/ml increments) as a maximum. So, a broad range would include 150-750 mg/ml and any range within the broad range using 10 mg/ml increments. One embodiment of the invention is a range of 350-750 mg/ml and another is 450-550 mg/ml GHB. One embodiment of the present invention uses a GHB formulation with a pH range of 6-10, another uses a pH range of between 6.5-8. For example, a minimum concentration includes 350, 360, 370, 380 mg/ml, and so on up to at least 730, 740, and 750 mg/ml and all concentrations (measured in 10 mg/ml increments in between).

pH adjusting agents can include acids, bases and many of the compounds found in U.S. Pat. No. 8,263,650. In some embodiments the pH adjusting agent is an acid selected from the group of: acetic, acetylsalicylic, barbital, barbituric, benzoic, benzyl penicillin, boric, caffeine, carbonic, citric, dichloroacetic, ethylenediaminetetra-acetic acid (EDTA), formic, glycerophosphoric, glycine, lactic, malic, mandelic, monochloroacetic, oxalic, phenobarbital, phenol, picric, propionic, saccharin, salicylic, sodium dihydrogen phosphate, succinic, sulfadiazine, sulfamerazine, sulfapyridine, sulfathiazole, tartaric, trichloroacetic, and the like, or inorganic acids such as hydrochloric, nitric, phosphoric or sulfuric, and the like.

GHB is commercially available as a sodium salt, however, it can also be formulated as a mixture of salts as shown in U.S. Ser. No. 13/739,886, which is incorporated by reference as stated above. For example, the mixture comprises one, two, or three or more salts selected from the group consisting of a sodium salt of hydroxybutyrate (Na.GHB), a potassium salt of gamma-hydroxybutyrate (K.GHB), a magnesium salt of gamma-hydroxybutyrate ($Mg.(GHB)_2$), and a calcium salt of gamma-hydroxybutyrate ($Ca.(GHB)_2$). The different salts may be present in different percentages. For example, in certain embodiments, the pharmaceutical composition comprises Na.GHB, K.GHB, and $Ca.(GHB)_2$. In certain embodiments, the Na.GHB salt is present in a wt/wt % of about 5% to about 40%, the K.GHB salt is present in a wt/wt % of about 10% to about 40%, and the $Ca.(GHB)_2$ salt is present in a wt/wt % of about 20% to about 80%. In certain embodiments, the Na.GHB, K.GHB, and $Ca.(GHB)_2$ salts are present in a wt/wt % ratio of about 11%:39%:50%, respectively.

Valproic Acid

Valproic acid (VPA, also called valproate or divalproex), an acidic chemical compound, has found clinical use as an anticonvulsant and mood-stabilizing drug, primarily in the treatment of epilepsy, bipolar disorder, and, less commonly, major depression. See G. Rosenberg, Cell. Mol. Life Sci. 64 (2007) 2090-2103. It is also used to treat migraine headaches and schizophrenia. A typical dose of valproate varies by indication. Dosages for seizures are between 10 to 15 mg/kg/day, with potential increases of 5 to 10 mg/kg/day. VPA is a liquid at room temperature, but it can be reacted with a base such as sodium hydroxide to form the salt sodium valproate, which is a solid. The acid, salt, or a mixture of the two (valproate semisodium, divalproate) are marketed under the various brand names Depakote, Depakote ER, Depakene, Depakene Crono (extended release in Spain), Depacon, Depakine, Valparin and Stavzor.

Valproate is believed to affect the function of the neurotransmitter GABA in the human brain, making it an alternative to lithium salts in treatment of bipolar disorder. Its mechanism of action includes enhanced neurotransmission of GABA (by inhibiting GABA transaminase, which breaks down GABA). However, several other mechanisms of action in neuropsychiatric disorders have been proposed for valproic acid in recent years. See Rosenberg G (2007). "The mechanisms of action of valproate in neuropsychiatric disorders: can we see the forest for the trees?". *Cellular and Molecular Life Sciences* 64 (16): 2090-103.

Valproic acid also blocks the voltage-gated sodium channels and T-type calcium channels. These mechanisms make valproic acid a broad-spectrum anticonvulsant drug. Valproic acid is an inhibitor of the enzyme histone deacetylase 1 (HDAC 1), hence it is a histone deacetylase inhibitor. Valproic acid may interact with carbamazepine, as valproates inhibit microsomal epoxide hydrolase (mEH), the enzyme responsible for the breakdown of carbamazepine-10,11 epoxide (the main active metabolite of carbamazepine) into inactive metabolites. (See Gonzalez, Frank J.; Robert H. Tukey (2006). "Drug Metabolism". In Laurence Brunton, John Lazo, Keith Parker (eds.). Goodman & Gilman's The Pharmacological Basis of Therapeutics (11th ed.). New York: McGraw-Hill. pp. 79.) By inhibiting mEH, valproic acid causes a buildup of the active metabolite, prolonging the effects of carbamazepine and delaying its excretion. Valproic acid also decreases the clearance of amitriptyline and nortriptyline.

Aspirin may decrease the clearance of valproic acid, leading to higher-than-intended serum levels of the anticonvulsant. Also, combining valproic acid with the benzodiazepine clonazepam can lead to profound sedation and increases the risk of absence seizures in patients susceptible to them.

Valproic acid and sodium valproate reduce the apparent clearance of lamotrigine (lamictal). In most patients, the lamotrigine dosage for coadministration with valproate must be reduced to half the monotherapy dosage.

Valproic acid is contraindicated in pregnancy, as it decreases the intestinal reabsorption of folate (folic acid), which leads to neural tube defects. Because of a decrease in folate, megaloblastic anemia may also result. Phenyloin also decreases folate absorption, which may lead to the same adverse effects as valproic acid.

Valproic acid, 2-propylvaleric acid, is synthesized by the alkylation of cyanoacetic ester with two moles of propylbromide, to give dipropylcyanoacetic ester. Hydrolysis and decarboxylation of the carboethoxy group gives dipropylacetonitrile, which is hydrolyzed into valproic acid. See U.S. Pat. Nos. 3,325,361 and 4,155,929 and GB Pat. Nos. 980279 and 1522450. See also, T. R. Henry, "The History of Valproate in Clinical Neuroscience." Psychopharmacology bulletin (2003) 37 (Suppl 2):5-16.

Diclofenac

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) taken to reduce inflammation and as an analgesic reducing pain in certain conditions. Diclofenac is used to treat pain, inflammatory disorders, and dysmenorrhea and is a commonly used NSAID. See Auler et al., Brazilian Jour. Med. Bio. Res., (1977) 30:369-374 and Hasan, et al., and Pakistan Jour. Pharmaceutical Sciences, vol. 18, No. 1, January 2005, pp 18-24 both are hereby incorporated by reference in their entireties.

The name is derived from its chemical name: 2-(2,6-dichloranilino)phenylacetic acid, it may be supplied as either the sodium or potassium salt. Diclofenac is available as a generic drug in a number of formulations; including Dichlofenac diethylammonium applied topically to joints. Over-the-counter (OTC) use is approved in some countries for minor aches and pains and fever associated with common infections.

Diclofenac is typically absorbed readily, but absorption is delayed upon administration with food. Its half-life varies from 1 to 3 hours with mean peak plasma levels of about 0.5 ug/ml to 1.0 ug/ml after 2 hours of a single dose of 25 mg. Diclofenac binds to human serum proteins, specifically albumin. See Hasan et al 2005.

Ibuprofen

Ibuprofen (from iso-butyl-propanoic-phenolic acid) is a nonsteroidal anti-inflammatory drug (NSAID) widely prescribed for pain relief, fever reduction, and swelling. Ibuprofen was derived from propanoic acid. Originally marketed as Brufen, ibuprofen is available under a variety of popular trademarks, including Motrin, Nurofen, Advil, and Nuprin. Ibuprofen is used primarily for fever, pain, dysmenorrhea and inflammatory diseases such as rheumatoid arthritis. It is also used for pericarditis and patent ductus arteriosus. It is a commonly used drug commercially available over the counter.

Nonsteroidal anti-inflammatory drugs such as ibuprofen work by inhibiting the enzyme cyclooxygenase (COX), which converts arachidonic acid to prostaglandin H2 (PGH2). PGH2, in turn, is converted by other enzymes to several other prostaglandins (which are mediators of pain, inflammation, and fever) and to thromboxane A2 (which stimulates platelet aggregation, leading to the formation of blood clots).

Like aspirin and indomethacin, ibuprofen is a nonselective COX inhibitor, in that it inhibits two isoforms of cyclooxygenase, COX-1 and COX-2. The analgesic, antipyretic, and

anti-inflammatory activity of NSAIDs appears to operate mainly through inhibition of COX-2, whereas inhibition of COX-1 would be responsible for unwanted effects on the gastrointestinal tract. However, the role of the individual COX isoforms in the analgesic, anti-inflammatory, and gastric damage effects of NSAIDs is uncertain and different compounds cause different degrees of analgesia and gastric damage.

The synthesis of this compound consisted of six steps, started with the Friedel-Crafts acetylation of isobutylbenzene. Reaction with ethyl chloroacetate (Darzens reaction) gave the α,β-epoxy ester, which was hydrolyzed and decarboxylated to the aldehyde. Reaction with hydroxylamine gave the oxime, which was converted to the nitrile, then hydrolyzed to the desired acid. See U.S. Pat. No. 3,385,886.

An improved synthesis by BHC required only three steps. After a similar acetylation, hydrogenation with Raney nickel gave the alcohol, which underwent palladium-catalyzed carbonylation.

Valproate, diclofenac, and ibruprofen are monocarboxylate transporter inhibitors. One embodiment of the present application is a method to improve safety by monitoring the combination of these compounds with GHB.

Monocarboxylate Transporters

Monocarboxylate transporters, or MCTs, constitute a family of proton-linked plasma membrane transporters that carry molecules having one carboxylate group (monocarboxylates), such as lactate and pyruvate, across biological membranes. See Halestrap A P, Meredith D (2004). "The SLC16 gene family-from monocarboxylate transporters (MCTs) to aromatic amino acid transporters and beyond". Pflugers Arch. 447 (5): 619-28.

MCTs are a series of transporters which move chemicals in body tissues, such as kidneys, blood/brain barrier, intestines, etc. They can transport chemical compounds back from urine to create a higher concentration in the blood than the urine. They can be used to treat an overdose or to prevent excretion of a compound. They can also be used to prevent absorption or transport into the brain or gut, or excretion via the urine. Exemplary MCT inhibitors include valproate, diclofenac, and ibuprofen.

Concomitant Administration of GHB and Drug-Drug Interactions

In one embodiment of the present invention the concomitant administration of MCT inhibitors, such as either valproate, diclofenac, or ibuprofen with GHB can effect GHB levels or activity and alter the GHB safety and efficacy profile to create an unsafe condition. For example, valproate can increase or prolong GHB effects and diclofenac can reduce or shorten GHB effects. For example, if the effects are increased, then there could be an increase of adverse events associated with too much GHB. Also, the effect of GHB may be prolonged to cause side effects, such as excessive daytime sleepiness (EDS), to last into the daytime. Prolongation of the effect would counter the purpose for providing the GHB and could create an unsafe situation for patients who wish to be alert and who may be engaged in otherwise dangerous activity. This concomitant administration can transform an otherwise safe dose of GHB into one with safety concerns. It is a health risk to patients and a medical challenge to health care workers.

The drug-drug interaction could also reduce the effects of GHB by altering its blood levels or otherwise. Reduction in the GHB level may also provide an unsafe condition due to excessive daytime sleepiness. In each situation, where GHB is increased, decreased or excessively cleared, those drug-drug interactions need to be identified to a health care worker to adjust the dose of GHB or discontinue the use of the other compound.

As recited on the product insert for Xyrem®, healthcare providers should caution patients about operating hazardous machinery, including automobiles or airplanes, until they are reasonably certain that GHB does not affect them adversely (e.g., impair judgment, thinking, or motor skills). Patients should not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery or a motor vehicle or flying an airplane, for at least 6, 7, 8 or 9 hours after taking the second nightly dose of GHB.

In some embodiments in which diclofenac or valproate is discontinued to avoid an adverse drug interaction, they are discontinued within at least 3 days prior to or after starting GHB therapy. In various embodiments, diclofenac or valproate is discontinued within at least 4 days, or at least 5 days, or at least 6 days, or at least 7 days (or one week), or at least 8 days, or at least 9 days, or at least 10 days, or at least 11 days, or at least 12 days, or at least 13 days, or at least 14 days (or two weeks), or at least 15 days, or at least 16 days, or at least 17 days, or at least 18 days, or at least 19 days, or at least 20 days, or at least 21 days (or three weeks) prior to or after starting GHB therapy. In some embodiments, the diclofenac or valproate is discontinued no later than 2 weeks or 1 week before starting GHB therapy.

In some embodiments, a method of optimizing GHB therapy when valproate is provided comprises titrating the dosage of GHB administered to a patient downward relative to a previously administered dosage in the patient, so the dose does not result in an increased exposure to GHB. In some embodiments, a method of optimizing GHB therapy when diclofenac is provided comprises titrating the dosage of GHB administered to a patient upward relative to a previously administered dosage in the patient, so the dose results in an effective exposure to GHB.

Thus, the present invention includes a method for treating a patient who is suffering from excessive daytime sleepiness, cataplexy, sleep paralysis, apnea, narcolepsy, sleep time disturbances, hypnagogic hallucinations, sleep arousal, insomnia, and nocturnal myoclonus with a salt of gamma-hydroxybutyrate (GHB), wherein said patient is also being treated with valproate or diclofenac, comprising: administering to the patient a daily dose of a GHB salt wherein said daily dose is administered at an amount sufficient to reduce or eliminate such additive effects.

In one embodiment of the present invention, a reduced amount of GHB is administered to a patient when concomitantly administered with valproate. In another embodiment of the present invention, an increased amount of GHB is administered to a patient when concomitantly administered with diclofenac.

When valproate is concomitantly administered with GHB, The amount of GHB can be reduced at least 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% of the normal dose of GHB. For example, if the normal dose is 9 g/day, then a dose that is adjusted to reduce the normal dose by 15% is 7.65 g/day. The GHB dose reduction may be taken for one or multiple GHB dosings. For example, GHB may be administered in two doses per night for narcolepsy. A typical adult range of doses for GHB are between 4.5 or 6 g as a minimum and 8 or 10 g/day as a maximum divided into two doses. The dose recommended on the package insert and approved by the FDA is between 4.5 and 9.0 g/day. Typical exemplary paediatric daily doses of GHB are between 1 g and 6 g/day for pediatric patients aged 0-6 years. Typical exemplary paediat-

ric daily doses of GHB are between 1 g and 9 g/day for pediatric patients aged 7-17 years. However, these ranges are not absolute and can be increased or decreased by 1-2 grams in either direction. One dose is typically administered prior to bed (night time sleep) and another dose administered 1-2 hours later. See the Xyrem® package insert (Xyrem® is a registered trademark of Jazz Pharmaceuticals plc or its subsidiaries). Either or both of the multiple doses may be reduced to present a safer administration profile. For example, the first dose may be reduced by the numbers referred to above or the second may be reduced by the same percentages, or both. Furthermore, the absolute amount of GHB per dose or per day may be reduced at least 0.5 g, 1 g, 1.5 g, 2.0 g, 2.5 g, 3.0 g, 3.5 g, or 4 g. An exemplary decrease in an adult dose would be to reduce the maximum dose to less than 8.5, 8, 7.5, 7, 6.5, 6, 5.5, 5, 4.5, 4, 3.5, 3 g/day and so on. The minimum dose will be reduced accordingly to 4, 3.5, 3, 2.5, 2, and so on.

In one embodiment of the present invention, diclofenac may dampen or delay the effect of GHB upon a patient during concomitant administration. In one embodiment, it may be useful to increase the amount of GHB that is administered to the patient. For example, GHB may be increased at least 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% of the normal dose of GHB. For example, if the normal dose is 10 g/day, then a dose that is adjusted to increase the normal dose by 15% is 11.5 g/day. The GHB dose increase may be taken for one or multiple GHB dosings. For example, GHB may be administered in two doses per night for narcolepsy. Either, or both, of the multiple doses may be increased to present a safer administration profile. For example, the first dose may be increased by the numbers referred to above or the second may be increased by the same percentages, or both. Furthermore, the absolute amount of GHB per dose or per day may be increased at least 0.5 g, 1 g, 1.5 g, 2.0 g, 2.5 g, 3.0 g, 3.5 g, or 4 g. An exemplary decrease in an adult dose would be to increase the minimum dose to 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5 g/day and so on. An increase in the maximum dose would be at least 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14 g/day and so on.

In another aspect, a package or kit is provided comprising GHB, optionally in a container, and a package insert, package label, instructions or other labelling including any one, two, three or more of the following information or recommendations: (a) use of diclofenac or valproate should be avoided or discontinued, (b) concomitant administration of GHB with drugs that are MCT inhibitors, such as diclofenac or valproate can alter the therapeutic effect or adverse reaction profile of GHB, (c) concomitant administration of GHB and valproate resulted in an increase in exposure to GHB, (d) concomitant administration of GHB and diclofenac resulted in a decrease in exposure to GHB, and/or (e) MCT inhibitors should be used with caution in patients receiving GHB due to the potential for increased GHB clearance.

Alternatively, diclofenac can be administered to counteract the effects of GHB toxicity using a reverse of the numerical relationships above. Similarly, valproate can be used to increase the effects of GHB in patients that cannot take higher amounts of GHB. In this regard, the present invention includes methods for reducing the effects of GHB toxicity in a patient in need thereof, comprising administering to said patient an effective amount of diclofenac such that potential toxic effects of GHB are reduced. The present invention also includes methods for potentiating the beneficial effects of GHB in a patient in need thereof comprising concomitantly administering to said patient an effective amount of valproate such that the beneficial effects of GHB are increased.

The examples below, which show drug interaction studies in healthy adults, demonstrated those instances, test conditions or metrics which showed a distinction between GHB and either of the test compounds, diclofenac, valproate, or ibuprofen. Additionally, drug interaction studies in healthy adults demonstrated pharmacokinetic or clinically significant pharmacodynamic interactions between GHB and diclofenac or valproate.

Example 1

This study was designed to compare Pharmacokinetic (PK) and Pharmacodynamic (PD) endpoints of Xyrem® sodium oxysorbate (GHB) with and without concomitant administration of diclofenac. A crossover design was employed to allow within-subject comparisons of the PK and PD of Xyrem® dosed alone and in combination with diclofenac. The PK and PD effects of Xyrem® upon those of diclofenac were also studied.

The PD parameters included a selection of automated tests of attention, information processing, working memory and skilled coordination from the CDR System. (Rapeport et al, 1996ab; Williams et al, 1996). (Wesnes et al, 1997). (Wesnes et al, 2000) (Modi et al, 2007).

Methods

This was a Phase 1, randomized, double-blind, placebo-controlled, three-period, crossover study in healthy subjects. 24 subjects were recruited to ensure that 18 completed the study. Following Screening and Baseline procedures, eligible subjects were entered into the study and received one of the following treatments per period, in randomized order:

Diclofenac placebo administered as one capsule qid (doses separated by 4 hours during the day, eg, approximately 8 am, 12 pm, 4 pm, and 8 pm) for 2 days before concomitant administration day. On concomitant administration day, one diclofenac placebo capsule administered at −1 h and 3 h, and 3 g of Xyrem® administered at 0 h and 4 h.

Diclofenac administered as 50 mg immediate-release (IR) tablet (overencapsulated) qid (doses separated by 4 hours during the day, eg, approximately 8 am, 12 pm, 4 pm, and 8 pm) for 2 days before concomitant administration day. On concomitant administration day, 50 mg diclofenac administered at −1 h and 3 h and 3 g of Xyrem® administered at 0 h and 4 h.

Diclofenac administered as 50 mg IR tablet (overencapsulated) qid (doses separated by 4 hours during the day, eg, approximately 8 am, 12 pm, 4 pm, and 8 pm) for 2 days before concomitant administration day. On concomitant administration day, 50 mg diclofenac administered at −1 h and 3 h and Xyrem® placebo (volume equivalent to 3 g of Xyrem® oral solution) administered at 0 h and 4 h.

Subjects were randomized to one of the above treatments on Day 1, crossed over to another treatment on Day 6, and crossed over again to the remaining treatment on Day 11 (Table 1). Subjects were dosed in groups of up to 12. A 2-day washout period followed each of the treatment periods. The treatments were as follows: A=Diclofenac placebo (qid 4 h apart on the 1st and 2nd day and 2 doses on the 3rd day of the period)+Xyrem® two 3 g doses 4 h apart on the 3rd day of the period. B=Diclofenac (50 mg qid 4 h apart on the 1st and 2nd day and 2 doses on the 3rd day of the period)+Xyrem® two 3 g doses 4 h apart on the 3rd day of the period. C=Diclofenac (50 mg qid 4 h apart on the 1st and 2nd day and 2 doses on the 3rd day of the period)+Xyrem® placebo two doses 4 h apart on the 3rd day of the period. PD parameters include the following: Cognitive Drug Research (CDR) System tasks: Karolinska Sleepiness Scale (KSS), Simple Reaction Time

(SRT), Digit Vigilance (DV), Choice Reaction Time (CRT), Tracking and Numeric Working Memory (NWM).

Results

Power of attention-On this measure of focussed attention and information processing Xyrem® when co-dosed with diclofenac produced significantly less impairment than Xyrem® alone at 0.5 h; while the smaller impairments with the combination narrowly missed significance at 1 and 4.5 h. Xyrem® when co-dosed with diclofenac also resulted in impairments at two timepoints compared to diclofenac alone which at 6.5 h was significant and a trend at 8 h. See FIG. **1** which shows Change from Baseline Figure (LSmean with 95% CI) for Power of Attention (ms) (PD Completer Population).

Digit Vigilance Accuracy-On this measure of focussed attention Xyrem® when co-dosed with diclofenac produced significantly less impairment than Xyrem® alone at 1 and 2.5 h. See FIG. **2** which shows Change from Baseline Figure (LSmean with 95% CI) for Digit Vigilance Accuracy (%) (PD Completer Population).

Digit Vigilance Mean Reaction Time-On this measure of focussed attention Xyrem® when co-dosed with diclofenac produced significantly less impairment than Xyrem® alone at 1 and 2.5 h. See FIG. **3** which shows Change from Baseline Figure (LSmean with 95% CI) for Digit Vigilance Mean Reaction Time (ms) (PD Completer Population).

Choice Reaction Time Mean-Impairments to this measure of attention and information processing were significantly smaller than with Xyrem® alone when co-dosed with diclofenac during the hour following the first dose of Xyrem®. See FIG. **4** which shows Change from Baseline Figure (LSmean with 95% CI) for Choice Reaction Time Mean (ms) (PD Completer Population).

While diclofenac alone had no effect on sleepiness or cognitive function, when co-dosed with Xyrem® it significantly reduced the effects of the compound on Power of Attention and two of the contributing scores, simple and choice reaction time; these effects being seen during the hour after the first dose of Xyrem®. On the other hand, there was no evidence on any measure of greater cognitive impairment or sleepiness when the two compounds were co-dosed.

The extent of the reductions in the impairments to the ability to focus attention and efficiently process information were quite notable, and likely to be of clinical relevance. It is interesting that protective effect of diclofenac was not seen on the subjects ratings of alertness, such a dissociation having been seen previously with haloperidol in healthy elderly volunteers (Beuzan et al, 1991).

In conclusion, evidence of an interaction was seen in this study over the hour following the first dose of Xyrem® on the study days, the impairments being notably smaller when diclofenac was co-dosed with Xyrem®. There was no interaction however on the feelings of sleepiness in the subjects.

Example 2

This study is designed to compare the pharmacokinetic (PK) and pharmacodynamic (PD) endpoints of Xyrem® with and without co-administration of divalproex sodium extended-release tablets. The crossover design allows within-subject comparisons of the PK and PD of Xyrem® dosed alone and in combination with divalproex sodium extended-release tablets. PD parameters include the following: Cognitive Drug Research (CDR) System tasks: Karolinska Sleepiness Scale (KSS), Simple Reaction Time (SRT), Digit Vigilance (DV), Choice Reaction Time (CRT), Tracking and Numeric Working Memory (NWM).

The objectives of this study were to evaluate the PK and PD of Xyrem® co-administered with divalproex sodium extended-release tablets and to evaluate and compare the safety and tolerability of Xyrem® with and without co-administration of divalproex sodium extended-release tablets.

This was a Phase 1, randomized, double-blind, placebo-controlled, five-period, crossover study in healthy male subjects. The study was conducted in approximately 24 healthy subjects to ensure completion of 16 subjects. Following Screening and Baseline procedures, eligible subjects were randomized to receive Xyrem® and Xyrem® placebo in a crossover fashion in Periods 1 and 2; were dosed with divalproex sodium extended-release tablets for 10 consecutive days in Period 3; and while continuing to take divalproex sodium extended-release tablets, were randomized to receive Xyrem® and Xyrem® placebo in a crossover fashion in Periods 4 and 5 (Table 1).

Periods 1 and 2:

Subjects were randomized to receive two 3 g doses of Xyrem® or Xyrem® placebo 4 hours apart in a crossover fashion at approximately 9 AM (first dose) and 1 PM (second dose) on Days 1 and 3. PK and PD parameters were evaluated during the 24 hours postdose.

Blood samples (4 mL) for sodium oxybate concentrations were collected at predose and at specified time-points up to 12 hours after the first dose of Xyrem® or Xyrem® placebo on Days 1 and 3. A PD Battery including the Karolinska Sleepiness Scale, Simple Reaction Time task, Digit Vigilance task, Choice Reaction Time task, Tracking task, and Numeric Working Memory task was administered at planned time-points up to X hours after first dose (X hours after second dose), and safety were monitored at specified timepoints on Days 1 and 3 as well as throughout the periods.

Period 3:

All subjects received divalproex sodium extended-release tablets 1250 mg at approximately 8 AM on Days 5 through 14. Blood samples (4 mL) for valproic acid concentrations were collected before the divalproex sodium dose (to determine trough concentration for assessment of steady state) on Days 13 and 14. Safety was monitored at specified timepoints as well as throughout the period.

Periods 4 and 5:

Subjects continued taking 1250 mg divalproex sodium extended-release tablets at approximately 8 AM on Days 15 through 18. Subjects were also randomized to receive two 3 g doses of Xyrem® or Xyrem® placebo in a crossover fashion at approximately 9 am (first dose) and 1 pm (second dose) on Days 15 and 18. The first dose of Xyrem® or Xyrem® placebo was taken approximately 1 hour after dosing with divalproex sodium extended-release tablets, and the second dose of Xyrem® or Xyrem® placebo was taken 4 hours after the first Xyrem®/Xyrem® placebo dose.

Blood samples (4 mL) to measure plasma sodium oxybate concentrations were collected at pre Xyrem®/Xyrem® placebo dose and at specified timepoints after the first Xyrem® or Xyrem® placebo dose on Days 15 and 18. Blood samples (4 mL) to measure plasma valproic acid concentrations were collected pre divalproex sodium dose and at specified time-points after the dose of divalproex sodium extended-release tablets on Day 15 and 18.

The PD battery was administered on Day 15 and 18, and safety was monitored at specified times on Days 15 and 18 as well as throughout the periods.

The treatments were as follows: A=Xyrem®, two 3 g doses, 4 hours apart at approximately 9 AM (1^{st} dose) and 1

PM (2nd dose); B=Xyrem® placebo, two doses, 4 hours apart; and C=Divalproex sodium 1250 mg, once a day at approximately 8 AM.

Results

The results below show the tests in which GHB administration was affected by concomitant administration of any of three MCT inhibitors, such as valproate, diclofenac, and ibubrofen.

Continuity of Attention

Xyrem® and divalproex sodium together (A+C) when compared to Xyrem® alone (A) showed a slightly delayed recovery for the combination at 4 hours and 8 hours. See FIG. **5** which shows Change from Baseline Figure (LSmean with 95% CI) for Continuity of Attention (#) (PD Population).

Simple Reaction Time Mean

At 1 hour and 4 hours, Xyrem® and divalproex sodium together produced statistically reliably greater impairments than Xyrem® alone. See FIG. **6**, which shows Change from Baseline Figure (LSmean with 95% CI) for Simple Reaction Time Mean (ms) (PD Population).

Digit Vigilance Accuracy

At 2.5 and 4 hours Xyrem® and divalproex sodium together were statistically reliably different greater impairment to Xyrem® alone. See FIG. **7**, which shows Change from Baseline Figure (LSmean with 95% CI) for Digit Vigilance Accuracy (%) (PD Population).

Tracking Distance from Target

Xyrem® and divalproex sodium together (A+C) when compared to Xyrem® alone (A) showed a statistically significant difference by a slightly delayed recovery for the combination at 4 and 8 hours. See FIG. **8** which shows the Change from Baseline Figure (LSmean with 95% CI) for Tracking Distance from Target (mm) (PD Population).

Numeric Working Memory Sensitivity Index

Xyrem® and divalproex sodium together (A+C) when compared to Xyrem® alone (A) showed a difference at 4.5 through 8 hours. See FIG. **9**, which shows the Change from Baseline Figure (LSmean with 95% CI) for Numeric Working Memory Sensitivity Index (#) (PD Population).

Numeric Working Memory Mean Reaction Time

Xyrem® and divalproex sodium together (A+C) when compared to Xyrem® alone (A) showed statistically significant differences at 2.5, 5 and 8 hours when the combination produced greater impairment. See FIG. **10**, which shows the Change from Baseline Figure (LSmean with 95% CI) for Numeric Working Memory Mean Reaction Time (ms) (PD Population).

In addition, it was observed that renal excretion of GHB increase 30% upon co-administration of Valproate.

We also found pk changes which were consistent with the inhibition of GHB dehydrogenase. This effect will increase the exposure of GHB to the subject and increase Cmax and AUC about 15%.

The combination of Xyrem® dosed with divalproex sodium was compared to divalproex sodium alone, more consistent statistically significant impairments over time were seen with the combination, than when Xyrem® was compared to its placebo, indicating that the effects of co-administration, when they appeared, were in the direction of increased impairments.

As has been seen previously, Xyrem® induces sleepiness and produces impairments to attention, working memory and performance on a tracking task in healthy volunteers. Divalproex sodium alone showed no consistent or notable effects on cognitive function or sleepiness. There were occasions when co-administration of Xyrem® and divalproex sodium produced greater deficits than Xyrem® alone. Further the combination also produced more consistent impairments when compared with divalproex sodium alone, than did Xyrem® when compared to its placebo. Thus this study has found evidence that co-administration of Xyrem® and divalproex produces greater impairments to cognitive function and sleepiness than were seen with Xyrem® alone.

Example 3

The effects of Ibuprofen were evaluated when combined with Xyrem® in a manner similar to the above. No differences were seen using the metrics above for Karolinska Sleepiness Scale (KSS), and the following CDR System tasks: Simple Reaction Time, Digit Vigilance, Choice Reaction Time, Tracking and Numeric Working Memory. However, it was observed that renal excretion of Xyrem® doubled upon concomitant administration of Ibuprofen and Xyrem®.

All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those skilled in the art in light of the teachings of the specification that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

What is claimed is:

1. A method for the treatment of cataplexy in narcolepsy or excessive daytime sleepiness in narcolepsy in a patient who is currently taking gamma-hydroxybutyrate (GHB) or a salt thereof comprising:

administering to the patient a dose of divalproex sodium concomitant to a dose of GHB or salt thereof; and

reducing the daily dosage amount of GHB or salt thereof administered to the patient by at least 20% wherein the daily dosage amount of GHB or salt thereof in the absence of concomitant administration of divalproex sodium is between 4.5 g to 9 g.

2. The method of claim **1** further comprising monitoring, patient response and adjusting the GHB dose to maintain the effect of the GHB.

3. The method of claim **1** wherein the daily dosage amount of GHB or salt thereof in the absence of concomitant administration of divalproex sodium is 4.5 g.

4. The method of claim **3** wherein the daily dosage amount of GHB or salt thereof administered to the patient is reduced to lower than 3.6 g.

5. The method of claim **1** wherein the daily dosage amount of GHB or salt thereof in the absence of concomitant administration of divalproex sodium is 6 g.

6. The method of claim **1** wherein the daily dosage amount of GHB or salt thereof in the absence of concomitant administration of divalproex sodium is 7.5 g.

7. The method of claim **1** wherein the daily dosage amount of GHB or salt thereof in the absence of concomitant administration of divalproex sodium is 9 g.

8. A method for the treatment of cataplexy in narcolepsy or excessive daytime sleepiness in narcolepsy in a patient who is currently taking gamma-hydroxybutyrate (GHB) or a salt thereof comprising:

reducing the daily dosage amount of GHB or salt thereof administered to the patient by at least 20% during concomitant administration of divalproex sodium, compared to the daily dosage amount of between 4.5 and 9 g of GHB or salt thereof currently used in the absence of concomitant administration of divalproex sodium.

9. The method of claim 8, wherein the daily dosage amount of GHB or salt thereof administered to the patient is reduced by at least 20% compared to the manufacturer's, recommended daily dosage amount of GHB or salt thereof.

10. The method of claim 8 further comprising monitoring patient response and adjusting the GHB dose to maintain the effect of the GHB.

11. The method of claim 8 wherein the daily dosage amount of GHB or salt thereof in the absence of concomitant administration of divalproex sodium is 4.5 g.

12. The method of claim 11 wherein the daily dosage amount of GHB or salt thereof administered to the patient is reduced to lower than 3.6 g.

13. A method for the treatment of cataplexy in narcolepsy or excessive daytime sleepiness in narcolepsy in a patient who is currently taking divalproex sodium comprising:

administering to the patient a starting daily dosage amount of gamma-hydroxybutyrate (GHB) or a salt thereof that is 20% lower than a manufacturer's recommended starting daily dosage amount of between 4.5 and 9 g in the absence of concomitant administration of divalproex sodium.

14. The method of claim 13 wherein the starting daily dosage amount of GHB or salt thereof administered to the patient is lower than 4.5 g.

15. The method of claim 14 wherein the starting daily dosage amount of GHB or salt thereof administered to the patient is divided in two equal doses.

16. The method of claim 15 wherein the first dose of the two equal doses of GHB or salt thereof administered to the patient is lower than 2.25 g.

17. The method of claim 15 wherein the second dose of the two equal doses of GHB or salt thereof administered to the patient is lower than 2.25 g.

18. The method of claim 13 further comprising monitoring patient response and adjusting the GHB dose to treat the patient.

19. The method of claim 13 wherein the manufacturer's recommended starting daily dosage amount of GHB or salt thereof in the absence of concomitant administration of divalproex sodium is 4.5 g.

20. A method for the treatment of cataplexy in narcolepsy or excessive daytime sleepiness in narcolepsy in a patient who is currently taking divalproex sodium comprising:

administering to the patient a starting daily dosage amount of gamma-hydroxybutyrate (GHB) or a salt thereof that is 20% lower than the starting daily dosage amount of between 4.5 to 9 g GHB that would otherwise have been recommended to the patient if the patient was not currently taking divalproex sodium.

21. The method of claim 20 wherein the starting daily dosage amount of GHB or salt thereof administered to the patient who is currently taking divalproex sodium is lower than 4.5 g.

22. The method of claim 21 wherein the starting daily dosage amount of GHB or salt thereof administered to the patient who is currently taking divalproex sodium is divided in two equal doses.

23. The method of claim 22 wherein the first dose of the two equal doses of GHB or salt thereof administered to the patient is lower than 2.25 g.

24. The method of claim 23 wherein the second dose of the two equal doses of GHB or salt thereof administered to the patient is lower than 2.25 g.

25. The method of claim 20 further comprising monitoring patient response and adjusting the GHB dose to treat the patient.

26. The method of claim 20 wherein the starting daily dosage amount of GHB or salt thereof that would otherwise have been recommended to the patient if the patient was not currently taking divalproex sodium is 4.5 g.

27. A method for the treatment of cataplexy in narcolepsy or excessive daytime sleepiness in narcolepsy in a patient who is currently taking divalproex sodium comprising the steps of:

administering to the patient a daily dosage amount of gamma-hydroxybutyrate (GHB) or a salt thereof that is lower than 4.5 g.

28. The method of claim 27 wherein the daily dosage amount of GHB or salt thereof administered to the patient is divided in two equal doses.

29. The method of claim 28 wherein the first dose of the two equal doses of GHB or salt thereof administered to the patient is lower than 2.25 g.

30. The method of claim 28 wherein the second dose of the two equal doses of GHB or salt thereof administered to the patient is lower than 2.25 g.

31. A method for the treatment of cataplexy in narcolepsy or excessive daytime sleepiness in narcolepsy in a patient who is currently taking divalproex sodium comprising the steps of:

administering to the patient a dose of gamma-hydroxybutyrate (GHB) or a salt thereof that is lower than 2.25 g; and

administering to the patient a second dose of GHB or salt thereof that is lower than 2.25 g.

* * * * *

EXHIBIT J

US009486426B2

(12) **United States Patent**
Eller

(10) **Patent No.: US 9,486,426 B2**
(45) **Date of Patent: *Nov. 8, 2016**

(54) **METHOD OF ADMINISTRATION OF GAMMA HYDROXYBUTYRATE WITH MONOCARBOXYLATE TRANSPORTERS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/707,914**

(22) Filed: **May 8, 2015**

(65) **Prior Publication Data**

US 2016/0015662 A1 Jan. 21, 2016

Related U.S. Application Data

(63) Continuation of application No. 13/837,714, filed on Mar. 15, 2013, now Pat. No. 9,050,302.

(60) Provisional application No. 61/771,557, filed on Mar. 1, 2013, provisional application No. 61/777,873, filed on Mar. 12, 2013.

(51) **Int. Cl.**

A01N 37/36	(2006.01)
A61K 31/19	(2006.01)
A61K 31/616	(2006.01)
A61K 31/20	(2006.01)
A61K 31/33	(2006.01)
A61K 31/505	(2006.01)
A61K 31/55	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/19*** (2013.01); ***A61K 31/20*** (2013.01); ***A61K 31/33*** (2013.01); ***A61K 31/505*** (2013.01); ***A61K 31/55*** (2013.01); ***A61K 31/616*** (2013.01)

(58) **Field of Classification Search**

USPC 514/188.3
IPC A61K 31/19
See application file for complete search history.

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(57) **ABSTRACT**

One embodiment of the present invention is to improve the safety and efficacy of the administration of GHB or a salt thereof to a patient. It has been discovered that the concomitant administration of an MCT inhibitor, such as diclofenac, valproate, or ibuprofen, will affect GHB administration. For example, it has been discovered that diclofenac lowers the effect of GHB in the body, thereby potentially causing an unsafe condition. Furthermore, it has been discovered that valproate increases the effect of GHB on the body, thereby potentially causing an unsafe condition.

31 Claims, 10 Drawing Sheets

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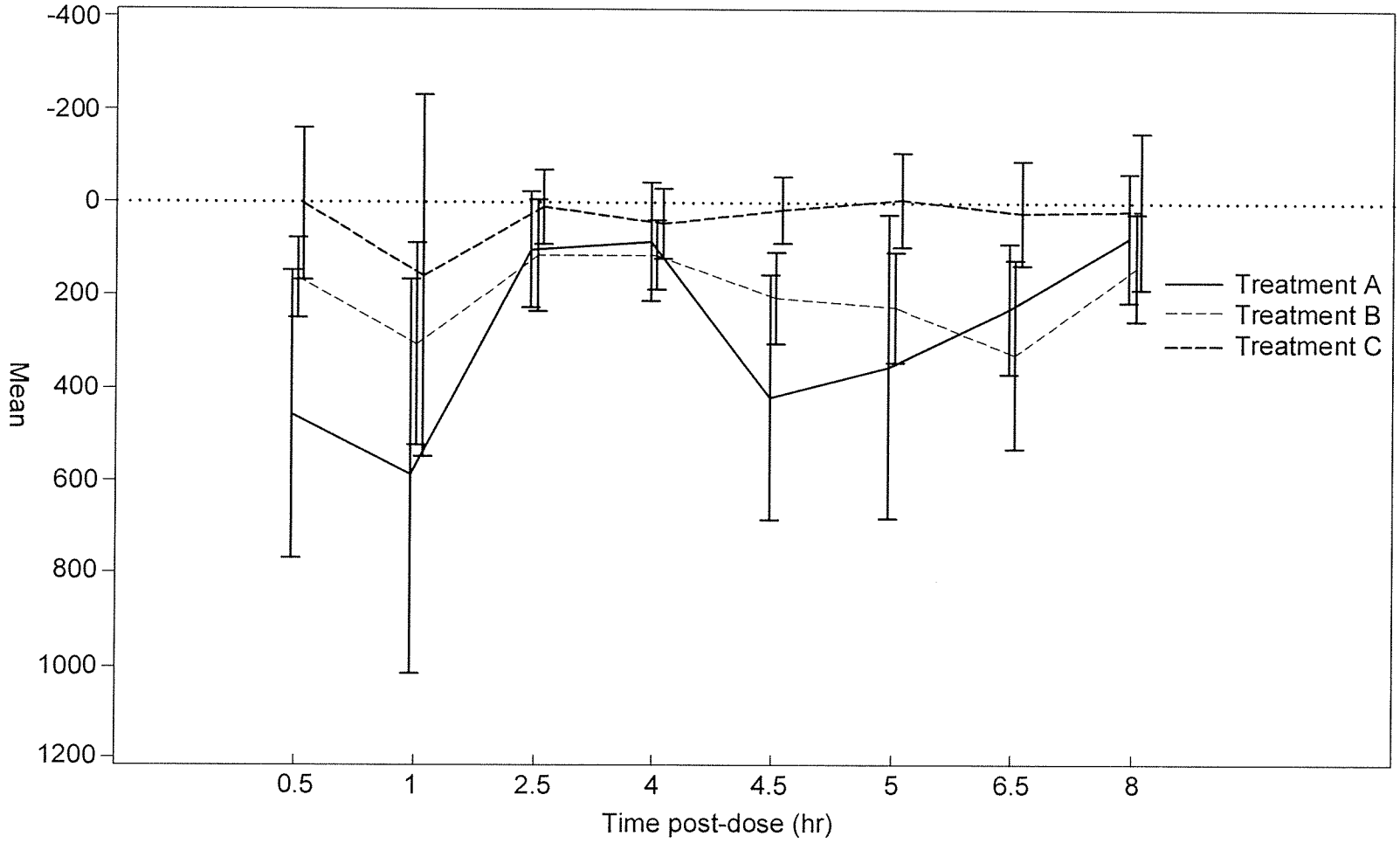
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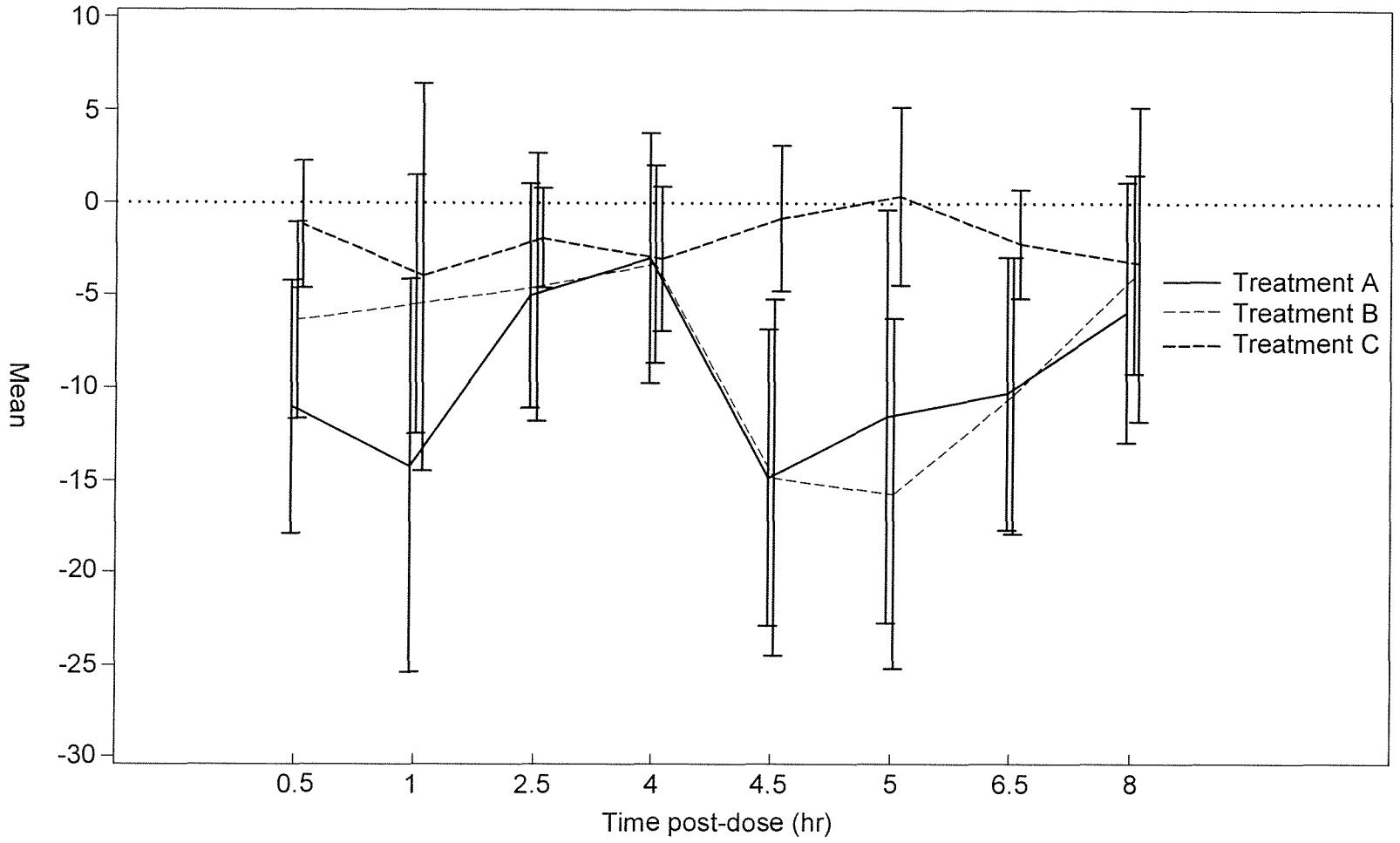
Time post-dose (hr)
Treatment A
Treatment B
Treatment C

FIG. 1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Time post-dose (hr)
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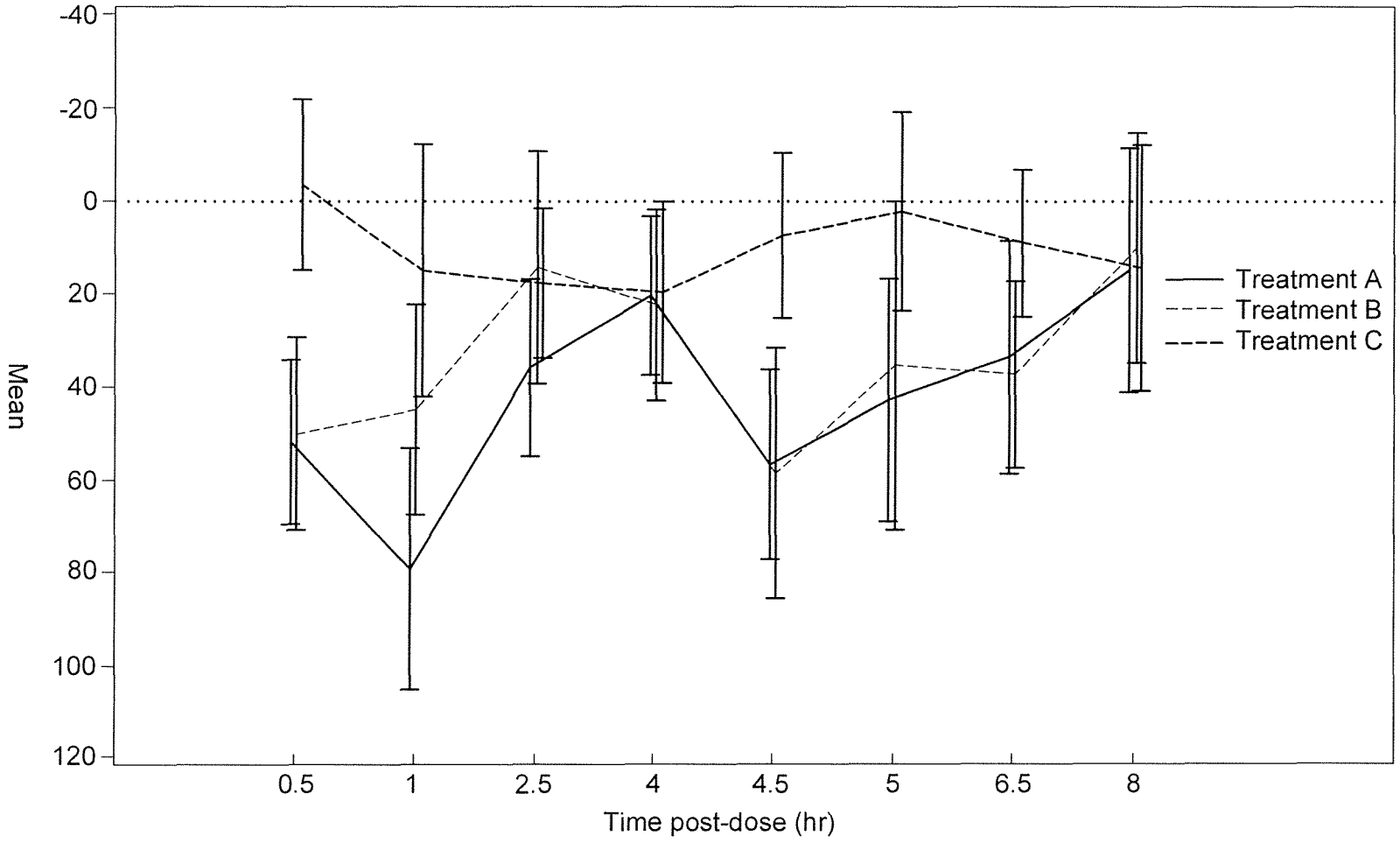
Treatment B
Treatment C

FIG. 2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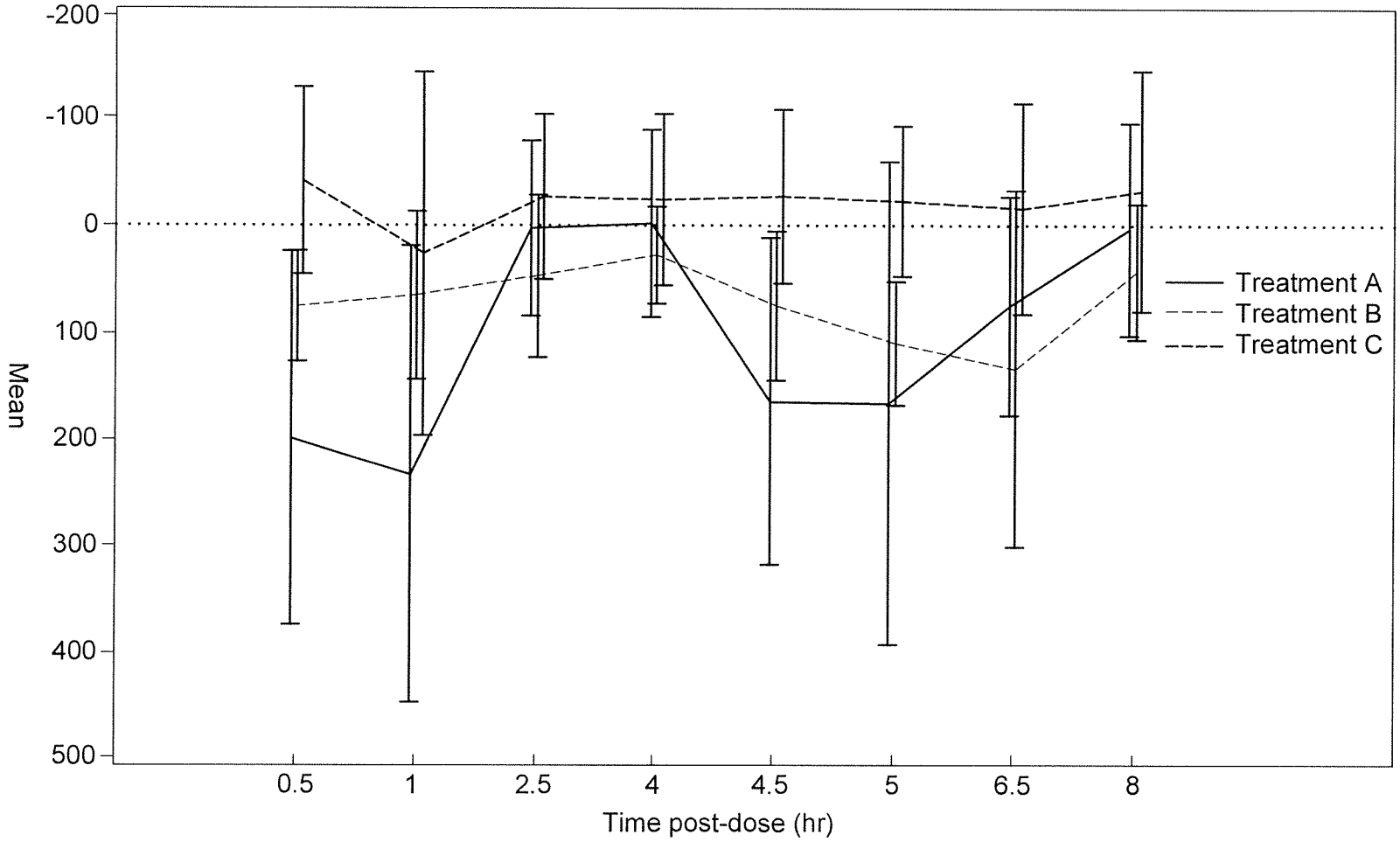
Time post-dose (hr)
Treatment A
Treatment B
Treatment C

FIG. 3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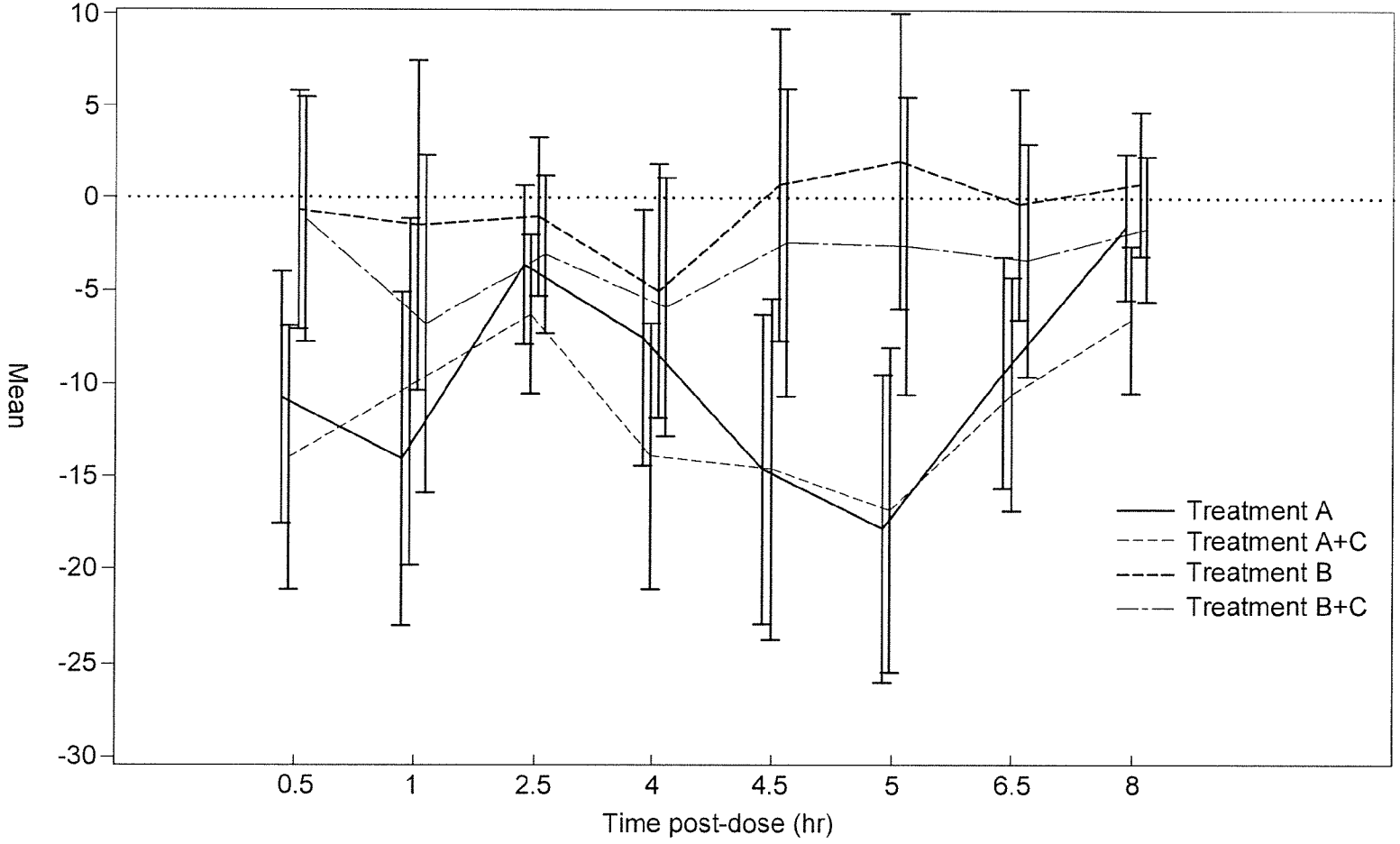
Time post-dose (hr)
Treatment A
Treatment B
Treatment C

FIG. 4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Mean
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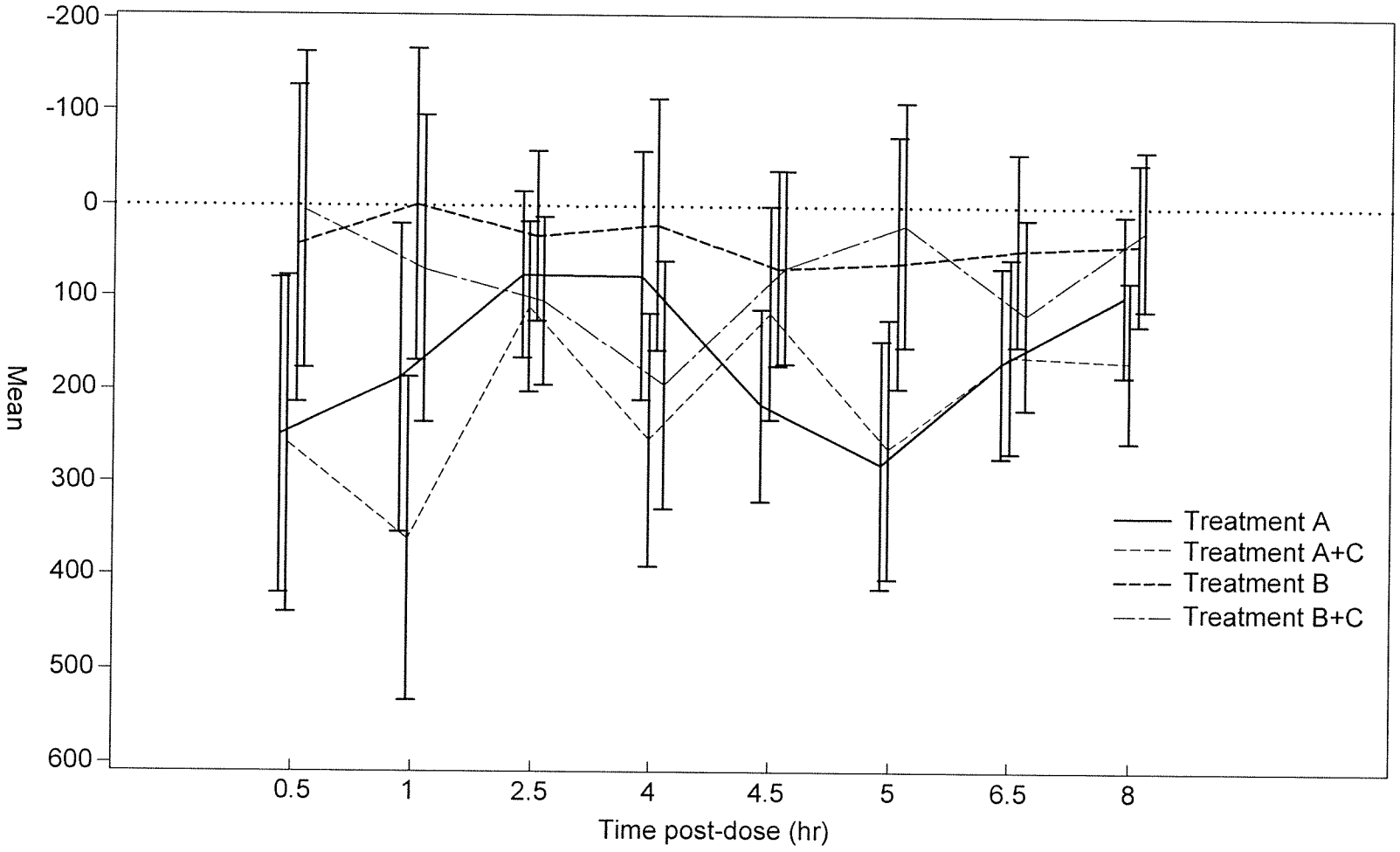
8
Time post-dose (hr)
Treatment A
Treatment A+C
Treatment B
Treatment B+C

FIG. 5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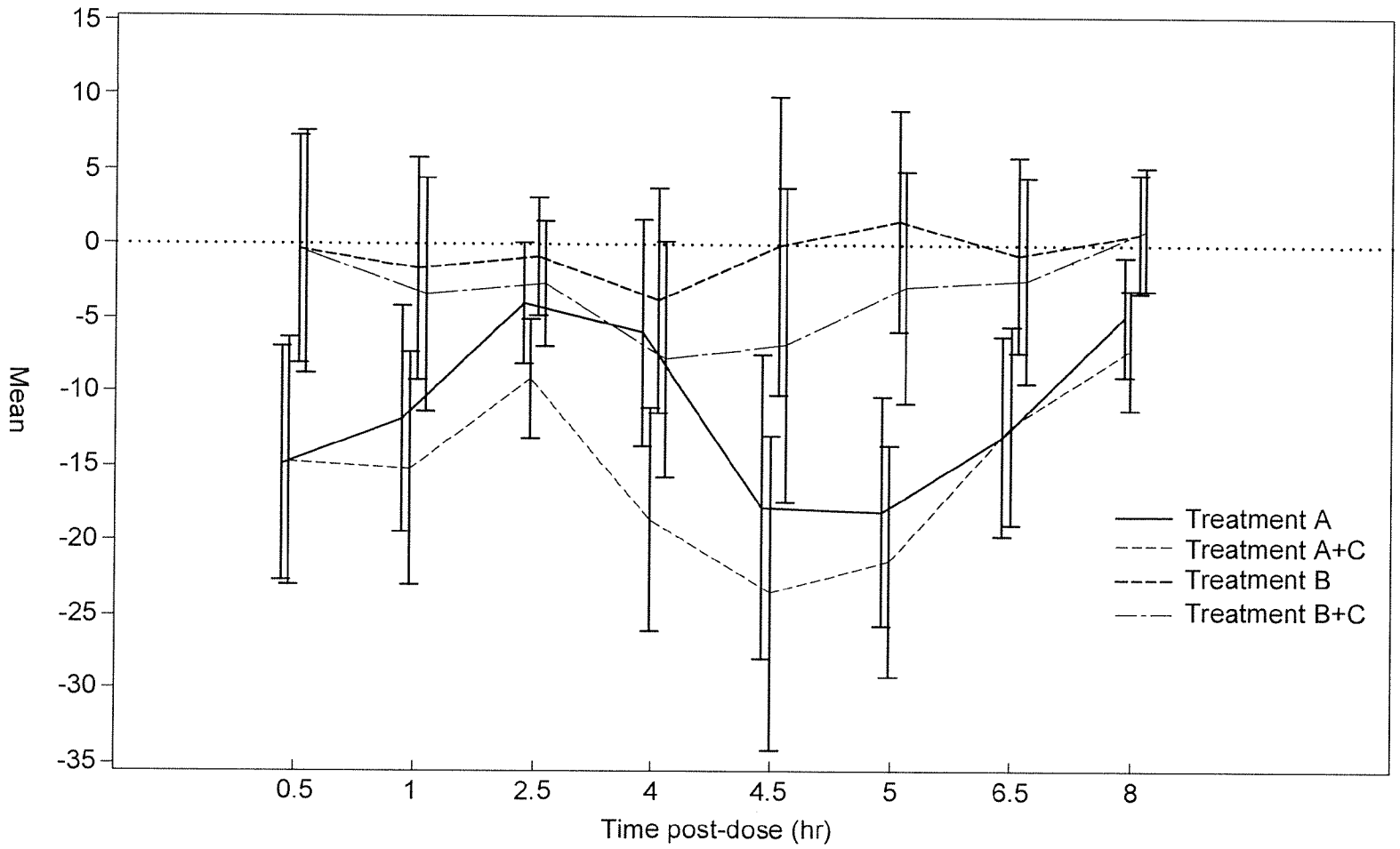
Time post-dose (hr)
Treatment A
Treatment A+C
Treatment B
Treatment B+C

FIG. 6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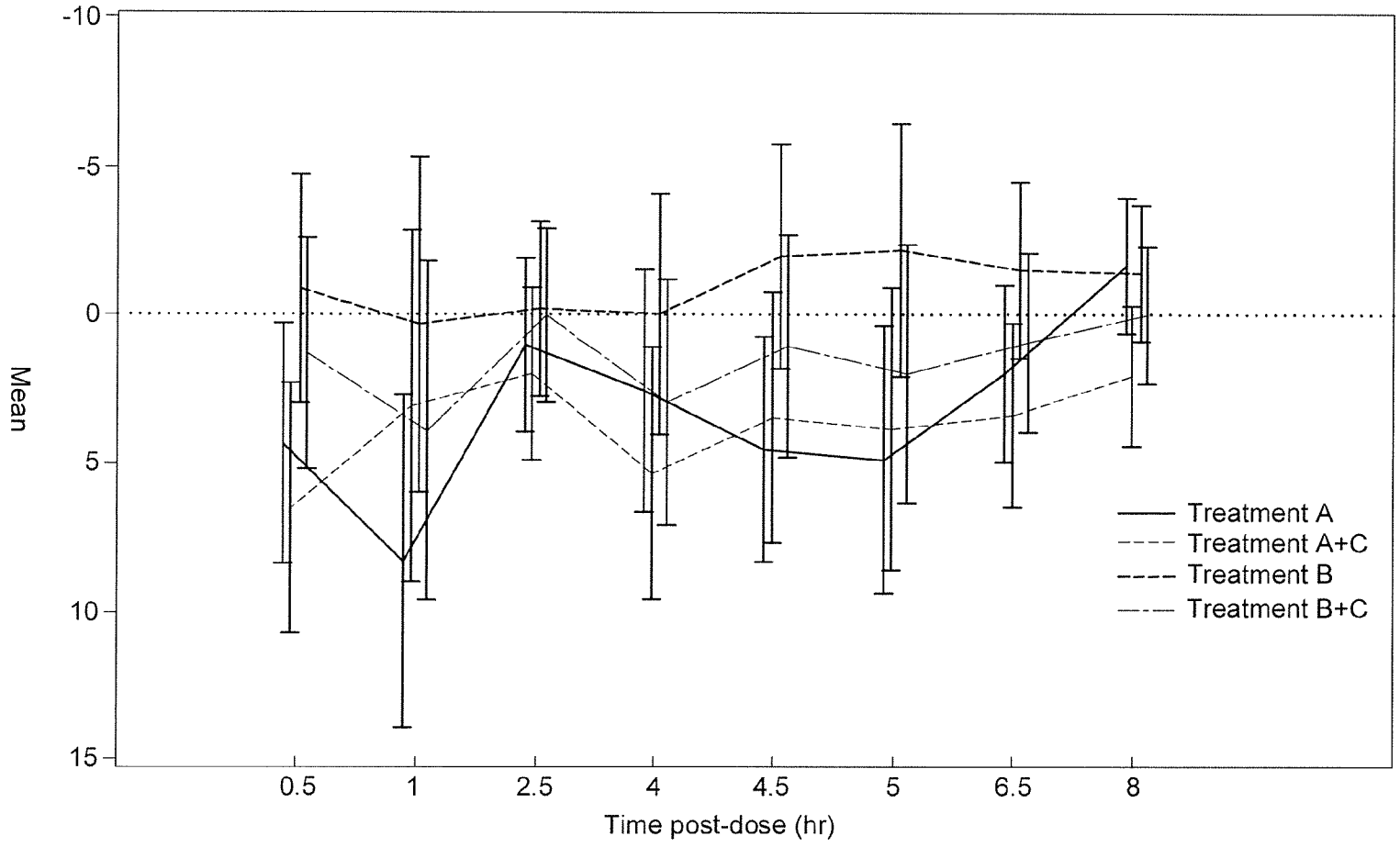
6.5
8
Time post-dose (hr)
Treatment A
Treatment A+C
Treatment B
Treatment B+C

FIG. 7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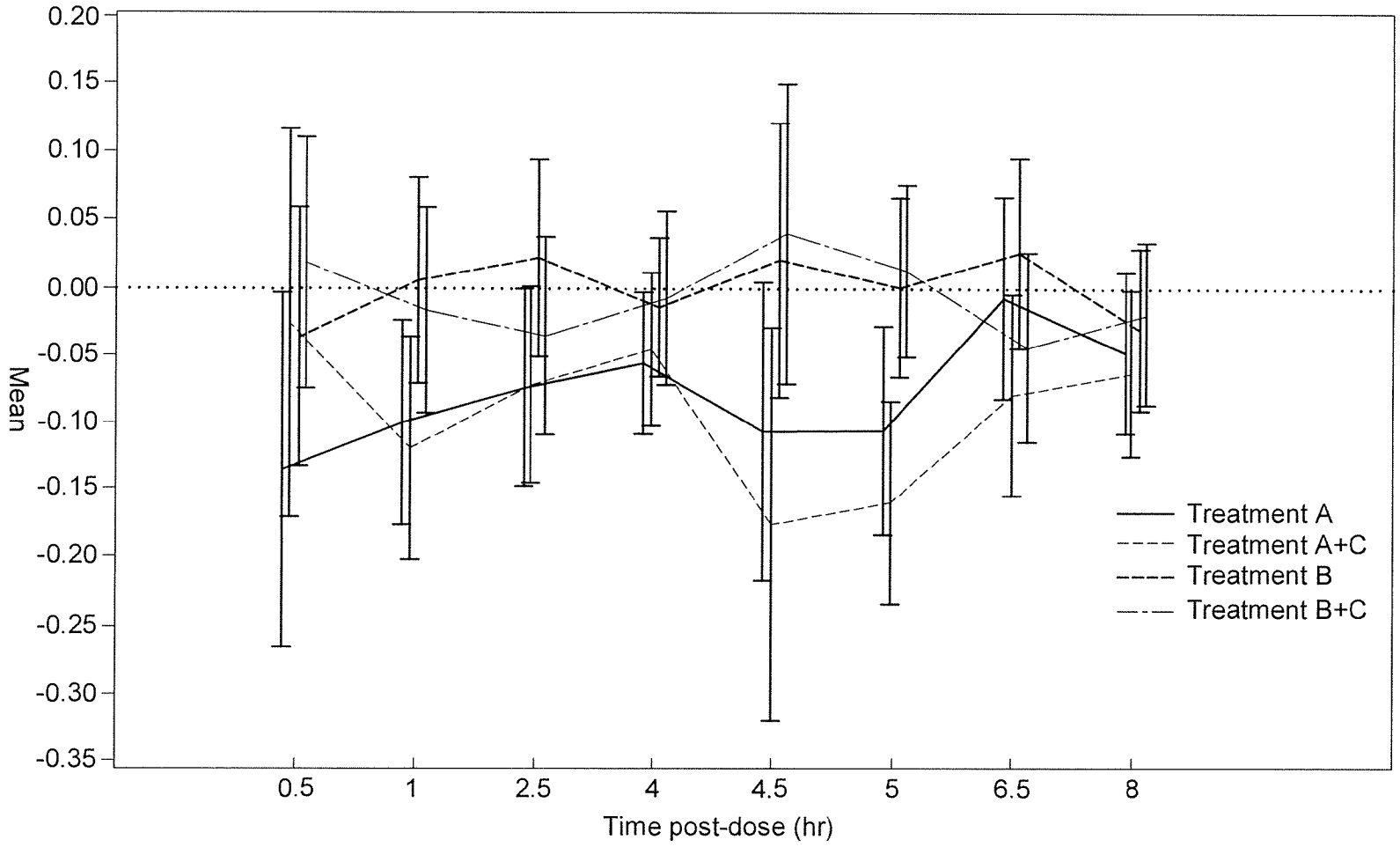
Time post-dose (hr)
Treatment A
Treatment A+C
Treatment B
Treatment B+C

FIG. 8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Mean
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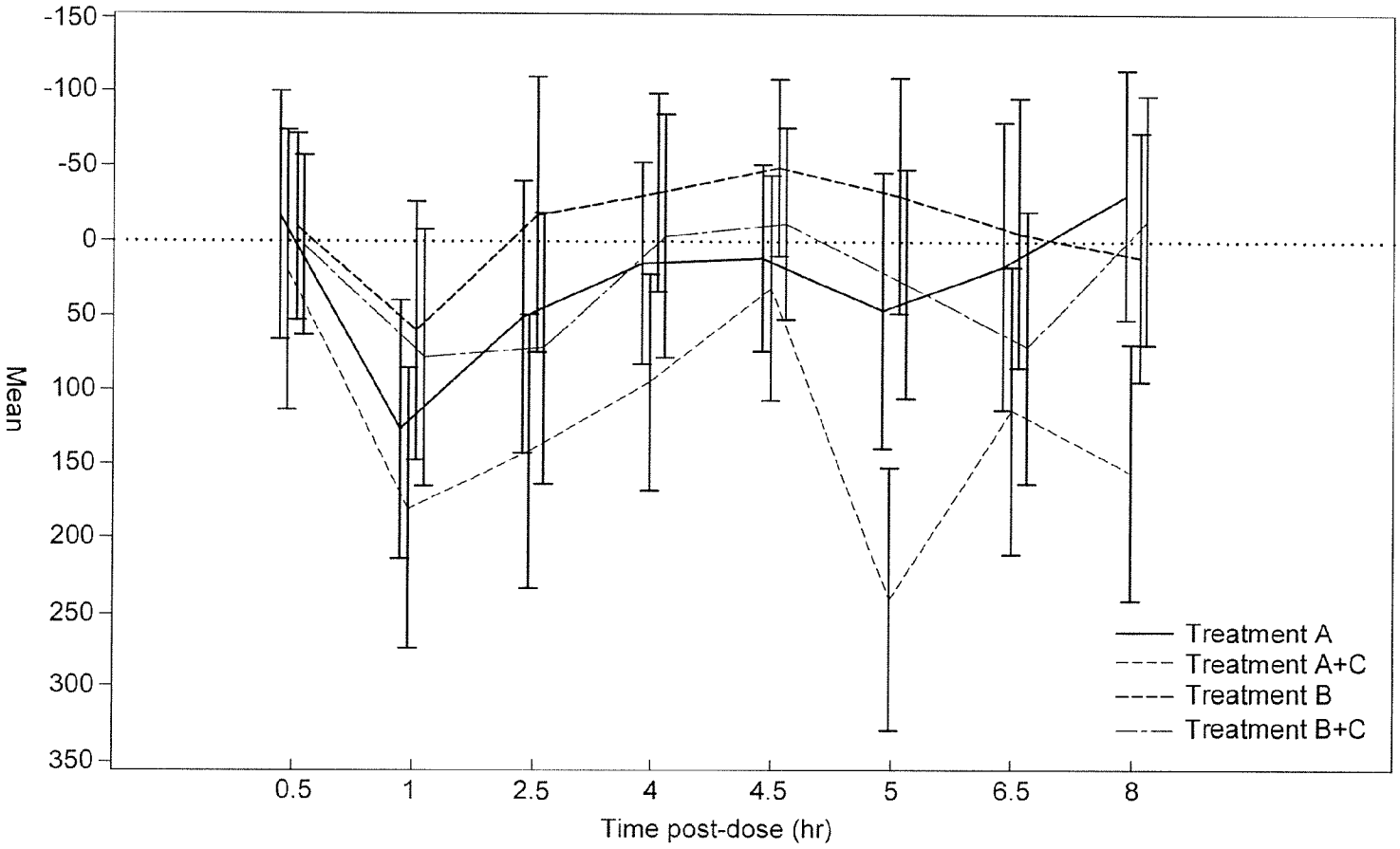
4.5
5
6.5
8
Time post-dose (hr)
Treatment A
Treatment A+C
Treatment B
Treatment B+C

FIG. 9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Mean
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4.5
5
6.5
8
Time post-dose (hr)
Treatment A
Treatment A+C
Treatment B
Treatment B+C

FIG. 10

METHOD OF ADMINISTRATION OF GAMMA HYDROXYBUTYRATE WITH MONOCARBOXYLATE TRANSPORTERS

This application is a continuation application of U.S. patent application Ser. No. 13/837,714, filed Mar. 15, 2013, which claims the benefit of U.S. Provisional Application No. 61/771,557, filed Mar. 1, 2013, and U.S. Provisional Application No. 61/777,873, filed Mar. 12, 2013, all of which applications are hereby incorporated by reference in their entireties.

BACKGROUND

This application relates to methods for safely administering gamma hydroxybutyrate (GHB) together with one or more other monocarboxylate transporter (MCT) inhibitors for therapeutic purposes. Example transporter inhibitors are valproate, diclofenac, and ibuprofen and combinations thereof.

SUMMARY OF THE INVENTION

One embodiment of the present invention is a method for treating a patient who is suffering from excessive daytime sleepiness, cataplexy, sleep paralysis, apnea, narcolepsy sleep time disturbances, hypnagogic hallucinations, sleep arousal, insomnia, and nocturnal myoclonus with gamma-hydroxybutyrate (GHB) or a salt thereof, comprising: orally administering to the patient in need of treatment, an adjusted dosage amount of the salt of GHB when the patient is receiving a concomitant administration of valproate. In certain embodiments, the adjusted amount is reduced at least about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% of the normal dose of the salt of GHB normally given to the patient. In certain embodiments, the amount of GHB is reduced at least about 10% and about 30% of the normal administration and the daily administration of the GHB salt is between 1 gram and 10 grams. In certain embodiments, the adjusted amount is reduced between the ranges of about 1% to 5%, about 5% to 10%, about 10% to 15%, about 15% to 20%, about 20% to 25%, about 25% to 30%, about 30% to 35%, about 35% to 40%, about 40% to 45%, or about 45% or 50%, relative to the normal dose of the salt of GHB normally given to the patient. In certain embodiments, the adjusted amount is reduced between the range of about 1% to 50%, about 1% to 45%, about 1% to 40%, about 1% to 35%, about 1% to 30%, about 1% to 25%, about 1% to 20%, about 1% to 15%, about 1% to 10%, about 1% to 5%, about 5% to 50%, about 5% to 45%, about 5% to 40%, about 5% to 35%, about 5% to 30%, about 5% to 25%, about 5% to 20%, about 5% to 15%, about 5% to 10%, about 10% to 50%, about 10% to 45%, about 10% to 40%, about 10% to 35%, about 10% to 30%, about 10% to 25%, about 10% to 20%, about 10% to 15%, about 15% to 50%, about 15% to 45%, about 15% to 40%, about 15% to 35%, about 15% to 30%, about 15% to 25%, about 15% to 20%, about 15% to 15%, about 15% to 10%, about 20% to 50%, about 20% to 45%, about 20% to 40%, about 20% to 35%, about 20% to 30%, about 20% to 25%, about 25% to 50%, about 25% to 45%, about 25% to 40%, about 25% to 35%, about 25% to 30%, about 30% to 50%, about 30% to 45%, about 30% to 40%, about 30% to 35%, about 35% to 50%, about 35% to 45%, about 35% to 40%, about 40% to 50%, relative to the normal dose of the salt of GHB normally given to the patient.

Another embodiment of the invention is a method of safely administering GHB a salt thereof for excessive daytime sleepiness, cataplexy, sleep paralysis, apnea, narcolepsy, sleep time disturbances, hypnagogic hallucinations, sleep arousal, insomnia, and nocturnal myoclonus in a human patient, comprising: determining if the patient is has taken, or will take a concomitant dose of valproate; orally administering a reduced amount of the GHB or GHB salt to the patient compared to the normal dose so as to diminish the additive effects of the GHB or GHB salt when administered with valproate. The amount of GHB is reduced at least 10% to 30%, or at least +15% of the normal administration.

One embodiment of the present invention is a method for treating a patient who is suffering from excessive daytime sleepiness, cataplexy, sleep paralysis, apnea, narcolepsy sleep time disturbances, hypnagogic hallucinations, sleep arousal, insomnia, and nocturnal myoclonus with GHB or a salt thereof, comprising: orally administering to the patient in need of treatment, an adjusted dosage amount of the salt of GHB when the patient is receiving a concomitant administration of diclofenac. In certain embodiments, the adjusted amount is at least about 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% higher than the normal dose of the salt of GHB normally given to the patient. In certain embodiments, the increased amount of GHB is at least about 15% more than the normal administration and the daily administration of the GHB salt is between 1 gram and 10 grams. In certain embodiments, the adjusted amount is increased between the range of about 1% to 5%, about 5% to 10%, about 10% to 15%, about 15% to 20%, about 20% to 25%, about 25% to 30%, about 30% to 35%, about 35% to 40%, about 40% to 45%, or about 45% or 50%, relative to the normal dose of the salt of GHB normally given to the patient. In certain embodiments, the adjusted amount is increased between the range of about 1% to 50%, about 1% to 45%, about 1% to 40%, about 1% to 35%, about 1% to 30%, about 1% to 25%, about 1% to 20%, about 1% to 15%, about 1% to 10%, about 1% to 5%, about 5% to 50%, about 5% to 45%, about 5% to 40%, about 5% to 35%, about 5% to 30%, about 5% to 25%, about 5% to 20%, about 5% to 15%, about 5% to 10%, about 10% to 50%, about 10% to 45%, about 10% to 40%, about 10% to 35%, about 10% to 30%, about 10% to 25%, about 10% to 20%, about 10% to 15%, about 15% to 50%, about 15% to 45%, about 15% to 40%, about 15% to 35%, about 15% to 30%, about 15% to 25%, about 15% to 20%, about 15% to 15%, about 15% to 10%, about 20% to 50%, about 20% to 45%, about 20% to 40%, about 20% to 35%, about 20% to 30%, about 20% to 25%, about 25% to 50%, about 25% to 45%, about 25% to 40%, about 25% to 35%, about 25% to 30%, about 30% to 50%, about 30% to 45%, about 30% to 40%, about 30% to 35%, about 35% to 50%, about 35% to 45%, about 35% to 40%, about 40% to 50%, relative to the normal dose of the salt of GHB normally given to the patient. See the product insert for normal dose ranges of GHB as sold by Jazz Pharmaceuticals. GHB is commercially known as Xyrem®.

In another embodiment, the invention is a method of safely administering a GHB salt for excessive daytime sleepiness, cataplexy, sleep paralysis, apnea, narcolepsy, sleep time disturbances, hypnagogic hallucinations, sleep arousal, insomnia, and nocturnal myoclonus in a human patient, comprising: determining if the patient has taken, or will take a concomitant dose of diclofenac; orally administering an increased amount of a GHB salt to the patient so as to compensate for the effects of diclofenac on the GHB salt when concomitantly administered.

Another embodiment of the present invention is a method for treating a patient who is suffering from narcolepsy wherein said patient is currently taking or has been prescribed GHB or a salt thereof, comprising determining if the patient is taking or has also been prescribed valproate or diclofenac; and adjusting the dose of the GHB or GHB salt to compensate for the effect caused by valproate or diclofenac. In certain embodiments, the method additionally comprises administering the adjusted dose to the patient.

Another embodiment of the present invention is a method for treating a patient who is suffering from excessive daytime sleepiness, cataplexy, sleep paralysis, apnea, narcolepsy, sleep time disturbances, hypnagogic hallucinations, sleep arousal, insomnia, and nocturnal myoclonus with a salt of gamma GHB, wherein said patient is also being treated with valproate or diclofenac, comprising: administering to the patient a daily dose of a GHB salt wherein said daily dose is administered at an amount sufficient to reduce or eliminate additive effects.

The embodiments of the present invention can administer the GHB at a level of between 1 and 4.5 grams/day or between 6 and 10 grams/day. The concentration of the formulation can be between 350-750 mg/ml or 450-550 mg/ml and a pH between 6-10 or 6.5-8.

Another embodiment of the present invention is a method for treating a patient who is suffering from narcolepsy, comprising: administering a salt of GHB or a salt thereof to a patient or determining whether the patient is currently on a GHB drug regimen; determining if the patient is also being administered ibuprofen; and advising a patient to cease or ceasing the administration of ibuprofen. In some embodiments, patients benefiting from this directive when the patient has will have a renal impairment.

Another embodiment of the present invention is a method for treating a patient who is suffering from narcolepsy, comprising: administering a therapeutically effective amount of a formulation containing GHB or a salt thereof to a patient at a concentration of between 450 and 550 mg/ml and a pH between 6 and 8, said formulation being administered before bed and 1-2 hours thereafter; determining if the patient is also being administered valproate; warning of a potential drug/drug interaction due to the combination of valproate and GHB; and reducing the dose of the GHB or GHB salt at least 15% to compensate for the effect caused by valproate. Another embodiment of the present invention is a method for treating a patient who is suffering from narcolepsy, comprising: administering a therapeutically effective amount of a formulation containing GHB or a salt thereof to a patient at a concentration of between 450 and 550 mg/ml and a pH between 6 and 8, said formulation being administered before bed and 1-2 hours thereafter; determining if the patient is also being administered diclofenac; warning of a potential drug/drug interaction due to the combination of diclofenac and the GHB salt; and increasing the dose of the GHB salt at least 15% to compensate for the effect caused by diclofenac.

In each of the embodiments of the invention the method includes administering GHB at between 1 and 4.5 grams/day or between 6 and 10 grams/day and at a concentration of between 350-750 or 450-550 mg/ml, and a pH between 6-10 or between 6.5-8. In further embodiments the valproate or diclofenac is administered within three days, one or two weeks (before or after) of GHB administration. In another embodiment, the present invention is a method wherein aspirin is also administered to the patient, especially with valproate.

In a further embodiment the method can include administering GHB as a single salt or a mixture of salts of GHB selected from the group consisting of a sodium salt of hydroxybutyrate (Na.GHB), a potassium salt of gamma-hydroxybutyrate (K.GHB), a magnesium salt of gamma-hydroxybutyrate ($Mg.(GHB)_2$), and a calcium salt of gamma-hydroxybutyrate ($Ca.(GHB)_2$).

In a further embodiment the method can include administering GHB to a patient suffering from excessive daytime sleepiness, comprising: administering a therapeutically effective amount of GHB to the patient; determining if the patient has concomitant administration of an MCT inhibitor; and adjusting the GHB dose or ceasing administering of the MCT inhibitor to maintain the effect of the GHB.

In any of the versions of the invention, the methods optionally further include administering aspirin to the patient.

In a further embodiment the method of administering GHB to a patient in need thereof comprises administering to the patient a therapeutically effective amount of GHB while avoiding concomitant of a diclofenac or valproate.

Another embodiment of the invention comprises a method of administering GHB or a salt thereof (GHB) to a patient with narcolepsy, wherein said patient is also in need of diclofenac, comprising administering to the patient a daily dosage of between 6 g and 10 g GHB or a GHB salt per day while avoiding diclofenac concomitant administration, and any one or more of the following: (a) advising the patient that diclofenac should be avoided or discontinued, (b) advising the patient that concomitant administration of GHB with drugs that are MCT inhibitors can alter the therapeutic effect or adverse reaction profile of GHB, (c) advising the patient that concomitant administration of GHB with diclofenac can alter the therapeutic effect or adverse reaction profile of GHB, (d) advising the patient that use of GHB in patients being treated with diclofenac is contraindicated, (e) advising the patient that concomitant administration of GHB and diclofenac resulted in an decrease in exposure to GHB, or (f) advising the patient MCT inhibitors should be used with caution in patients receiving GHB due to the potential for increased GHB clearance.

Another embodiment of the invention comprises a administering GHB to a patient with narcolepsy, wherein said patient is also in need of valproate, comprising administering to the patient a daily dosage of between 6 g and 10 g GHB per day while avoiding valproate concomitant administration, and any one or more of the following: (a) advising the patient that valproate should be avoided or discontinued, (b) advising the patient that concomitant administration of GHB with drugs that are MCT inhibitors can alter the therapeutic effect or adverse reaction profile of GHB, (c) advising the patient that concomitant administration of GHB with valproate can alter the therapeutic effect or adverse reaction profile of GHB, (d) advising the patient that use of GHB in patients being treated with valproate is contraindicated, (e) advising the patient that concomitant administration of GHB and valproate resulted in an increase in exposure to GHB, or (f) advising the patient that MCT inhibitors should be used with caution in patients receiving GHB due to the potential for increased GHB clearance.

In another embodiment, the present invention is a method for distributing a drug containing GHB or a salt thereof to an approved pharmacy, the method comprising: identifying an approved pharmacy that has an established management system to dispense information concerning the risks associated with ingesting a MCT inhibitor concomitantly to said drug to patients that are prescribed said drug; providing said

pharmacy with said information related to the risks; and authorizing distribution of said drug to said pharmacy, wherein said pharmacy dispenses the drug with said information when filling a prescription for said drug. The method may also comprise including an electronic or written alert, which can explain the risks, to employees to dispense said information with said drug when prescriptions are filled. Also, the information can be dispensed when a subject refills said prescription. The warnings would be as recited above.

The methods of the present invention may include a warning for patients not to operate hazardous machinery, including automobiles or airplanes, until they are reasonably certain that GHB does not affect them adversely and not to engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery or a motor vehicle or flying an airplane, for at least 6, 7, 8 or 9 hours after taking the second nightly dose of GHB. Any information dispensed with said drug advises patients of the potential for enhanced potency of said drug if said patients also take valproate or advises patients of the potential for decreased potency of said drug if said patients also take diclofenac.

Another embodiment of the present invention is a method of administering GHB to a patient in need thereof, comprising administering to the patient a therapeutically effective amount of GHB while avoiding concomitant administration of diclofenac or valproate.

The invention may also comprise a method for reducing the effects of GHB toxicity in a patient in need thereof, comprising administering to said patient an effective amount of diclofenac such that the toxic effects of GHB are reduced. It may also comprise a method for potentiating the beneficial effects of GHB in a patient in need thereof comprising concomitantly administering to said patient an effective amount of valproate such that the beneficial effects of GHB are increased.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows change from baseline figure (LS mean with 95% CI) for Power of Attention (ms) (PD Completer Population). Treatment A=diclofenac placebo+Xyrem®. Treatment B=diclofenac+Xyrem®. Treatment C=diclofenac+Xyrem® placebo.

FIG. **2** shows change from baseline figure (LSmean with 95% CI) for Digit Vigilance Accuracy (%) (PD Completer Population).

FIG. **3** shows change from baseline figure (LSmean with 95% CI) for Digit Vigilance Mean Reaction Time (ms) (PD Completer Population).

FIG. **4** shows change from baseline figure (LSmean with 95% CI) for Choice Reaction Time Mean (ms) (PD Completer Population).

FIG. **5** shows change from baseline figure (LSmean with 95% CI) for Continuity of Attention (#) (PD Population). Treatment A=Xyrem®. Treatment B=Xyrem® placebo. Treatment C=valproate.

FIG. **6** shows change from baseline figure (LSmean with 95% CI) for Simple Reaction Time Mean (ms) (PD Population).

FIG. **7** shows change from baseline figure (LSmean with 95% CI) for Digit Vigilance Accuracy (%) (PD Population).

FIG. **8** shows change from baseline figure (LSmean with 95% CI) for Tracking Distance from Target (mm) (PD Population).

FIG. **9** shows change from baseline figure (LSmean with 95% CI) for Numeric Working Memory Sensitivity Index (#) (PD Population).

FIG. **10** shows change from baseline figure (LSmean with 95% CI) for Numeric Working Memory Mean Reaction Time (ms) (PD Population).

DETAILED DESCRIPTION OF THE INVENTION

The following patents and applications are hereby incorporated by reference in their entireties for all purposes: U.S. Pat. Nos. 6,472,431, 6,780,889, 7,262,219, 7,851,506, 8,263,650, 8,324,275; 7,895,059; 7,797,171; 7,668,730; 7,765,106; 7,765,107; 61/317,212, Ser. Nos. 13/071,369, 13/739,886, 12/264,709, PCT/US2010/033572, PCT/US2009/061312, 2009/0137565; and 2012/0076865. The following patents are also incorporated by reference: U.S. Pat. No. 5,380,937; U.S. Pat. No. 4,393,236 German Patent DD 237,309 A1; and British Pat. No. 922,029.

Objects, features and advantages of the methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

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In the specification and claims that follow, references will be made to a number of terms which shall be defined to have the following meaning.

The terms "a" and "an" do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced item. The term "or" means "and/or". The terms "comprising", "having", "including", and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to").

"Concomitant" and "concomitantly" as used herein refer to the administration of at least two drugs to a patient either subsequently, simultaneously, or consequently within a time period during which the effects of the first administered drug are still operative in the patient. Thus, if the first drug is, e.g., Xyrem®, or GHB, and the second drug is valproate, the concomitant administration of the second drug occurs within two weeks, preferably within one week or even three days, before or after the administration of the first drug.

"Dosage amount" means an amount of a drug suitable to be taken during a fixed period, usually during one day (i.e., daily).

"Dosage amount adapted for oral administration" means a dosage amount that is of an amount deemed safe and effective for the particular patient under the conditions specified. As used herein and in the claims, this dosage

amount is determined by following the recommendations of the drug manufacturer's Prescribing Information as approved by the US Food and Drug Administration.

"Dosing regimen" means the dose of a drug taken at a first time by a patient and the interval (time or symptomatic) and dosage amounts at which any subsequent doses of the drug are taken by the patient. Each dose may be of the same or a different dosage amount.

A "dose" means the measured quantity of a drug to be taken at one time by a patient.

A "patient" means a human in need of medical treatment. In one embodiment medical treatment can include treatment of an existing condition, such as a disease or disorder, prophylactic or preventative treatment, or diagnostic treatment. In another embodiment, medical treatment also includes administration to treat excessive daytime sleepiness, cataplexy, sleep paralysis, apnea, narcolepsy, sleep time disturbances, hypnagogic hallucinations, sleep arousal, insomnia, and nocturnal myoclonus.

"Providing" means giving, administering, selling, distributing, transferring (for profit or not), manufacturing, compounding, or dispensing.

The terms "therapeutically effective amount," as used herein, refer to an amount of a compound sufficient to treat, ameliorate, or prevent the identified disease or condition, or to exhibit a detectable therapeutic, prophylactic, or inhibitory effect. The effect can be detected by, for example, an improvement in clinical condition, or reduction in symptoms. The precise effective amount for a subject will depend upon the subject's body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Where a drug has been approved by the U.S. Food and Drug Administration (FDA), a "therapeutically effective amount" refers to the dosage approved by the FDA or its counterpart foreign agency for treatment of the identified disease or condition.

"Side effect" means a secondary effect resulting from taking a drug. The secondary effect can be a negative (unfavorable) effect (i.e., an adverse side effect) or a positive (favorable) effect.

Pharmacokinetic parameters referred to herein describe the in vivo characteristics of drug (or a metabolite or a surrogate marker for the drug) over time. These include plasma concentration (C), as well as C_{max}, C_n, C_{24}, T_{max}, and AUC. The term "T_{max}" refers to the time from drug administration until C_{max} is reached. "AUC" is the area under the curve of a graph of the measured plasma concentration of an active agent vs. time, measured from one time point to another time point. For example AUC_{0-t} is the area under the curve of plasma concentration versus time from time 0 to time t, where time 0 is the time of initial administration of the drug. Time t can be the last time point with measurable plasma concentration for an individual formulation. The $AUC_{0-.infin.}$ or AUC_{0-INF} is the calculated area under the curve of plasma concentration versus time from time 0 to time infinity. In steady-state studies, $AUC_{0-.tau.}$ is the area under the curve of plasma concentration over the dosing interval (i.e., from time 0 to time .tau. (tau), where tau is the length of the dosing interval.

It may be advantageous to incorporate a pharmacy management system into the method of the present invention. Pharmacy management systems are computer-based systems that are used by commercial pharmacies to manage prescriptions and to provide pharmacy and medical personnel with warnings and guidance regarding drugs being administered to patients. Such systems typically provide alerts warning either or both of health care providers and patients when a drug that may be harmful to the particular patient is prescribed. For example, such systems can provide alerts warning that a patient has an allergy to a prescribed drug, or is receiving concomitant administration of a drug that can have a dangerous interaction with a prescribed drug. U.S. Pat. Nos. 7,895,059; 7,797,171; 7,668,730; 7,765,106; 7,765,107; 5,758,095, 5,833,599, 5,845,255, 6,014,631, 6,067,524, 6,112,182, 6,317,719, 6,356,873, and 7,072,840, each of which is incorporated herein by reference, disclose various pharmacy management systems and aspects thereof. Example pharmacy management systems are now commercially available, e.g., CENTRICITY Pharmacy from BDM Information Systems Ltd., General Electric Healthcare, Waukesha, Wis., Rx30 Pharmacy Systems from Transaction Data Systems, Inc., Ocoee, Fla., SPEED SCRIPT from Digital Simplistics, Inc., Lenexa, Kans., and various pharmacy management systems from OPUS-ISM, Hauppauge, N.Y.

In some embodiments, a pharmacy management system may be required or preferred as part of a drug distribution program. For example, the present invention includes a method for distributing a drug containing GHB or a salt thereof to an approved pharmacy, the method comprising: (1) Identifying an approved pharmacy that has an established management system to dispense information concerning the risks associated with ingesting a MCT inhibitors concomitantly to said drug to patients that are prescribed said drug; (2) Providing said pharmacy with said information related to the risks; and (3) Authorizing distribution of said drug to said pharmacy, wherein said pharmacy dispenses the drug with said information when filling a prescription for said drug. The established management system may include an electronic alert to employees to dispense said information with said drug when prescriptions are filled. Such information may be dispensed in written form, for example in a brochure explaining the risks of concomitant ingestion of GHB and an MCT inhibitor such as diclofenac, valproate, or ibuprofen or combinations thereof. For example, the information dispensed with GHB may advise a patient of the potential for enhanced potency of GHB if the patient also takes valproate. Alternatively, or in addition thereto, the information dispensed with GHB may advise a patient of the potential for decreased potency of GHB if the patient also takes diclofenac. Such information may also be dispensed in verbal form. Distributors may maintain a directory of approved pharmacies, for example in a computer readable storage medium, to further ensure that GHB is dispensed only to patients who are advised of the additive effects.

In addition, the system can prevent the dispensing of GHB or salt thereof until proper testing or confirmation is obtained that the patient is not taking or going to take valproate or diclofenac concomitantly with GHB. Alternatively, the patient can be warned of the adverse effect and instructed to modify the dose of GHB to accommodate the increased or reduced effects of GHB due to valproate or diclofenac.

A pharmacy management system of the present invention can be a REMS system as shown in U.S. Pat. Nos. 7,895,059; 7,797,171; and 7,668,730 and also include monitoring for concomitant use of diclofenac, valproate, or ibuprofen, or combinations thereof. Warnings may be administered through the existing pharmacy management system as described in the patents above.

One embodiment of the present invention, without being limited by theory, is the discovery of drug interactions that change either, or both, the efficacy or safety profile of GHB.

The three compounds are valproate, diclofenac, and ibuprofen or combinations thereof. To achieve the above benefits, GHB of the present invention can be administered in a reduced amount when a second compound, such as valproate, is concomitantly administered with GHB. It can also be administered in an increased amount to overcome any effects of diclofenac. The compounds can also be avoided or discontinued to prevent unsafe concomitant administration.

In one embodiment of the present invention, concomitant administration of GHB with other agents is monitored and potential changes to the doses of GHB are made, or changes in the administration of other compounds are made. In one embodiment of the present invention, when GHB was concomitantly administered with ibuprofen, there were pharmacokinetic (PK) changes consistent with monocarboxylic transporter (MCT) inhibition and renal excretion of GHB doubled (statistically significant). Plasma levels were about ~5% lower, which was statistically significant. In another embodiment of the present invention, when GHB and Diclofenac are concomitantly administered, PD effects were significantly reduced. In another embodiment of the present invention, when GHB and divalproate were concomitantly administered, PK showed both MCT and GHB dehydrogenase inhibition, with the latter predominating. MCT inhibition caused renal clearance to be increased 30% (statistically significant). GHB dehydrogenase inhibition caused systemic exposure (plasma AUC) to be increased 26%. Both measures are statistically significant and outside FDA "equivalence window". PD shows more pronounced effects with concomitant administration.

One embodiment is a method of administering a therapeutically effective amount of GHB to a patient in need of treatment, such as with narcolepsy, the invention provides an improvement that comprises avoiding or discontinuing administration of a compound that affects GHB potency and administering a therapeutically effective amount of GHB. The compound can be diclofenac or valproate and they can alter the therapeutic effect or adverse reaction profile of GHB.

Gamma Hydroxybutyrate (GHB)

GHB (also called oxysorbate or oxybate) is approved in the United States (US) for the treatment of excessive daytime sleepiness (EDS) and for the treatment of cataplexy, both in patients with narcolepsy. GHB is commercially sold as Xyrem® sodium oxybate by Jazz Pharmaceuticals. Sodium oxybate is the sodium salt of the endogenous neurotransmitter gamma hydroxybutyrate (GHB), which is found in many tissues of the body. "GHB", oxybate, a GHB salt or Xyrem® will be used to refer to these active forms. It can be used as a sodium, calcium, potassium, or magnesium salt. See U.S. patent application Ser. No. 13/739,886.

GHB is present, for example, in the mammalian brain and other tissues. In the brain, the highest GHB concentration is found in the hypothalamus and basal ganglia and GHB is postulated to function as a neurotransmitter. The neuropharmacologic effects of GHB include increases in brain acetylcholine, increases in brain dopamine, inhibition of GABA-ketoglutarate transaminase and depression of glucose utilization but not oxygen consumption in the brain. GHB is converted to succinate and then metabolized via the Krebs cycle. Clinical trials have shown that GHB increases delta sleep and improves the continuity of sleep (Laborit, 1973; Lapierre et al., 1988; Lapierre et al., 1990; Yamada et al., 1967; Scharf, 1985).

GHB treatment substantially reduces the signs and symptoms of narcolepsy, i.e. excessive daytime sleepiness, cataplexy, sleep paralysis, apnea, narcolepsy, sleep time disturbances, hypnagogic hallucinations, sleep arousal, insomnia, and nocturnal myoclonus. In addition, GHB increases total sleep time and REM sleep, and it decreases REM latency (Mamelak et al, 1973; Yamada et al., 1967; Bedard et al., 1989), reduces sleep apnea (Scrima et al., 1987), and improves general anesthesia (Hasenbos and Gielen, 1985).

GHB has several clinical applications other than narcolepsy and sleep disorders. GHB has been reported to reduce alcohol craving, the number of daily drinks consumed, and the symptoms of alcohol withdrawal in patients (Gallimberti et al., 1989; Gallimberti et al., 1992; Gessa et al., 1992). GHB has been used to decrease the symptoms of opiate withdrawal, including both heroin and methadone withdrawal (Gallimberti et al., 1994; Gallimberti et al., 1993). It has analgesic effects that make it suitable as a pain reliever (U.S. Pat. No. 4,393,236). Intravenous administration of GHB has been reported to reduce intracranial pressure in patients (Strong, A. 1984). Also, administration of GHB was reported to increase growth hormone levels in patients (Gessa et al, 1994).

A good safety profile for GHB consumption, when used long term for treatment of narcolepsy has been reported. Patients have been safely treated for many years with GHB without development of tolerance (Scharf, 1985). Clinical laboratory tests carried out periodically on many patients have not indicated organ or other toxicities (Lammers, 1993; Scrima, 1990; Scharf, 1985; Mamelack, 1977; Mamelak, 1979; Gessa, 1992). The side effects of GHB treatment have been minimal in incidence and degree of severity, though they include sleepwalking, enuresis, headache, nausea and dizziness (Broughton and Mamelak, 1979; Mamelak et al., 1981; Mamelak et al., 1977; Scrima et al., 1989; Scrima et al., 1990; Scharf et al., 1985). Therefore, it is critical to identify adverse drug-drug interactions to maintain the positive safety profile for GHB.

GHB Pharmacology

GHB has at least two distinct binding sites (See Wu, et al., 2004) in the central nervous system. GHB is an agonist at the GHB receptor, which is excitatory, (Cash et al., 2009) and it is a weak agonist at the GABAB receptor, which is inhibitory. GHB acts in a similar fashion to some neurotransmitters in the mammalian brain and is probably synthesized from GABA in GABAergic neurons, and released when the neurons fire. If taken orally, GABA itself does not effectively cross the blood-brain-barrier. (See Kuriyama et al., 2005).

GHB induces the accumulation of either a derivative of tryptophan or tryptophan itself in the extracellular space, possibly by increasing tryptophan transport across the blood-brain barrier. The blood content of certain neutral amino-acids, including tryptophan, is also increased by peripheral GHB administration. GHB-induced stimulation of tissue serotonin turnover may be due to an increase in tryptophan transport to the brain and in its uptake by serotonergic cells. As the serotonergic system may be involved in the regulation of sleep, mood, and anxiety, the stimulation of this system by high doses of GHB may be involved in certain neuropharmacological events induced by GHB administration.

However, at therapeutic doses, GHB reaches much higher concentrations in the brain and activates GABAB receptors, which are primarily responsible for its sedative effects. (See Dimitrijevic et al., 2005). GHB's sedative effects are blocked by GABAB antagonists.

The role of the GHB receptor in the behavioral effects induced by GHB is more complex. GHB receptors are densely expressed in many areas of the brain, including the cortex and hippocampus, and these are the receptors that

GHB displays the highest affinity for. There has been somewhat limited research into the GHB receptor; however, there is evidence that activation of the GHB receptor in some brain areas results in the release of glutamate, the principal excitatory neurotransmitter. Drugs that selectively activate the GHB receptor cause absence seizures in high doses, as do GHB and GABA(B) agonists. (See Banerjee et al., 1995.)

Activation of both the GHB receptor and GABA(B) is responsible for the addictive profile of GHB. GHB's effect on dopamine release is biphasic. (See Hechler et al., 1991). Low concentrations stimulate dopamine release via the GHB receptor. (See Maitre et al., 1990). Higher concentrations inhibit dopamine release via GABA(B) receptors as do other GABA(B) agonists such as baclofen and phenibut. (See Smolders et al., 1995). After an initial phase of inhibition, dopamine release is then increased via the GHB receptor. Both the inhibition and increase of dopamine release by GHB are inhibited by opioid antagonists such as naloxone and naltrexone. Dynorphin may play a role in the inhibition of dopamine release via kappa opioid receptors. (See Mamelak 1989).

This may explain the paradoxical mix of sedative and stimulatory properties of GHB, as well as the so-called "rebound" effect, experienced by individuals using GHB as a sleeping agent, wherein they awake suddenly after several hours of GHB-induced deep sleep. That is to say that, over time, the concentration of GHB in the system decreases below the threshold for significant GABAB receptor activation and activates predominantly the GHB receptor, leading to wakefulness. However, one embodiment of the present invention is the unexpected discovery that drugs change the PD profile of GHB to alter its effects and its safety profile. Example drugs are include valproate and diclofenac. It is important for efficacy safety purposes that the effect of GHB be maintained consistently and not subject to variation due to the effects of other drugs.

Both of the metabolic breakdown pathways shown for GHB can run in either direction, depending on the concentrations of the substances involved, so the body can make its own GHB either from GABA or from succinic semialdehyde. Under normal physiological conditions, the concentration of GHB in the body is rather low, and the pathways would run in the reverse direction to what is shown here to produce endogenous GHB. However, when GHB is consumed for recreational or health promotion purposes, its concentration in the body is much higher than normal, which changes the enzyme kinetics so that these pathways operate to metabolize GHB rather than produce it.

The pharmacokinetics of GHB have been investigated in alcohol dependent patients (Ferrara et al., 1992) and in normal healthy males (Palatini et al., 1993) after oral administration. GHB possesses a rapid onset and short pharmacological effect (Ferrara et al., 1992; Palatine et al., 1993; Lettieri and Fung, 1978; Arena and Fung, 1980; Roth and Giarman, 1966; Vickers, 1969; Lee, 1977). In alcohol dependent patients, GHB absorption into and elimination from the systemic circulation were fast processes. Virtually no unchanged drug could be recovered in the urine. There were preliminary indications that the pharmacokinetics of GHB might be non-linear or dose-dependent (Ferrara et al., 1992). In the healthy volunteers study, the pharmacokinetics of three rising GHB doses (12.5, 25, and 50 mg/kg) were investigated. These findings indicate that both the oral absorption and elimination processes of GHB were capacity-limited though the degree of dose dependency was moderate (Palatini et al., 1993).

Methods of making GHB salts are described, for example, in U.S. Pat. No. 4,393,236, and U.S. patent application Ser. No. 13/739,886 which are incorporated herein by reference.

It has been discovered that there are unexpected drug-drug interactions (DDI) between GHB and common drugs frequently prescribed for other ailments. It is one goal of the present invention to warn when those interactions may affect the safety profile of GHB. In one embodiment of the present invention, drugs that may affect GHB administration include valproate, diclofenac, and ibuprofen and combinations thereof.

GHB is a central nervous system (CNS) depressant. Alcohol and sedative hypnotics are contraindicated in patients who are using GHB. The concurrent use of GHB with other CNS depressants, including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death. If use of these CNS depressants in combination with GHB is required, dose reduction or discontinuation of one or more CNS depressants (including GHB) should be considered. In addition, if short-term use of an opioid (e.g. post- or perioperative) is required, interruption of treatment with GHB should be considered. See the package insert for Xyrem®.

GHB may impair respiratory drive, especially with overdoses associated with interactions with other drugs and alcohol. Since valproate may potentiate the effect of GHB, a warning should accompany any use of valproate and GHB as stated herein. The warning should address the use of additional drugs that may further enhance the effect of GHB, such as alcohol or aspirin, for example.

Healthcare providers should caution patients about operating hazardous machinery, including automobiles or airplanes, until they are reasonably certain that GHB does not affect them adversely (e.g., impair judgment, thinking, or motor skills). Patients should not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery or a motor vehicle or flying an airplane, for at least 6, 7, 8 or 9 hours after taking the second nightly dose of GHB. Patients should be queried about potential adverse events, such as excessive daytime sleepiness, CNS depression related events, etc. upon initiation of GHB therapy and periodically thereafter. These queries should include info regarding additional medication such as diclofenac and valproate for example. See the Xyrem® package insert.

In one embodiment described herein, patients are warned that combination of GHB with valproate can increase plasma levels and potentiate the activity of GHB and exacerbate all the effects and adverse event associated with GHB. These effects include the intended effects of drowsiness, sedation, and sleep and typically unintended events such as depressed respiration, CNS depression, excessive drowsiness, hepatic impairment, and depression, among other things.

In another embodiment, diclofenac mitigates and protects against the pharmacodynamic effects the effects of GHB. However, the mixture of GHB and diclofenac does not affect sleepiness and does not make a patient more attentive. Without wishing to be bound by theory, the effects may be due to the interaction between diclofenac and the GHB receptor in lieu of the MCT inhibitor activity.

Typical concentrations of GHB formulations are shown in U.S. Pat. Nos. 8,263,650 and 8,324,275, for example. They include minimum concentrations starting from 150 mg/ml to

450 mg/ml (at 10 mg/ml increments) and increasing to 600 mg/ml to 750 mg/ml (at 10 mg/ml increments) as a maximum. So, a broad range would include 150-750 mg/ml and any range within the broad range using 10 mg/ml increments. One embodiment of the invention is a range of 350-750 mg/ml and another is 450-550 mg/ml GHB. One embodiment of the present invention uses a GHB formulation with a pH range of 6-10, another uses a pH range of between 6.5-8. For example, a minimum concentration includes 350, 360, 370, 380 mg/ml, and so on up to at least 730, 740, and 750 mg/ml and all concentrations (measured in 10 mg/ml increments in between).

pH adjusting agents can include acids, bases and many of the compounds found in U.S. Pat. No. 8,263,650. In some embodiments the pH adjusting agent is an acid selected from the group of: acetic, acetylsalicylic, barbital, barbituric, benzoic, benzyl penicillin, boric, caffeine, carbonic, citric, dichloroacetic, ethylenediaminetetra-acetic acid (EDTA), formic, glycerophosphoric, glycine, lactic, malic, mandelic, monochloroacetic, oxalic, phenobarbital, phenol, picric, propionic, saccharin, salicylic, sodium dihydrogen phosphate, succinic, sulfadiazine, sulfamerazine, sulfapyridine, sulfathiazole, tartaric, trichloroacetic, and the like, or inorganic acids such as hydrochloric, nitric, phosphoric or sulfuric, and the like.

GHB is commercially available as a sodium salt, however, it can also be formulated as a mixture of salts as shown in U.S. Ser. No. 13/739,886, which is incorporated by reference as stated above. For example, the mixture comprises one, two, or three or more salts selected from the group consisting of a sodium salt of hydroxybutyrate (Na.GHB), a potassium salt of gamma-hydroxybutyrate (K.GHB), a magnesium salt of gamma-hydroxybutyrate ($Mg.(GHB)_2$), and a calcium salt of gamma-hydroxybutyrate ($Ca.(GHB)_2$). The different salts may be present in different percentages. For example, in certain embodiments, the pharmaceutical composition comprises Na.GHB, K.GHB, and $Ca.(GHB)_2$. In certain embodiments, the Na.GHB salt is present in a wt/wt % of about 5% to about 40%, the K.GHB salt is present in a wt/wt % of about 10% to about 40%, and the $Ca.(GHB)_2$ salt is present in a wt/wt % of about 20% to about 80%. In certain embodiments, the Na.GHB, K.GHB, and $Ca.(GHB)_2$ salts are present in a wt/wt % ratio of about 11%:39%:50%, respectively.

Valproic Acid

Valproic acid (VPA, also called valproate or divalproex), an acidic chemical compound, has found clinical use as an anticonvulsant and mood-stabilizing drug, primarily in the treatment of epilepsy, bipolar disorder, and, less commonly, major depression. See G. Rosenberg, Cell. Mol. Life Sci. 64 (2007) 2090-2103. It is also used to treat migraine headaches and schizophrenia. A typical dose of valproate varies by indication. Dosages for seizures are between 10 to 15 mg/kg/day, with potential increases of 5 to 10 mg/kg/day. VPA is a liquid at room temperature, but it can be reacted with a base such as sodium hydroxide to form the salt sodium valproate, which is a solid. The acid, salt, or a mixture of the two (valproate semisodium, divalproate) are marketed under the various brand names Depakote, Depakote ER, Depakene, Depakene Crono (extended release in Spain), Depacon, Depakine, Valparin and Stavzor.

Valproate is believed to affect the function of the neurotransmitter GABA in the human brain, making it an alternative to lithium salts in treatment of bipolar disorder. Its mechanism of action includes enhanced neurotransmission of GABA (by inhibiting GABA transaminase, which breaks down GABA). However, several other mechanisms of action in neuropsychiatric disorders have been proposed for valproic acid in recent years. See Rosenberg G (2007). "The mechanisms of action of valproate in neuropsychiatric disorders: can we see the forest for the trees?". *Cellular and Molecular Life Sciences* 64 (16): 2090-103.

Valproic acid also blocks the voltage-gated sodium channels and T-type calcium channels. These mechanisms make valproic acid a broad-spectrum anticonvulsant drug. Valproic acid is an inhibitor of the enzyme histone deacetylase 1 (HDAC1), hence it is a histone deacetylase inhibitor. Valproic acid may interact with carbamazepine, as valproates inhibit microsomal epoxide hydrolase (mEH), the enzyme responsible for the breakdown of carbamazepine-10,11 epoxide (the main active metabolite of carbamazepine) into inactive metabolites. (See Gonzalez, Frank J.; Robert H. Tukey (2006). "Drug Metabolism". In Laurence Brunton, John Lazo, Keith Parker (eds.). Goodman & Gilman's The Pharmacological Basis of Therapeutics (11th ed.). New York: McGraw-Hill. pp. 79.) By inhibiting mEH, valproic acid causes a buildup of the active metabolite, prolonging the effects of carbamazepine and delaying its excretion. Valproic acid also decreases the clearance of amitriptyline and nortriptyline.

Aspirin may decrease the clearance of valproic acid, leading to higher-than-intended serum levels of the anticonvulsant. Also, combining valproic acid with the benzodiazepine clonazepam can lead to profound sedation and increases the risk of absence seizures in patients susceptible to them.

Valproic acid and sodium valproate reduce the apparent clearance of lamotrigine (lamictal). In most patients, the lamotrigine dosage for coadministration with valproate must be reduced to half the monotherapy dosage.

Valproic acid is contraindicated in pregnancy, as it decreases the intestinal reabsorption of folate (folic acid), which leads to neural tube defects. Because of a decrease in folate, megaloblastic anemia may also result. Phenytoin also decreases folate absorption, which may lead to the same adverse effects as valproic acid.

Valproic acid, 2-propylvaleric acid, is synthesized by the alkylation of cyanoacetic ester with two moles of propylbromide, to give dipropylcyanoacetic ester. Hydrolysis and decarboxylation of the carboethoxy group gives dipropylacetonitrile, which is hydrolyzed into valproic acid. See U.S. Pat. Nos. 3,325,361 and 4,155,929 and GB Pat. Nos. 980279 and 1522450. See also, T. R. Henry, "The History of Valproate in Clinical Neuroscience." Psychopharmacology bulletin (2003) 37 (Suppl 2):5-16.

Diclofenac

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) taken to reduce inflammation and as an analgesic reducing pain in certain conditions. Diclofenac is used to treat pain, inflammatory disorders, and dysmenorrhea and is a commonly used NSAID. See Auler et al., Brazilian Jour. Med. Bio. Res., (1977) 30:369-374 and Hasan, et al., and Pakistan Jour. Pharmaceutical Sciences, vol. 18, No. 1, January 2005, pp 18-24 both are hereby incorporated by reference in their entireties.

The name is derived from its chemical name: 2-(2,6-dichloranilino) phenylacetic acid, it may be supplied as either the sodium or potassium salt. Diclofenac is available as a generic drug in a number of formulations; including Dichlofenac diethylammonium applied topically to joints. Over-the-counter (OTC) use is approved in some countries for minor aches and pains and fever associated with common infections.

Diclofenac is typically absorbed readily, but absorption is delayed upon administration with food. Its half-life varies from 1 to 3 hours with mean peak plasma levels of about 0.5 ug/ml to 1.0 ug/ml after 2 hours of a single dose of 25 mg. Diclofenac binds to human serum proteins, specifically albumin. See Hasan et al 2005.

Ibuprofen

Ibuprofen (from iso-butyl-propanoic-phenolic acid) is a nonsteroidal anti-inflammatory drug (NSAID) widely prescribed for pain relief, fever reduction, and swelling. Ibuprofen was derived from propanoic acid. Originally marketed as Brufen, ibuprofen is available under a variety of popular trademarks, including Motrin, Nurofen, Advil, and Nuprin. Ibuprofen is used primarily for fever, pain, dysmenorrhea and inflammatory diseases such as rheumatoid arthritis. It is also used for pericarditis and patent ductus arteriosus. It is a commonly used drug commercially available over the counter.

Nonsteroidal anti-inflammatory drugs such as ibuprofen work by inhibiting the enzyme cyclooxygenase (COX), which converts arachidonic acid to prostaglandin H2 (PGH2). PGH2, in turn, is converted by other enzymes to several other prostaglandins (which are mediators of pain, inflammation, and fever) and to thromboxane A2 (which stimulates platelet aggregation, leading to the formation of blood clots).

Like aspirin and indomethacin, ibuprofen is a nonselective COX inhibitor, in that it inhibits two isoforms of cyclooxygenase, COX-1 and COX-2. The analgesic, antipyretic, and anti-inflammatory activity of NSAIDs appears to operate mainly through inhibition of COX-2, whereas inhibition of COX-1 would be responsible for unwanted effects on the gastrointestinal tract. However, the role of the individual COX isoforms in the analgesic, anti-inflammatory, and gastric damage effects of NSAIDs is uncertain and different compounds cause different degrees of analgesia and gastric damage.

The synthesis of this compound consisted of six steps, started with the Friedel-Crafts acetylation of isobutylbenzene. Reaction with ethyl chloroacetate (Darzens reaction) gave the α,β-epoxy ester, which was hydrolyzed and decarboxylated to the aldehyde. Reaction with hydroxylamine gave the oxime, which was converted to the nitrile, then hydrolyzed to the desired acid. See U.S. Pat. No. 3,385,886.

An improved synthesis by BHC required only three steps. After a similar acetylation, hydrogenation with Raney nickel gave the alcohol, which underwent palladium-catalyzed carbonylation.

Valproate, diclofenac, and ibuprofen are monocarboxylate transporter inhibitors. One embodiment of the present application is a method to improve safety by monitoring the combination of these compounds with GHB.

Monocarboxylate Transporters

Monocarboxylate transporters, or MCTs, constitute a family of proton-linked plasma membrane transporters that carry molecules having one carboxylate group (monocarboxylates), such as lactate and pyruvate, across biological membranes. See Halestrap A P, Meredith D (2004). "The SLC16 gene family—from monocarboxylate transporters (MCTs) to aromatic amino acid transporters and beyond". Pflugers Arch. 447 (5): 619-28.

MCTs are a series of transporters which move chemicals in body tissues, such as kidneys, blood/brain barrier, intestines, etc. They can transport chemical compounds back from urine to create a higher concentration in the blood than the urine. They can be used to treat an overdose or to prevent excretion of a compound. They can also be used to prevent absorption or transport into the brain or gut, or excretion via the urine. Exemplary MCT inhibitors include valproate, diclofenac, and ibuprofen.

Concomitant Administration of GHB and Drug-Drug Interactions

In one embodiment of the present invention the concomitant administration of MCT inhibitors, such as either valproate, diclofenac, or ibuprofen with GHB can effect GHB levels or activity and alter the GHB safety and efficacy profile to create an unsafe condition. For example, valproate can increase or prolong GHB effects and diclofenac can reduce or shorten GHB effects. For example, if the effects are increased, then there could be an increase of adverse events associated with too much GHB. Also, the effect of GHB may be prolonged to cause side effects, such as excessive daytime sleepiness (EDS), to last into the daytime. Prolongation of the effect would counter the purpose for providing the GHB and could create an unsafe situation for patients who wish to be alert and who may be engaged in otherwise dangerous activity. This concomitant administration can transform an otherwise safe dose of GHB into one with safety concerns. It is a health risk to patients and a medical challenge to health care workers.

The drug-drug interaction could also reduce the effects of GHB by altering its blood levels or otherwise. Reduction in the GHB level may also provide an unsafe condition due to excessive daytime sleepiness. In each situation, where GHB is increased, decreased or excessively cleared, those drug-drug interactions need to be identified to a health care worker to adjust the dose of GHB or discontinue the use of the other compound.

As recited on the product insert for Xyrem®, healthcare providers should caution patients about operating hazardous machinery, including automobiles or airplanes, until they are reasonably certain that GHB does not affect them adversely (e.g., impair judgment, thinking, or motor skills). Patients should not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery or a motor vehicle or flying an airplane, for at least 6, 7, 8 or 9 hours after taking the second nightly dose of GHB.

In some embodiments in which diclofenac or valproate is discontinued to avoid an adverse drug interaction, they are discontinued within at least 3 days prior to or after starting GHB therapy. In various embodiments, diclofenac or valproate is discontinued within at least 4 days, or at least 5 days, or at least 6 days, or at least 7 days (or one week), or at least 8 days, or at least 9 days, or at least 10 days, or at least 11 days, or at least 12 days, or at least 13 days, or at least 14 days (or two weeks), or at least 15 days, or at least 16 days, or at least 17 days, or at least 18 days, or at least 19 days, or at least 20 days, or at least 21 days (or three weeks) prior to or after starting GHB therapy. In some embodiments, the diclofenac or valproate is discontinued no later than 2 weeks or 1 week before starting GHB therapy.

In some embodiments, a method of optimizing GHB therapy when valproate is provided comprises titrating the dosage of GHB administered to a patient downward relative to a previously administered dosage in the patient, so the dose does not result in an increased exposure to GHB. In some embodiments, a method of optimizing GHB therapy when diclofenac is provided comprises titrating the dosage of GHB administered to a patient upward relative to a previously administered dosage in the patient, so the dose results in an effective exposure to GHB.

Thus, the present invention includes a method for treating a patient who is suffering from excessive daytime sleepiness,

cataplexy, sleep paralysis, apnea, narcolepsy, sleep time disturbances, hypnagogic hallucinations, sleep arousal, insomnia, and nocturnal myoclonus with a salt of gamma-hydroxybutyrate (GHB), wherein said patient is also being treated with valproate or diclofenac, comprising: administering to the patient a daily dose of a GHB salt wherein said daily dose is administered at an amount sufficient to reduce or eliminate such additive effects.

In one embodiment of the present invention, a reduced amount of GHB is administered to a patient when concomitantly administered with valproate. In another embodiment of the present invention, an increased amount of GHB is administered to a patient when concomitantly administered with diclofenac.

When valproate is concomitantly administered with GHB, The amount of GHB can be reduced at least 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% of the normal dose of GHB. For example, if the normal dose is 9 g/day, then a dose that is adjusted to reduce the normal dose by 15% is 7.65 g/day. The GHB dose reduction may be taken for one or multiple GHB dosings. For example, GHB may be administered in two doses per night for narcolepsy. A typical adult range of doses for GHB are between 4.5 or 6 g as a minimum and 8 or 10 g/day as a maximum divided into two doses. The dose recommended on the package insert and approved by the FDA is between 4.5 and 9.0 g/day. Typical exemplary pediatric daily doses of GHB are between 1 g and 6 g/day for pediatric patients aged 0-6 years. Typical exemplary pediatric daily doses of GHB are between 1 g and 9 g/day for pediatric patients aged 7-17 years. However, these ranges are not absolute and can be increased or decreased by 1-2 grams in either direction. One dose is typically administered prior to bed (night time sleep) and another dose administered 1-2 hours later. See the Xyrem® package insert (Xyrem® is a registered trademark of Jazz Pharmaceuticals plc or its subsidiaries.). Either or both of the multiple doses may be reduced to present a safer administration profile. For example, the first dose may be reduced by the numbers referred to above or the second may be reduced by the same percentages, or both. Furthermore, the absolute amount of GHB per dose or per day may be reduced at least 0.5 g, 1 g, 1.5 g, 2.0 g, 2.5 g, 3.0 g, 3.5 g, or 4 g. An exemplary decrease in an adult dose would be to reduce the maximum dose to less than 8.5, 8, 7.5, 7, 6.5, 6, 5.5, 5, 4.5, 4, 3.5, 3 g/day and so on. The minimum dose will be reduced accordingly to 4, 3.5, 3, 2.5, 2, and so on.

In one embodiment of the present invention, diclofenac may dampen or delay the effect of GHB upon a patient during concomitant administration. In one embodiment, it may be useful to increase the amount of GHB that is administered to the patient. For example, GHB may be increased at least 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% of the normal dose of GHB. For example, if the normal dose is 10 g/day, then a dose that is adjusted to increase the normal dose by 15% is 11.5 g/day. The GHB dose increase may be taken for one or multiple GHB dosings. For example, GHB may be administered in two doses per night for narcolepsy. Either, or both, of the multiple doses may be increased to present a safer administration profile. For example, the first dose may be increased by the numbers referred to above or the second may be increased by the same percentages, or both. Furthermore, the absolute amount of GHB per dose or per day may be increased at least 0.5 g, 1 g, 1.5 g, 2.0 g, 2.5 g, 3.0 g, 3.5 g, or 4 g. An exemplary decrease in an adult dose would be to increase the minimum dose to 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5 g/day and so on. An increase in the maximum dose would be at least 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14 g/day and so on.

In another aspect, a package or kit is provided comprising GHB, optionally in a container, and a package insert, package label, instructions or other labelling including any one, two, three or more of the following information or recommendations: (a) use of diclofenac or valproate should be avoided or discontinued, (b) concomitant administration of GHB with drugs that are MCT inhibitors, such as diclofenac or valproate can alter the therapeutic effect or adverse reaction profile of GHB, (c) concomitant administration of GHB and valproate resulted in an increase in exposure to GHB, (d) concomitant administration of GHB and diclofenac resulted in a decrease in exposure to GHB, and/or (e) MCT inhibitors should be used with caution in patients receiving GHB due to the potential for increased GHB clearance.

Alternatively, diclofenac can be administered to counteract the effects of GHB toxicity using a reverse of the numerical relationships above. Similarly, valproate can be used to increase the effects of GHB in patients that cannot take higher amounts of GHB. In this regard, the present invention includes methods for reducing the effects of GHB toxicity in a patient in need thereof, comprising administering to said patient an effective amount of diclofenac such that potential toxic effects of GHB are reduced. The present invention also includes methods for potentiating the beneficial effects of GHB in a patient in need thereof comprising concomitantly administering to said patient an effective amount of valproate such that the beneficial effects of GHB are increased.

The examples below, which show drug interaction studies in healthy adults, demonstrated those instances, test conditions or metrics which showed a distinction between GHB and either of the test compounds, diclofenac, valproate, or ibuprofen. Additionally, drug interaction studies in healthy adults demonstrated pharmacokinetic or clinically significant pharmacodynamic interactions between GHB and diclofenac or valproate.

Example 1

This study was designed to compare Pharmacokinetic (PK) and Pharmacodynamic (PD) endpoints of Xyrem® sodium oxysorbate (GHB) with and without concomitant administration of diclofenac. A crossover design was employed to allow within-subject comparisons of the PK and PD of Xyrem® dosed alone and in combination with diclofenac. The PK and PD effects of Xyrem® upon those of diclofenac were also studied.

The PD parameters included a selection of automated tests of attention, information processing, working memory and skilled coordination from the CDR System. (Rapeport et al, 1996ab; Williams et al, 1996). (Wesnes et al, 1997). (Wesnes et al, 2000) (Modi et al, 2007).

Methods

This was a Phase 1, randomized, double-blind, placebo-controlled, three-period, crossover study in healthy subjects. 24 subjects were recruited to ensure that 18 completed the study. Following Screening and Baseline procedures, eligible subjects were entered into the study and received one of the following treatments per period, in randomized order:

Diclofenac placebo administered as one capsule qid (doses separated by 4 hours during the day, eg, approximately 8 am, 12 pm, 4 pm, and 8 pm) for 2 days before concomitant administration day. On concomitant adminis-

tration day, one diclofenac placebo capsule administered at −1 h and 3 h, and 3 g of Xyrem® administered at 0 h and 4 h.

Diclofenac administered as 50 mg immediate-release (IR) tablet (overencapsulated) qid (doses separated by 4 hours during the day, eg, approximately 8 am, 12 pm, 4 pm, and 8 pm) for 2 days before concomitant administration day. On concomitant administration day, 50 mg diclofenac administered at −1 h and 3 h and 3 g of Xyrem® administered at 0 h and 4 h.

Diclofenac administered as 50 mg IR tablet (overencapsulated) qid (doses separated by 4 hours during the day, eg, approximately 8 am, 12 pm, 4 pm, and 8 pm) for 2 days before concomitant administration day. On concomitant administration day, 50 mg diclofenac administered at −1 h and 3 h and Xyrem® placebo (volume equivalent to 3 g of Xyrem® oral solution) administered at 0 h and 4 h.

Subjects were randomized to one of the above treatments on Day 1, crossed over to another treatment on Day 6, and crossed over again to the remaining treatment on Day 11 (Table 1). Subjects were dosed in groups of up to 12. A 2-day washout period followed each of the treatment periods. The treatments were as follows: A=Diclofenac placebo (qid 4 h apart on the 1st and 2nd day and 2 doses on the 3rd day of the period)+Xyrem® two 3 g doses 4 h apart on the 3rd day of the period. B=Diclofenac (50 mg qid 4 h apart on the 1st and 2nd day and 2 doses on the 3rd day of the period)+Xyrem® two 3 g doses 4 h apart on the 3rd day of the period. C=Diclofenac (50 mg qid 4 h apart on the 1st and 2nd day and 2 doses on the 3rd day of the period)+Xyrem® placebo two doses 4 h apart on the 3rd day of the period. PD parameters include the following: Cognitive Drug Research (CDR) System tasks: Karolinska Sleepiness Scale (KSS), Simple Reaction Time (SRT), Digit Vigilance (DV), Choice Reaction Time (CRT), Tracking and Numeric Working Memory (NWM).

Results

Power of attention-On this measure of focussed attention and information processing Xyrem® when co-dosed with diclofenac produced significantly less impairment than Xyrem® alone at 0.5 h; while the smaller impairments with the combination narrowly missed significance at 1 and 4.5 h. Xyrem® when co-dosed with diclofenac also resulted in impairments at two timepoints compared to diclofenac alone which at 6.5 h was significant and a trend at 8 h. See FIG. **1** which shows Change from Baseline Figure (LSmean with 95% CI) for Power of Attention (ms) (PD Completer Population).

Digit Vigilance Accuracy-On this measure of focussed attention Xyrem® when co-dosed with diclofenac produced significantly less impairment than Xyrem® alone at 1 and 2.5 h. See FIG. **2** which shows Change from Baseline Figure (LSmean with 95% CI) for Digit Vigilance Accuracy (%) (PD Completer Population).

Digit Vigilance Mean Reaction Time-On this measure of focussed attention Xyrem® when co-dosed with diclofenac produced significantly less impairment than Xyrem® alone at 1 and 2.5 h. See FIG. **3** which shows Change from Baseline Figure (LSmean with 95% CI) for Digit Vigilance Mean Reaction Time (ms) (PD Completer Population).

Choice Reaction Time Mean-Impairments to this measure of attention and information processing were significantly smaller than with Xyrem® alone when co-dosed with diclofenac during the hour following the first dose of Xyrem®. See FIG. **4** which shows Change from Baseline Figure (LSmean with 95% CI) for Choice Reaction Time Mean (ms) (PD Completer Population).

While diclofenac alone had no effect on sleepiness or cognitive function, when co-dosed with Xyrem® it significantly reduced the effects of the compound on Power of Attention and two of the contributing scores, simple and choice reaction time; these effects being seen during the hour after the first dose of Xyrem®. On the other hand, there was no evidence on any measure of greater cognitive impairment or sleepiness when the two compounds were co-dosed.

The extent of the reductions in the impairments to the ability to focus attention and efficiently process information were quite notable, and likely to be of clinical relevance. It is interesting that protective effect of diclofenac was not seen on the subjects ratings of alertness, such a dissociation having been seen previously with haloperidol in healthy elderly volunteers (Beuzan et al, 1991).

In conclusion, evidence of an interaction was seen in this study over the hour following the first dose of Xyrem® on the study days, the impairments being notably smaller when diclofenac was co-dosed with Xyrem®. There was no interaction however on the feelings of sleepiness in the subjects.

Example 2

This study is designed to compare the pharmacokinetic (PK) and pharmacodynamic (PD) endpoints of Xyrem® with and without co-administration of divalproex sodium extended-release tablets. The crossover design allows within-subject comparisons of the PK and PD of Xyrem® dosed alone and in combination with divalproex sodium extended-release tablets. PD parameters include the following: Cognitive Drug Research (CDR) System tasks: Karolinska Sleepiness Scale (KSS), Simple Reaction Time (SRT), Digit Vigilance (DV), Choice Reaction Time (CRT), Tracking and Numeric Working Memory (NWM).

The objectives of this study were to evaluate the PK and PD of Xyrem® co-administered with divalproex sodium extended-release tablets and to evaluate and compare the safety and tolerability of Xyrem® with and without co-administration of divalproex sodium extended-release tablets.

This was a Phase 1, randomized, double-blind, placebo-controlled, five-period, crossover study in healthy male subjects. The study was conducted in approximately 24 healthy subjects to ensure completion of 16 subjects. Following Screening and Baseline procedures, eligible subjects were randomized to receive Xyrem® and Xyrem® placebo in a crossover fashion in Periods 1 and 2; were dosed with divalproex sodium extended-release tablets for 10 consecutive days in Period 3; and while continuing to take divalproex sodium extended-release tablets, were randomized to receive Xyrem® and Xyrem® placebo in a crossover fashion in Periods 4 and 5 (Table 1).

Periods 1 and 2:

Subjects were randomized to receive two 3 g doses of Xyrem® or Xyrem® placebo 4 hours apart in a crossover fashion at approximately 9 AM (first dose) and 1 PM (second dose) on Days 1 and 3. PK and PD parameters were evaluated during the 24 hours postdose.

Blood samples (4 mL) for sodium oxybate concentrations were collected at predose and at specified time-points up to 12 hours after the first dose of Xyrem® or Xyrem® placebo on Days 1 and 3. A PD Battery including the Karolinska Sleepiness Scale, Simple Reaction Time task, Digit Vigilance task, Choice Reaction Time task, Tracking task, and Numeric Working Memory task was administered at planned timepoints up to X hours after first dose (X hours after second dose), and safety were monitored at specified timepoints on Days 1 and 3 as well as throughout the periods.

Period 3:

All subjects received divalproex sodium extended-release tablets 1250 mg at approximately 8 AM on Days 5 through 14. Blood samples (4 mL) for valproic acid concentrations were collected before the divalproex sodium dose (to determine trough concentration for assessment of steady state) on Days 13 and 14. Safety was monitored at specified timepoints as well as throughout the period.

Periods 4 and 5:

Subjects continued taking 1250 mg divalproex sodium extended-release tablets at approximately 8 AM on Days 15 through 18. Subjects were also randomized to receive two 3 g doses of Xyrem® or Xyrem® placebo in a crossover fashion at approximately 9 am (first dose) and 1 pm (second dose) on Days 15 and 18. The first dose of Xyrem® or Xyrem® placebo was taken approximately 1 hour after dosing with divalproex sodium extended-release tablets, and the second dose of Xyrem® or Xyrem® placebo was taken 4 hours after the first Xyrem®/Xyrem® placebo dose.

Blood samples (4 mL) to measure plasma sodium oxybate concentrations were collected at pre Xyrem®/Xyrem® placebo dose and at specified timepoints after the first Xyrem® or Xyrem® placebo dose on Days 15 and 18. Blood samples (4 mL) to measure plasma valproic acid concentrations were collected pre divalproex sodium dose and at specified timepoints after the dose of divalproex sodium extended-release tablets on Day 15 and 18.

The PD battery was administered on Day 15 and 18, and safety was monitored at specified times on Days 15 and 18 as well as throughout the periods.

The treatments were as follows: A=Xyrem®, two 3 g doses, 4 hours apart at approximately 9 AM (1^{st} dose) and 1 PM (2^{nd} dose); B=Xyrem® placebo, two doses, 4 hours apart; and C=Divalproex sodium 1250 mg, once a day at approximately 8 AM.

Results

The results below show the tests in which GHB administration was affected by concomitant administration of any of three MCT inhibitors, such as valproate, diclofenac, and ibuprofen.

Continuity of Attention

Xyrem® and divalproex sodium together (A+C) when compared to Xyrem® alone (A) showed a slightly delayed recovery for the combination at 4 hours and 8 hours. See FIG. **5** which shows Change from Baseline Figure (LSmean with 95% CI) for Continuity of Attention (#) (PD Population).

Simple Reaction Time Mean

At 1 hour and 4 hours, Xyrem® and divalproex sodium together produced statistically reliably greater impairments than Xyrem® alone. See FIG. **6**, which shows Change from Baseline Figure (LSmean with 95% CI) for Simple Reaction Time Mean (ms) (PD Population).

Digit Vigilance Accuracy

At 2.5 and 4 hours Xyrem® and divalproex sodium together were statistically reliably different greater impairment to Xyrem® alone. See FIG. **7**, which shows Change from Baseline Figure (LSmean with 95% CI) for Digit Vigilance Accuracy (%) (PD Population).

Tracking Distance from Target

Xyrem® and divalproex sodium together (A+C) when compared to Xyrem® alone (A) showed a statistically significant difference by a slightly delayed recovery for the combination at 4 and 8 hours. See FIG. **8** which shows the Change from Baseline Figure (LSmean with 95% CI) for Tracking Distance from Target (mm) (PD Population).

Numeric Working Memory Sensitivity Index

Xyrem® and divalproex sodium together (A+C) when compared to Xyrem® alone (A) showed a difference at 4.5 through 8 hours. See FIG. **9**, which shows the Change from Baseline Figure (LSmean with 95% CI) for Numeric Working Memory Sensitivity Index (#) (PD Population).

Numeric Working Memory Mean Reaction Time

Xyrem® and divalproex sodium together (A+C) when compared to Xyrem® alone (A) showed statistically significant differences at 2.5, 5 and 8 hours when the combination produced greater impairment. See FIG. **10**, which shows the Change from Baseline Figure (LSmean with 95% CI) for Numeric Working Memory Mean Reaction Time (ms) (PD Population).

In addition, it was observed that renal excretion of GHB increase 30% upon co-administration of Valproate.

We also found pk changes which were consistent with the inhibition of GHB dehydrogenase. This effect will increase the exposure of GHB to the subject and increase Cmax and AUC about 15%.

The combination of Xyrem® dosed with divalproex sodium was compared to divalproex sodium alone, more consistent statistically significant impairments over time were seen with the combination, than when Xyrem® was compared to its placebo, indicating that the effects of co-administration, when they appeared, were in the direction of increased impairments.

As has been seen previously, Xyrem® induces sleepiness and produces impairments to attention, working memory and performance on a tracking task in healthy volunteers. Divalproex sodium alone showed no consistent or notable effects on cognitive function or sleepiness. There were occasions when co-administration of Xyrem® and divalproex sodium produced greater deficits than Xyrem® alone. Further the combination also produced more consistent impairments when compared with divalproex sodium alone, than did Xyrem® when compared to its placebo. Thus this study has found evidence that co-administration of Xyrem® and divalproex produces greater impairments to cognitive function and sleepiness than were seen with Xyrem® alone.

Example 3

The effects of Ibuprofen were evaluated when combined with Xyrem® in a manner similar to the above. No differences were seen using the metrics above for Karolinska Sleepiness Scale (KSS), and the following CDR System tasks: Simple Reaction Time, Digit Vigilance, Choice Reaction Time, Tracking and Numeric Working Memory. However, it was observed that renal excretion of Xyrem® doubled upon concomitant administration of Ibuprofen and Xyrem®.

All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those skilled in the art in light of the teachings of the specification that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

What is claimed is:

1. A method for the treatment of cataplexy in narcolepsy or excessive daytime sleepiness in narcolepsy in a patient who is currently taking gamma-hydroxybutyrate (GHB) or a salt thereof comprising: administering to the patient a dose of divalproex sodium concomitant to a dose of GHB or salt

thereof; and reducing the daily dosage amount of GHB or salt thereof administered to the patient between about 5% and about 50% wherein the daily dosage amount of GHB or salt thereof in the absence of concomitant administration of divalproex sodium is between 4.5 g to 9 g.

2. The method of claim **1** further comprising monitoring patient response and adjusting the GHB dose to maintain the effect of the GHB.

3. The method of claim **1** wherein the daily dosage amount of GHB or salt thereof in the absence of concomitant administration of divalproex sodium is 4.5 g.

4. The method of claim **1** wherein the daily dosage amount of GHB or salt thereof in the absence of concomitant administration of divalproex sodium is 6 g.

5. The method of claim **1** wherein the daily dosage amount of GHB or salt thereof in the absence of concomitant administration of divalproex sodium is 7.5 g.

6. The method of claim **1** wherein the daily dosage amount of GHB or salt thereof in the absence of concomitant administration of divalproex sodium is 9 g.

7. The method of claim **1** wherein the daily dosage amount of GHB or salt thereof administered to the patient is reduced between about 15% and about 50%.

8. The method of claim **1** wherein the daily dosage amount of GHB or salt thereof administered to the patient is reduced by between about 20% and about 50%.

9. A method for the treatment of cataplexy in narcolepsy or excessive daytime sleepiness in narcolepsy in a patient who is currently taking gamma-hydroxybutyrate (GHB) or a salt thereof comprising: reducing the daily dosage amount of GHB or salt thereof administered to the patient between about 5% and about 50% during concomitant administration of divalproex sodium, compared to the daily dosage amount of between 4.5 g and 9 g of GHB or salt thereof currently used in the absence of concomitant administration of divalproex sodium.

10. The method of claim **9**, wherein the daily dosage amount of GHB or salt thereof administered to the patient is reduced by between about 15% and about 50% compared to the manufacturer's recommended daily dosage amount of GHB or salt thereof.

11. The method of claim **9** further comprising monitoring patient response and adjusting the GHB dose to maintain the effect of the GHB.

12. The method of claim **9** wherein the daily dosage amount of GHB or salt thereof in the absence of concomitant administration of divalproex sodium is 4.5 g.

13. The method of claim **12** wherein the daily dosage amount of GHB or salt thereof administered to the patient is reduced by between about 15% and about 50%.

14. The method of claim **13** wherein the daily dosage amount of GHB or salt thereof administered to the patient is reduced at least 20%.

15. A method for the treatment of cataplexy in narcolepsy or excessive daytime sleepiness in narcolepsy in a patient who is currently taking divalproex sodium comprising: administering to the patient a starting daily dosage amount of gamma-hydroxybutyrate (GHB) or a salt thereof that is between about 15% and about 25% lower than a manufacturer's recommended starting daily dosage amount of between 4.5 g and 9 g in the absence of concomitant administration of divalproex sodium.

16. The method of claim **15** wherein the starting daily dosage amount of GHB or salt thereof administered to the patient is lower than 4.5 g.

17. The method of claim **16** wherein the starting daily dosage amount of GHB or salt thereof administered to the patient is divided into two equal doses.

18. The method of claim **17** wherein the first or second dose of the two equal doses of GHB or salt thereof administered to the patient is lower than 2.25 g.

19. The method of claim **15** wherein the starting daily dosage amount of GHB or a salt thereof is reduced by between about 20% and about 25%.

20. The method of claim **15** further comprising monitoring patient response and adjusting the GHB dose to treat the patient.

21. The method of claim **15** wherein the manufacturer's recommended starting daily dosage amount of GHB or salt thereof in the absence of concomitant administration of divalproex sodium is 4.5 g.

22. A method for the treatment of cataplexy in narcolepsy or excessive daytime sleepiness in narcolepsy in a patient who is currently taking divalproex sodium comprising: administering to the patient a starting daily dosage amount of gamma-hydroxybutyrate (GHB) or a salt thereof that is between about 15% and about 30% lower than the starting daily dosage amount of between 4.5 g and 9 g GHB that would otherwise have been recommended to the patient if the patient was not currently taking divalproex sodium.

23. The method of claim **22** wherein the starting daily dosage amount of GHB or salt thereof administered to the patient who is currently taking divalproex sodium is lower than 4.5 g.

24. The method of claim **23** wherein the starting daily dosage amount of GHB or salt thereof administered to the patient who is currently taking divalproex sodium is divided into two equal doses.

25. The method of claim **24** wherein the first or second dose of the two equal doses of GHB or salt thereof administered to the patient is lower than 2.25 g.

26. The method of claim **22** further comprising monitoring patient response and adjusting the GHB dose to treat the patient.

27. The method of claim **22** wherein the starting daily dosage amount of GHB or a salt thereof is reduced by between about 20% and about 30%.

28. A method for the treatment of cataplexy in narcolepsy or excessive daytime sleepiness in narcolepsy in a patient who is currently taking divalproex sodium comprising the steps of: administering to the patient a daily dosage amount of gamma-hydroxybutyrate (GHB) or a salt thereof that is between about 15% and about 30% lower than 4.5 g.

29. The method of claim **28** wherein the daily dosage amount of GHB or salt thereof administered to the patient is divided into two equal doses.

30. The method of claim **29** wherein the first dose of the two equal doses of GHB or salt thereof administered to the patient is lower than 2.25 g.

31. The method of claim **29** wherein the second dose of the two equal doses of GHB or salt thereof administered to the patient is lower than 2.25 g.

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