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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC. and BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG,

Plaintiffs,

v.

LUPIN ATLANTIS HOLDINGS SA and LUPIN LIMITED,

Defendants.

Civil Action No. _____

(Filed Electronically)

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs Boehringer Ingelheim Pharmaceuticals, Inc. and Boehringer Ingelheim Pharma GmbH & Co. KG (collectively, "Plaintiffs" or "Boehringer Ingelheim"), by their undersigned attorneys, bring this action against Lupin Atlantis Holdings SA and Lupin Limited (collectively, "Defendants" or "Lupin"), and hereby allege as follows:

NATURE OF THE ACTION

1. This action for patent infringement, brought pursuant to the patent laws of the United States, 35 U.S.C. § 1, *et seq*., and in particular under 35 U.S.C §§ 271 (a–c, e–g), arises from Lupin's submission of Abbreviated New Drug Application ("ANDA") No. 211287 to the United States Food and Drug Administration ("FDA"). Through this ANDA, Lupin seeks approval to market a generic version of the pharmaceutical product SPIRIVA® HandiHaler®, prior to the expiration of United States Patent Nos. 6,777,423, 6,908,928, 7,309,707, and 7,642,268 (the "patents-in-suit"). Plaintiffs seek injunctive relief precluding infringement, attorneys' fees, and any other relief the Court deems just and proper.

2. This is also an action under 28 U.S.C. §§ 2201–02 for a declaratory judgment of patent infringement arising under the patent laws of the United States, 35 U.S.C. §§ 1, *et seq*., and in particular under 35 U.S.C. § 271.

THE PARTIES

3. Plaintiff Boehringer Ingelheim Pharmaceuticals, Inc. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 900 Ridgebury Road, Ridgefield, Connecticut 06877.

4. Plaintiff Boehringer Ingelheim Pharma GmbH & Co. KG is a corporation organized and existing under the laws of Germany, having a principal place of business at Binger Str. 173, 55216 Ingelheim, Germany.

5. On information and belief, defendant Lupin Atlantis Holdings SA is a corporation organized and existing under the laws of Switzerland, having its principal place of business at Landis & Gyr-Strasse 1, Zug, Switzerland 6300.

6. On information and belief, defendant Lupin Limited is a corporation organized and existing under the laws of India, having its principal place of business at Laxmi Towers, 'B' Wing, 5th Floor, Bandra Kurla Complex, Bandra (East), Mumbai, India 40051.

7. On information and belief, Lupin Atlantis Holdings SA is a wholly owned subsidiary of Lupin Limited.

8. On information and belief, Lupin Atlantis Holdings SA, in collaboration with Lupin Limited, prepared and submitted ANDA No. 211287 (the "Lupin ANDA") and continues to collaborate in seeking FDA approval of that application.

9. On information and belief, Lupin intends to commercially manufacture, market, offer for sale, and sell the product described in the Lupin ANDA (the "ANDA Product") throughout the United States, including in the State of New Jersey, in the event FDA approves the Lupin ANDA.

JURISDICTION AND VENUE

10. This civil action for patent infringement arises under the patent laws of the United States, including 35 U.S.C. § 271, and alleges infringement of United States Patent Nos. 6,777,423 ("the '423 patent"), 6,908,928 ("the '928 patent"), 7,309,707 ("the '707 patent"), and 7,642,268 ("the '268 patent"). This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338, and 2201–02.

11. This Court has jurisdiction over Lupin because the requirements of Federal Rule of Civil Procedure 4(k)(2) are met as (a) Plaintiffs' claims arise under federal law; (b) Lupin Atlantis Holdings SA and Lupin Limited are foreign defendants not subject to general personal jurisdiction in the courts of any state; and (c) Lupin Atlantis Holdings SA and Lupin Limited have sufficient contacts with the United States as a whole, including, but not limited to,

preparing and submitting ANDAs to FDA and/or manufacturing, importing, offering to sell, and/or selling pharmaceutical products that are distributed throughout the United States, such that this Court's exercise of jurisdiction over Lupin Atlantis Holdings SA and Lupin Limited satisfies due process.

12. On information and belief, this Court also has jurisdiction over Lupin because, *inter alia*, this action arises from actions of Lupin directed toward New Jersey and because Lupin has purposefully availed itself of the rights and benefits of New Jersey law by engaging in systematic and continuous contacts with New Jersey.

13. On information and belief, Lupin regularly and continuously transacts business within the State of New Jersey, including by selling pharmaceutical products in New Jersey, either on its own or through an affiliate. Upon information and belief, Lupin derives substantial revenue from the sale of those products in New Jersey and has availed itself of the privilege of conducting business within the State of New Jersey. Further, Lupin has committed, or aided, abetted, contributed to, and/or participated in the commission of, acts of patent infringement that will lead to foreseeable harm and injury to Plaintiffs, which manufactures SPIRIVA® HandiHaler® for sale and use throughout the United States, including this Judicial District.

14. On information and belief, Lupin Atlantis Holdings SA has submitted, caused to be submitted, or aided and abetted in the preparation or submission of the Lupin ANDA. On information and belief, in the event that FDA approves the Lupin ANDA, Lupin Atlantis Holdings SA, with the participation of Lupin Limited, intends to commercially manufacture, import, market, offer for sale, and sell the ANDA Product throughout the United States and in this Judicial District.

15. Lupin has previously been sued in this Judicial District without objecting on the basis of lack of personal jurisdiction and has availed itself of the rights, benefits, and privileges of New Jersey by asserting claims or counterclaims involving pharmaceutical drug patent disputes in this Judicial District, including in the following cases: *Boehringer Ingelheim Pharmaceuticals, Inc., et al. v. Lupin Atlantis Holdings SA, et al.*, Civil Action No. 18-12663; *Otsuka Pharmaceutical Co. Ltd. v. Lupin Limited, et al.*, Civil Action No. 14-7105; and *Taro Pharmaceuticals USA, Inc., et al. v. Lupin Limited, et al.*, Civil Action No. 18-4228.

16. At least because, on information and belief, Lupin is a foreign corporation, venue is proper in this Judicial District pursuant to 28 U.S.C. §§ 1391(c)(3) and 1400(b).

BOEHRINGER INGELHEIM'S APPROVED SPIRIVA® DRUG PRODUCT AND PATENTS-IN-SUIT

17. Boehringer Ingelheim makes and sells SPIRIVA® HandiHaler®, a product that is used as an anticholinergic indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), and for reducing COPD exacerbations. A true and correct copy of the prescribing label for SPIRIVA® HandiHaler® is attached as Exhibit A.

18. Boehringer Ingelheim Pharmaceuticals, Inc. is the holder of New Drug Application ("NDA") No. 021395 for SPIRIVA® HandiHaler® and the licensee of the patents-in-suit. FDA approved NDA No. 021395 for SPIRIVA® HandiHaler® in January 2004.

19. Boehringer Ingelheim Pharma GmbH & Co. KG owns the '423 patent, which is listed in the Approved Drug Products With Therapeutic Equivalence Evaluations (an FDA publication commonly known as the "Orange Book") for SPIRIVA® HandiHaler®.

20. The '423 patent is entitled "Crystalline Tiotropium Bromide Monohydrate, Processes for the Preparation Thereof, and Pharmaceutical Compositions," and was duly and

lawfully issued by the USPTO on August 17, 2004. A true and correct copy of the '423 patent is attached as Exhibit B.

21. Boehringer Ingelheim Pharma GmbH & Co. KG owns the '928 patent, which is listed in the Orange Book for SPIRIVA® HandiHaler®.

22. The '928 patent is entitled "Crystalline Tiotropium Bromide Monohydrate, Processes for the Preparation Thereof, and Pharmaceutical Compositions," and was duly and lawfully issued by the USPTO on June 21, 2005. A true and correct copy of the '928 patent is attached as Exhibit C.

23. Boehringer Ingelheim Pharma GmbH & Co. KG owns the '707 patent, which is listed in the Orange Book for SPIRIVA® HandiHaler®.

24. The '707 patent is entitled "Crystalline Micronisate, Process for the Manufacture Thereof and Use Thereof for the Preparation of a Medicament," and was duly and lawfully issued by the USPTO on December 18, 2007. A true and correct copy of the '707 patent is attached as Exhibit D.

25. Boehringer Ingelheim Pharma GmbH & Co. KG owns the '268 patent, which is listed in the Orange Book for SPIRIVA® HandiHaler®.

26. The '268 patent is entitled "Crystalline Micronisate, Process for the Manufacture Thereof and Use Thereof for the Preparation of a Medicament," and was duly and lawfully issued by the USPTO on January 5, 2010. A true and correct copy of the '268 patent is attached as Exhibit E.

LUPIN'S ANDA

27. On information and belief, Lupin has submitted or caused to be submitted ANDA No. 211287 to FDA under 21 U.S.C. § 355(j), in order to obtain approval to engage in the

commercial manufacture, use, or sale of tiotropium bromide inhalation powder, 18 mcg/capsule, as a purported generic version of SPIRIVA® HandiHaler®, prior to the expiration of the patents-in-suit.

28. On information and belief, on or about June 26, 2018, Lupin mailed Plaintiffs a letter regarding "Notification of Certification" of Invalidity, Unenforceability, and/or Non-Infringement for U.S. Patent Nos. 7,070,800 B2 and 7,694,676 B2. The letter represented that Lupin had submitted to FDA the Lupin ANDA and a purported Paragraph IV certification to obtain approval to engage in the commercial manufacture, use, or sale of the product described in the Lupin's ANDA before the expiration of the '800 and '676 patents, which are listed in the Orange Book for SPIRIVA® HandiHaler®.

29. Plaintiffs and Boehringer Ingelheim International GmbH filed a complaint for infringement of the '800 and '676 patents in this jurisdiction on August 10, 2018, which was assigned Civil Action No. 18-12663 (BRM)(TJB).

30. On information and belief, on or about October 16, 2018, Lupin mailed Plaintiffs a letter regarding "Notification and Certification of Invalidity, Unenforceability, and/or Non-Infringement for U.S. Patent Nos. 6,777,423 B2, 6,908,928 B2, 7,309,707 B2, and 7,642,268 B2" (the "Notice Letter"). The Notice Letter represented that Lupin had amended the Lupin ANDA to contain a Paragraph IV certification to obtain approval to engage in the commercial manufacture, use, or sale of the product described in the Lupin's ANDA before the expiration of the patents-in-suit, which are listed in the Orange Book for SPIRIVA® HandiHaler®. Hence, Lupin's purpose in submitting the Lupin ANDA is to manufacture and market the ANDA Product before the expiration of the patents-in-suit.

31. Lupin's Notice Letter stated that the Paragraph IV certification in the Lupin ANDA alleges that the '423 patent is invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of the ANDA Product.

32. Lupin's Notice Letter stated that the Paragraph IV certification in the Lupin ANDA alleges that the '928 patent is invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of the ANDA Product.

33. Lupin's Notice Letter stated that the Paragraph IV certification in the Lupin ANDA alleges that the '707 patent is invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of the ANDA Product.

34. Lupin's Notice Letter stated that the Paragraph IV certification in the Lupin ANDA alleges that the '268 patent is invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of the ANDA Product.

35. Lupin's Notice Letter contained a purported detailed statement of the factual and legal basis for its Paragraph IV certification ("Detailed Statement").

36. On information and belief, Lupin has participated in the preparation and submission of the Lupin ANDA, has provided material support to the preparation and submission of the Lupin ANDA, and intends to support the further prosecution of the Lupin ANDA.

37. On information and belief, if FDA approves the Lupin ANDA, Lupin will manufacture, offer for sale, or sell the ANDA Product within the United States, including within New Jersey, or will import the ANDA Product into the United States, including New Jersey.

38. Alternatively, on information and belief, if FDA approves the Lupin ANDA, Lupin will actively induce or contribute to the manufacture, use, offer for sale, or sale of the

ANDA Product within the United States, including within New Jersey, or will import the ANDA Product into the United States, including New Jersey.

39. This action is being filed on November 30, 2018, which is within forty-five days of Plaintiffs' receipt of the Notice Letter, pursuant to 21 U.S.C. § 355(j)(5)(B)(iii).

COUNT I
INFRINGEMENT OF THE '423 PATENT

40. Plaintiffs incorporate by reference paragraphs 1–39 as if fully set forth herein.

41. On information and belief, Lupin has submitted or caused the submission of the Lupin ANDA to FDA and continues to seek FDA approval of the Lupin ANDA.

42. Lupin has infringed the '423 patent under 35 U.S.C. § 271(e)(2)(A) by submitting the Lupin ANDA with a Paragraph IV certification and seeking FDA approval of the Lupin ANDA prior to the expiration of the '423 patent.

43. On information and belief, if the Lupin ANDA is approved, Lupin and its affiliates will make, offer for sale, sell, import, or otherwise distribute the ANDA Product in the United States, including in the State of New Jersey, thereby directly infringing the '423 patent.

44. Lupin's commercial manufacture, use, offer for sale, sale, or importation into the United States of the ANDA Product would actively induce and/or contribute to infringement of the '423 patent. Accordingly, unless enjoined by this Court, upon FDA approval of ANDA No. 211287, Lupin will make, use, offer to sell, or sell the ANDA Product within the United States, or will import the ANDA Product into the United States, and will thereby contribute to the infringement of and/or induce the infringement of one or more claims of the '423 patent.

45. Lupin had actual and constructive notice of the '423 patent prior to filing the Lupin ANDA and was aware that the filing of the Lupin ANDA with the request for FDA approval prior to the expiration of the '423 patent would constitute an act of infringement of the

’423 patent. Lupin had no reasonable basis for asserting that the commercial manufacture, use, offer for sale, or sale of the ANDA Product will not directly infringe, contribute to the infringement of, and/or induce the infringement of the ’423 patent.

46. In addition, Lupin filed the Lupin ANDA without adequate justification for asserting the ’423 patent to be invalid, unenforceable, and/or not infringed by the commercial manufacture, use, offer for sale, or sale of the ANDA Product. Lupin’s conduct in certifying invalidity, unenforceability, and/or non-infringement with respect to the ’423 patent thus renders this case “exceptional” under 35 U.S.C. § 285.

47. Plaintiffs will be irreparably harmed if Lupin is not enjoined from infringing and from actively inducing or contributing to the infringement of the ’423 patent. Plaintiffs do not have an adequate remedy at law, and considering the balance of hardships between Plaintiffs and Lupin, a remedy in equity is warranted. Further, the public interest would not be disserved by the entry of a permanent injunction.

COUNT II
INFRINGEMENT OF THE ’928 PATENT

48. Plaintiffs incorporate by reference paragraphs 1–47 as if fully set forth herein.

49. On information and belief, Lupin has submitted or caused the submission of the Lupin ANDA to FDA and continues to seek FDA approval of the Lupin ANDA.

50. Lupin has infringed the ’928 patent under 35 U.S.C. § 271(e)(2)(A) by submitting the Lupin ANDA with a Paragraph IV certification and seeking FDA approval of the Lupin ANDA prior to the expiration of the ’928 patent.

51. On information and belief, if the Lupin ANDA is approved, Lupin and its affiliates will make, offer for sale, sell, import, or otherwise distribute the ANDA Product in the United States, including in the State of New Jersey, thereby directly infringing the ’928 patent.

52. Lupin's commercial manufacture, use, offer for sale, sale, or importation into the United States of the ANDA Product would actively induce and/or contribute to infringement of the '928 patent. Accordingly, unless enjoined by this Court, upon FDA approval of ANDA No. 211287, Lupin will make, use, offer to sell, or sell the ANDA Product within the United States, or will import the ANDA Product into the United States, and will thereby contribute to the infringement of and/or induce the infringement of one or more claims of the '928 patent.

53. Lupin had actual and constructive notice of the '928 patent prior to filing the Lupin ANDA and was aware that the filing of the Lupin ANDA with the request for FDA approval prior to the expiration of the '928 patent would constitute an act of infringement of the '928 patent. Lupin had no reasonable basis for asserting that the commercial manufacture, use, offer for sale, or sale of the ANDA Product will not directly infringe, contribute to the infringement of, and/or induce the infringement of the '928 patent.

54. In addition, Lupin filed the Lupin ANDA without adequate justification for asserting the '928 patent to be invalid, unenforceable, and/or not infringed by the commercial manufacture, use, offer for sale, or sale of the ANDA Product. Lupin's conduct in certifying invalidity, unenforceability, and/or non-infringement with respect to the '928 patent renders this case "exceptional" under 35 U.S.C. § 285.

55. Plaintiffs will be irreparably harmed if Lupin is not enjoined from infringing and from actively inducing or contributing to the infringement of the '928 patent. Plaintiffs do not have an adequate remedy at law, and considering the balance of hardships between Plaintiffs and Lupin, a remedy in equity is warranted. Further, the public interest would not be disserved by the entry of a permanent injunction.

COUNT III
INFRINGEMENT OF THE ’707 PATENT

56. Plaintiffs incorporate by reference paragraphs 1–55 as if fully set forth herein.

57. On information and belief, Lupin has submitted or caused the submission of the Lupin ANDA to FDA and continues to seek FDA approval of the Lupin ANDA.

58. Lupin has infringed the ’707 patent under 35 U.S.C. § 271(e)(2)(A) by submitting the Lupin ANDA with a Paragraph IV certification and seeking FDA approval of the Lupin ANDA prior to the expiration of the ’707 patent.

59. On information and belief, if the Lupin ANDA is approved, Lupin and its affiliates will make, offer for sale, sell, import, or otherwise distribute the ANDA Product in the United States, including in the State of New Jersey, thereby directly infringing the ’707 patent.

60. Lupin’s commercial manufacture, use, offer for sale, sale, or importation into the United States of the ANDA Product would actively induce and/or contribute to infringement of the ’707 patent. Accordingly, unless enjoined by this Court, upon FDA approval of ANDA No. 211287, Lupin will make, use, offer to sell, or sell the ANDA Product within the United States, or will import the ANDA Product into the United States, and will thereby contribute to the infringement of and/or induce the infringement of one or more claims of the ’707 patent.

61. Lupin had actual and constructive notice of the ’707 patent prior to filing the Lupin ANDA and was aware that the filing of the Lupin ANDA with the request for FDA approval prior to the expiration of the ’707 patent would constitute an act of infringement of the ’707 patent. Lupin had no reasonable basis for asserting that the commercial manufacture, use, offer for sale, or sale of the ANDA Product will not directly infringe, contribute to the infringement of, and/or induce the infringement of the ’707 patent.

62. In addition, Lupin filed the Lupin ANDA without adequate justification for asserting the '707 patent to be invalid, unenforceable, and/or not infringed by the commercial manufacture, use, offer for sale, or sale of the ANDA Product. Lupin's conduct in certifying invalidity, unenforceability, and/or non-infringement with respect to the '707 patent thus renders this case "exceptional" under 35 U.S.C. § 285.

63. Plaintiffs will be irreparably harmed if Lupin is not enjoined from infringing and from actively inducing or contributing to the infringement of the '707 patent. Plaintiffs do not have an adequate remedy at law, and considering the balance of hardships between Plaintiffs and Lupin, a remedy in equity is warranted. Further, the public interest would not be disserved by the entry of a permanent injunction.

COUNT IV
INFRINGEMENT OF THE '268 PATENT

64. Plaintiffs incorporate by reference paragraphs 1–63 as if fully set forth herein.

65. On information and belief, Lupin has submitted or caused the submission of the Lupin ANDA to FDA and continues to seek FDA approval of the Lupin ANDA.

66. Lupin has infringed the '268 patent under 35 U.S.C. § 271(e)(2)(A) by submitting the Lupin ANDA with a Paragraph IV certification and seeking FDA approval of the Lupin ANDA prior to the expiration of the '268 patent.

67. On information and belief, if the Lupin ANDA is approved, Lupin and its affiliates will make, offer for sale, sell, import, or otherwise distribute the ANDA Product in the United States, including in the State of New Jersey, thereby directly infringing the '268 patent.

68. Lupin's commercial manufacture, use, offer for sale, sale, or importation into the United States of the ANDA Product would actively induce and/or contribute to infringement of the '268 patent. Accordingly, unless enjoined by this Court, upon FDA approval of ANDA No.

211287, Lupin will make, use, offer to sell, or sell the ANDA Product within the United States, or will import the ANDA Product into the United States, and will thereby contribute to the infringement of and/or induce the infringement of one or more claims of the ’268 patent.

69. Lupin had actual and constructive notice of the ’268 patent prior to filing the Lupin ANDA and was aware that the filing of the Lupin ANDA with the request for FDA approval prior to the expiration of the ’268 patent would constitute an act of infringement of the ’268 patent. Lupin had no reasonable basis for asserting that the commercial manufacture, use, offer for sale, or sale of the ANDA Product will not directly infringe, contribute to the infringement of, and/or induce the infringement of the ’268 patent.

70. In addition, Lupin filed the Lupin ANDA without adequate justification for asserting the ’268 patent to be invalid, unenforceable, and/or not infringed by the commercial manufacture, use, offer for sale, or sale of the ANDA Product. Lupin’s conduct in certifying invalidity, unenforceability, and/or non-infringement with respect to the ’268 patent renders this case “exceptional” under 35 U.S.C. § 285.

71. Plaintiffs will be irreparably harmed if Lupin is not enjoined from infringing and from actively inducing or contributing to the infringement of the ’268 patent. Plaintiffs do not have an adequate remedy at law, and considering the balance of hardships between Plaintiffs and Lupin, a remedy in equity is warranted. Further, the public interest would not be disserved by the entry of a permanent injunction.

COUNT V
DECLARATORY JUDGMENT OF INFRINGEMENT OF THE ’423 PATENT

72. Plaintiffs incorporate by reference paragraphs 1–71 as if fully set forth herein.

73. Plaintiffs’ claims also arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

74. On information and belief, if the Lupin ANDA is approved, the ANDA Product will be made, offered for sale, sold, or otherwise distributed in the United States, including in the State of New Jersey, by or through Lupin and its affiliates.

75. On information and belief, Lupin knows that health care professionals or patients will use the ANDA Product in accordance with the labeling sought by the Lupin ANDA and Lupin will therefore contribute to the infringement of and/or induce the infringement of one or more claims of the '423 patent under one or more of 35 U.S.C. §§ 271(a), (b), (c), (f), and (g).

76. On information and belief, Lupin's infringing activity, including the commercial manufacture, use, offer to sell, sale, or importation of the ANDA Product complained of herein will begin immediately after FDA approves the Lupin ANDA. Any such conduct before the '423 patent expires will contribute to the infringement of and/or induce the infringement of one or more claims of the '423 patent under one or more of 35 U.S.C. §§ 271(a), (b), (c), (f), and (g).

77. As a result of the foregoing facts, there is a real, substantial, and continuing justiciable controversy between Plaintiffs and Lupin concerning liability for the infringement of the '423 patent for which this Court may grant declaratory relief consistent with Article III of the United States Constitution.

78. Plaintiffs will be substantially and irreparably harmed by Lupin's infringing activities unless those activities are enjoined by this Court. Plaintiffs have no adequate remedy at law.

79. This case is exceptional, and Plaintiffs are entitled to an award of attorneys' fees under 35 U.S.C. § 285.

COUNT VI
DECLARATORY JUDGMENT OF INFRINGEMENT OF THE ’928 PATENT

80. Plaintiffs incorporate by reference paragraphs 1–79 as if fully set forth herein.

81. Plaintiffs’ claims also arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

82. On information and belief, if the Lupin ANDA is approved, the ANDA Product will be made, offered for sale, sold, or otherwise distributed in the United States, including in the State of New Jersey, by or through Lupin and its affiliates.

83. On information and belief, Lupin knows that health care professionals or patients will use the ANDA Product in accordance with the labeling sought by the Lupin ANDA and Lupin will therefore contribute to the infringement of and/or induce the infringement of one or more claims of the ’928 patent under one or more of 35 U.S.C. §§ 271(a), (b), (c), (f), and (g).

84. On information and belief, Lupin’s infringing activity, including the commercial manufacture, use, offer to sell, sale, or importation of the ANDA Product complained of herein will begin immediately after FDA approves the Lupin ANDA. Any such conduct before the ’928 patent expires will contribute to the infringement of and/or induce the infringement of one or more claims of the ’928 patent under one or more of 35 U.S.C. §§ 271(a), (b), (c), (f), and (g).

85. As a result of the foregoing facts, there is a real, substantial, and continuing justiciable controversy between Plaintiffs and Lupin concerning liability for the infringement of the ’928 patent for which this Court may grant declaratory relief consistent with Article III of the United States Constitution.

86. Plaintiffs will be substantially and irreparably harmed by Lupin’s infringing activities unless those activities are enjoined by this Court. Plaintiffs have no adequate remedy at law.

87. This case is exceptional, and Plaintiffs are entitled to an award of attorneys' fees under 35 U.S.C. § 285.

COUNT VII
DECLARATORY JUDGMENT OF INFRINGEMENT OF THE '707 PATENT

88. Plaintiffs incorporate by reference paragraphs 1–87 as if fully set forth herein.

89. Plaintiffs' claims also arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

90. On information and belief, if the Lupin ANDA is approved, the ANDA Product will be made, offered for sale, sold, or otherwise distributed in the United States, including in the State of New Jersey, by or through Lupin and its affiliates.

91. On information and belief, Lupin knows that health care professionals or patients will use the ANDA Product in accordance with the labeling sought by the Lupin ANDA and Lupin will therefore contribute to the infringement of and/or induce the infringement of one or more claims of the '707 patent under one or more of 35 U.S.C. §§ 271(a), (b), (c), (f), and (g).

92. On information and belief, Lupin's infringing activity, including the commercial manufacture, use, offer to sell, sale, or importation of the ANDA Product complained of herein will begin immediately after FDA approves the Lupin ANDA. Any such conduct before the '707 patent expires will contribute to the infringement of and/or induce the infringement of one or more claims of the '707 patent under one or more of 35 U.S.C. §§ 271(a), (b), (c), (f), and (g).

93. As a result of the foregoing facts, there is a real, substantial, and continuing justiciable controversy between Plaintiffs and Lupin concerning liability for the infringement of the '707 patent for which this Court may grant declaratory relief consistent with Article III of the United States Constitution.

94. Plaintiffs will be substantially and irreparably harmed by Lupin's infringing activities unless those activities are enjoined by this Court. Plaintiffs have no adequate remedy at law.

95. This case is exceptional, and Plaintiffs are entitled to an award of attorneys' fees under 35 U.S.C. § 285.

COUNT VIII
DECLARATORY JUDGMENT OF INFRINGEMENT OF THE '268 PATENT

96. Plaintiffs incorporate by reference paragraphs 1–95 as if fully set forth herein.

97. Plaintiffs' claims also arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

98. On information and belief, if the Lupin ANDA is approved, the ANDA Product will be made, offered for sale, sold, or otherwise distributed in the United States, including in the State of New Jersey, by or through Lupin and its affiliates.

99. On information and belief, Lupin knows that health care professionals or patients will use the ANDA Product in accordance with the labeling sought by the Lupin ANDA and Lupin will therefore contribute to the infringement of and/or induce the infringement of one or more claims of the '268 patent under one or more of 35 U.S.C. §§ 271(a), (b), (c), (f), and (g).

100. On information and belief, Lupin's infringing activity, including the commercial manufacture, use, offer to sell, sale, or importation of the ANDA Product complained of herein will begin immediately after FDA approves the Lupin ANDA. Any such conduct before the '268 patent expires will contribute to the infringement of and/or induce the infringement of one or more claims of the '268 patent under one or more of 35 U.S.C. §§ 271(a), (b), (c), (f), and (g).

101. As a result of the foregoing facts, there is a real, substantial, and continuing justiciable controversy between Plaintiffs and Lupin concerning liability for the infringement of

the ’268 patent for which this Court may grant declaratory relief consistent with Article III of the United States Constitution.

102. Plaintiffs will be substantially and irreparably harmed by Lupin’s infringing activities unless those activities are enjoined by this Court. Plaintiffs have no adequate remedy at law.

103. This case is exceptional, and Plaintiffs are entitled to an award of attorneys’ fees under 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request the following relief:

A. A Judgment that Lupin infringes one or more claims of the ’423, ’928, ’707, and ’268 patents under 35 U.S.C. § 271(e)(2)(A);

B. A Declaratory Judgment that under one or more of 35 U.S.C. §§ 271(a), (b), (c), (f) and (g), Lupin’s commercial manufacture, use, offer for sale, or sale in, or importation into, the United States of the ANDA Product, or inducing or contributing to such conduct, would constitute infringement of one or more claims of the ’423, ’928, ’707, and ’268 patents;

C. A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Lupin, its affiliates and subsidiaries, and all persons and entities acting in concert with Lupin from commercially manufacturing, using, offering for sale, or selling or importing any product that infringes any of the ’423, ’928, ’707, and ’268 patents, including the ANDA Product described in ANDA No. 211287;

D. The entry of an Order, pursuant to 35 U.S.C. § 271(e)(4)(A), that the effective date of any FDA approval of ANDA No. 211287 shall be no earlier than the expiration date of

the ’423, ’928, ’707, and ’268 patents, or any later expiration of exclusivity for the ’423, ’928, ’707, and ’268 patents, including any extensions or regulatory exclusivities;

E. A Declaration under 28 U.S.C. § 2201 that if Lupin, its officers, agents, servants, employees, licensees, representatives, and attorneys, and any other persons acting or attempting to act in active concert or participation with them or acting on their behalf, engages in the commercial manufacture, use, offer for sale, sale, and/or importation of the product described in ANDA No. 211287, it will constitute an act of direct and/or indirect infringement of the ’423, ’928, ’707, and ’268 patents;

F. An award of damages or other relief, pursuant to 35 U.S.C. § 271(e)(4)(C), if Lupin engages in the commercial manufacture, use, offer for sale, sale, and/or importation of the ANDA Product, or any product that infringes one or more of the ’423, ’928, ’707, and ’268 patents, or induces or contributes to such conduct, prior to the expiration of the ’423, ’928, ’707, and ’268 patents, or any later expiration of exclusivity for the ’423, ’928, ’707, and ’268 patents, including any extensions or regulatory exclusivities;

G. The entry of Judgment declaring that Lupin’s acts render this case an exceptional case, and awarding Plaintiffs their attorneys’ fees pursuant to 35 U.S.C. §§ 271(e)(4) and 285;

H. An award to Plaintiffs of their costs and expenses in this action; and

I. Such other and further relief as the Court may deem just and proper.

Dated: November 30, 2018

By: s/ Charles M. Lizza

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CERTIFICATION PURSUANT TO LOCAL CIVIL RULES 11.2 & 40.1

I hereby certify that the matter captioned *Boehringer Ingelheim Pharmaceuticals, Inc., et al. v. Lupin Atlantis Holdings SA, et al.*, Civil Action No. 18-12663 (BRM)(TJB) is related to the matter in controversy because the matter in controversy involves two of the same plaintiffs and the same defendants seeking FDA approval to market a generic version of the same pharmaceutical product.

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

Dated: November 30, 2018

By: s/ Charles M. Lizza
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EXHIBIT A

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SPIRIVA HANDIHALER safely and effectively. See full prescribing information for SPIRIVA HANDIHALER.

SPIRIVA® HANDIHALER® (tiotropium bromide inhalation powder), for oral inhalation use
Initial U.S. Approval: 2004

----------INDICATIONS AND USAGE----------
SPIRIVA HANDIHALER is an anticholinergic indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), and for reducing COPD exacerbations (1)

----------DOSAGE AND ADMINISTRATION----------
- **For oral inhalation only. DO NOT swallow SPIRIVA capsules. Only use SPIRIVA capsules with the HANDIHALER device** (2)
- Two inhalations of the powder contents of a single SPIRIVA capsule (18 mcg) once daily (2)

----------DOSAGE FORMS AND STRENGTHS----------
Inhalation powder: SPIRIVA capsules contain 18 mcg tiotropium powder for use with HANDIHALER device (3)

----------CONTRAINDICATIONS----------
Hypersensitivity to tiotropium, ipratropium, or any components of SPIRIVA capsules (4)

----------WARNINGS AND PRECAUTIONS----------
- Not for acute use: Not a rescue medication (5.1)
- Immediate hypersensitivity reactions: Discontinue SPIRIVA HANDIHALER at once and consider alternatives if immediate hypersensitivity reactions, including angioedema, urticaria, rash, bronchospasm, or anaphylaxis, occur. Use with caution in patients with severe hypersensitivity to milk proteins. (5.2)
- Paradoxical bronchospasm: Discontinue SPIRIVA HANDIHALER and consider other treatments if paradoxical bronchospasm occurs (5.3)
- Worsening of narrow-angle glaucoma may occur. Use with caution in patients with narrow-angle glaucoma and instruct patients to consult a physician immediately if this occurs. (5.4)
- Worsening of urinary retention may occur. Use with caution in patients with prostatic hyperplasia or bladder-neck obstruction and instruct patients to consult a physician immediately if this occurs. (5.5)

----------ADVERSE REACTIONS----------
The most common adverse reactions (>5% incidence in the 1-year placebo-controlled trials) were upper respiratory tract infection, dry mouth, sinusitis, pharyngitis, non-specific chest pain, urinary tract infection, dyspepsia, and rhinitis (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or (800) 459-9906 TTY, or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
Anticholinergics: May interact additively with concomitantly used anticholinergic medications. Avoid administration of SPIRIVA HANDIHALER with other anticholinergic-containing drugs. (7.2)

----------USE IN SPECIFIC POPULATIONS----------
Patients with moderate to severe renal impairment should be monitored closely for potential anticholinergic side effects (2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 2/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SPIRIVA HANDIHALER (tiotropium bromide inhalation powder) is indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. SPIRIVA HANDIHALER is indicated to reduce exacerbations in COPD patients.

2 DOSAGE AND ADMINISTRATION

For oral inhalation only. Do not swallow SPIRIVA capsules, as the intended effects on the lungs will not be obtained. The contents of the SPIRIVA capsules should only be used with the HANDIHALER device *[see Overdosage (10)]***.**

The recommended dose of SPIRIVA HANDIHALER is two inhalations of the powder contents of one SPIRIVA capsule, once-daily, with the HANDIHALER device *[see Patient Counseling Information (17)]*. Do not take more than one dose in 24 hours.

For administration of SPIRIVA HANDIHALER, a SPIRIVA capsule is placed into the center chamber of the HANDIHALER device. The SPIRIVA capsule is pierced by pressing and releasing the green piercing button on the side of the HANDIHALER device. The tiotropium formulation is dispersed into the air stream when the patient inhales through the mouthpiece *[see Patient Counseling Information (17)]*.

No dosage adjustment is required for geriatric, hepatically-impaired, or renally-impaired patients. However, patients with moderate to severe renal impairment given SPIRIVA HANDIHALER should be monitored closely for anticholinergic effects *[see Warnings and Precautions (5.6), Use in Specific Populations (8.5, 8.6, 8.7), and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Inhalation Powder: SPIRIVA HANDIHALER consists of SPIRIVA capsules containing tiotropium powder for oral inhalation and a HANDIHALER device. SPIRIVA capsules contain 18 mcg of tiotropium in a light green, hard gelatin capsule with TI 01 printed on one side and Boehringer Ingelheim company logo on the other side. The HANDIHALER device is only intended for use with the SPIRIVA capsules.

4 CONTRAINDICATIONS

SPIRIVA HANDIHALER is contraindicated in patients with a hypersensitivity to tiotropium, ipratropium, or any components of this product *[see Warnings and Precautions (5.2)]*. In clinical trials and postmarketing experience with SPIRIVA HANDIHALER, immediate hypersensitivity reactions, including angioedema (including swelling of the lips, tongue, or throat), itching, or rash have been reported *[see Warnings and Precautions (5.2)]***.**

5 WARNINGS AND PRECAUTIONS

5.1 Not for Acute Use

SPIRIVA HANDIHALER is intended as a once-daily maintenance treatment for COPD and should not be used for relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm.

5.2 Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions, including urticaria, angioedema (including swelling of the lips, tongue, or throat), rash, bronchospasm, anaphylaxis, or itching, may occur after administration of SPIRIVA HANDIHALER. If such a reaction occurs, therapy with SPIRIVA HANDIHALER should be stopped at once and alternative treatments should be considered. Given the similar structural formula of atropine to tiotropium, patients with a history of hypersensitivity reactions to atropine or its derivatives should be closely monitored for similar hypersensitivity reactions to SPIRIVA HANDIHALER. In addition, SPIRIVA HANDIHALER should be used with caution in patients with severe hypersensitivity to milk proteins.

5.3 Paradoxical Bronchospasm

Inhaled medicines, including SPIRIVA HANDIHALER, may cause paradoxical bronchospasm. If this occurs, it should be treated immediately with an inhaled short-acting beta$_2$-agonist such as albuterol. Treatment with SPIRIVA HANDIHALER should be stopped and other treatments considered.

5.4 Worsening of Narrow-Angle Glaucoma

SPIRIVA HANDIHALER should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

5.5 Worsening of Urinary Retention

SPIRIVA HANDIHALER should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

5.6 Renal Impairment

As a predominantly renally excreted drug, patients with moderate to severe renal impairment (creatinine clearance of <60 mL/min) treated with SPIRIVA HANDIHALER should be monitored closely for anticholinergic side effects *[see Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

The following adverse reactions are described, or described in greater detail, in other sections:

- Immediate hypersensitivity reactions *[see Warnings and Precautions (5.2)]*

- Paradoxical bronchospasm *[see Warnings and Precautions (5.3)]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.4)]*
- Worsening of urinary retention *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the incidence of adverse reactions observed in the clinical trials of a drug cannot be directly compared to the incidences in the clinical trials of another drug and may not reflect the incidences observed in practice.

6-Month to 1-Year Trials

The data described below reflect exposure to SPIRIVA HANDIHALER in 2663 patients. SPIRIVA HANDIHALER was studied in two 1-year placebo-controlled trials, two 1-year active-controlled trials, and two 6-month placebo-controlled trials in patients with COPD. In these trials, 1308 patients were treated with SPIRIVA HANDIHALER at the recommended dose of 18 mcg once a day. The population had an age ranging from 39 to 87 years with 65% to 85% males, 95% Caucasian, and had COPD with a mean pre-bronchodilator forced expiratory volume in one second (FEV_1) percent predicted of 39% to 43%. Patients with narrow-angle glaucoma, or symptomatic prostatic hypertrophy or bladder outlet obstruction were excluded from these trials. An additional 6-month trial conducted in a Veteran's Affairs setting is not included in this safety database because only serious adverse events were collected.

The most commonly reported adverse drug reaction was dry mouth. Dry mouth was usually mild and often resolved during continued treatment. Other reactions reported in individual patients and consistent with possible anticholinergic effects included constipation, tachycardia, blurred vision, glaucoma (new onset or worsening), dysuria, and urinary retention.

Four multicenter, 1-year, placebo-controlled and active-controlled trials evaluated SPIRIVA HANDIHALER in patients with COPD. Table 1 shows all adverse reactions that occurred with a frequency of ≥3% in the SPIRIVA HANDIHALER group in the 1-year placebo-controlled trials where the rates in the SPIRIVA HANDIHALER group exceeded placebo by ≥1%. The frequency of corresponding reactions in the ipratropium-controlled trials is included for comparison.

Table 1 Adverse Reactions (% Patients) in One-Year COPD Clinical Trials

Body System (Event)	**Placebo-Controlled Trials**		**Ipratropium-Controlled Trials**	
	SPIRIVA (n = 550)	**Placebo (n = 371)**	**SPIRIVA (n = 356)**	**Ipratropium (n = 179)**
Body as a Whole				
Chest Pain (non-specific)	7	5	5	2
Edema, Dependent	5	4	3	5
Gastrointestinal System Disorders				
Dry Mouth	16	3	12	6
Dyspepsia	6	5	1	1
Abdominal Pain	5	3	6	6
Constipation	4	2	1	1
Vomiting	4	2	1	2
Musculoskeletal System				
Myalgia	4	3	4	3
Resistance Mechanism Disorders				
Infection	4	3	1	3
Moniliasis	4	2	3	2
Respiratory System (Upper)				
Upper Respiratory Tract Infection	41	37	43	35
Sinusitis	11	9	3	2
Pharyngitis	9	7	7	3
Rhinitis	6	5	3	2
Epistaxis	4	2	1	1
Skin and Appendage Disorders				
Rash	4	2	2	2
Urinary System				
Urinary Tract Infection	7	5	4	2

Arthritis, coughing, and influenza-like symptoms occurred at a rate of ≥3% in the SPIRIVA HANDIHALER treatment group, but were <1% in excess of the placebo group.

Other reactions that occurred in the SPIRIVA HANDIHALER group at a frequency of 1% to 3% in the placebo-controlled trials where the rates exceeded that in the placebo group include: *Body as a Whole:* allergic reaction, leg pain; *Central and Peripheral Nervous System:* dysphonia, paresthesia; *Gastrointestinal System Disorders:* gastrointestinal disorder not otherwise specified (NOS), gastroesophageal reflux, stomatitis (including ulcerative stomatitis); *Metabolic and Nutritional Disorders:* hypercholesterolemia, hyperglycemia; *Musculoskeletal System Disorders:* skeletal pain; *Cardiac Events:* angina pectoris (including aggravated angina pectoris); *Psychiatric Disorder:* depression; *Infections:* herpes zoster; *Respiratory System Disorder (Upper):* laryngitis; *Vision Disorder:* cataract. In addition, among the adverse reactions observed in the clinical trials with an incidence of <1% were atrial fibrillation, supraventricular tachycardia, angioedema, and urinary retention.

In the 1-year trials, the incidence of dry mouth, constipation, and urinary tract infection increased with age *[see Use in Specific Populations (8.5)]*.

Two multicenter, 6-month, controlled studies evaluated SPIRIVA HANDIHALER in patients with COPD. The adverse reactions and the incidence rates were similar to those seen in the 1-year controlled trials.

4-Year Trial

The data described below reflect exposure to SPIRIVA HANDIHALER in 5992 COPD patients in a 4-year placebo-controlled trial. In this trial, 2986 patients were treated with SPIRIVA HANDIHALER at the recommended dose of 18 mcg once a day. The population had an age range from 40 to 88 years, was 75% male, 90% Caucasian, and had COPD with a mean pre-bronchodilator FEV_1 percent predicted of 40%. Patients with narrow-angle glaucoma, or symptomatic prostatic hypertrophy or bladder outlet obstruction were excluded from these trials. When the adverse reactions were analyzed with a frequency of ≥3% in the SPIRIVA HANDIHALER group where the rates in the SPIRIVA HANDIHALER group exceeded placebo by ≥1%, adverse reactions included (SPIRIVA HANDIHALER, placebo): pharyngitis (12.5%, 10.8%), sinusitis (6.5%, 5.3%), headache (5.7%, 4.5%), constipation (5.1%, 3.7%), dry mouth (5.1%, 2.7%), depression (4.4%, 3.3%), insomnia (4.4%, 3.0%), and arthralgia (4.2%, 3.1%).

Additional Adverse Reactions

Other adverse reactions not previously listed that were reported more frequently in COPD patients treated with SPIRIVA HANDIHALER than placebo include: dehydration, skin ulcer, stomatitis, gingivitis, oropharyngeal candidiasis, dry skin, skin infection, and joint swelling.

6.2 Postmarketing Experience

Adverse reactions have been identified during worldwide post-approval use of SPIRIVA HANDIHALER. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These adverse reactions are: application site irritation (glossitis, mouth ulceration, and pharyngolaryngeal pain), dizziness, dysphagia, hoarseness, intestinal obstruction including ileus paralytic, intraocular pressure increased, oral candidiasis, palpitations, pruritus, tachycardia, throat irritation, and urticaria.

7 DRUG INTERACTIONS

7.1 Sympathomimetics, Methylxanthines, Steroids

SPIRIVA HANDIHALER has been used concomitantly with short-acting and long-acting sympathomimetic (beta-agonists) bronchodilators, methylxanthines, and oral and inhaled steroids without increases in adverse reactions.

7.2 Anticholinergics

There is potential for an additive interaction with concomitantly used anticholinergic medications. Therefore, avoid coadministration of SPIRIVA HANDIHALER with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects *[see Warnings and Precautions (5.4, 5.5) and Adverse Reactions (6)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited human data with SPIRIVA HANDIHALER use during pregnancy are insufficient to inform a drug-associated risk of adverse pregnancy-related outcomes. Based on animal reproduction studies, no structural abnormalities were observed when tiotropium was administered by inhalation to pregnant rats and rabbits during the period of organogenesis at doses 790 and 8 times, respectively, the maximum recommended human daily inhalation dose (MRHDID). Increased post-implantation loss was observed in rats and rabbits administered tiotropium at maternally toxic doses 430 times and 40 times the MRHDID, respectively *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In 2 separate embryo-fetal development studies, pregnant rats and rabbits received tiotropium during the period of organogenesis at doses up to approximately 790 and 8 times the MRHDID, respectively (on a mcg/m^2 basis at inhalation doses of 1471 and 7 mcg/kg/day in rats and rabbits, respectively). No evidence of structural abnormalities was observed in rats or rabbits. However, in rats, tiotropium caused fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pup sexual maturation at tiotropium doses of approximately 40 times the MRHDID (on a mcg/m^2 basis at a maternal inhalation dose of 78 mcg/kg/day). In rabbits, tiotropium caused an increase in post-implantation loss at a tiotropium dose of approximately 430 times the MRHDID (on a mcg/m^2 basis at a maternal inhalation dose of 400 mcg/kg/day). Such effects were not observed at approximately 5 and 95 times the MRHDID, respectively (on a mcg/m^2 basis at inhalation doses of 9 and 88 mcg/kg/day in rats and rabbits, respectively).

8.2 Lactation

Risk Summary

There are no data on the presence of tiotropium in human milk, the effects on the breastfed infant, or the effects on milk production. Tiotropium is present in milk of lactating rats; however, due to species-specific differences in lactation physiology, the clinical relevance of these data are not clear *[see Data]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SPIRIVA HANDIHALER and any potential adverse effects on the breastfed child from SPIRIVA HANDIHALER or from the underlying maternal condition.

Data

The distribution of tiotropium bromide into milk was investigated after a single intravenous administration of 10 mg/kg to lactating rats. Tiotropium and/or its metabolites are present in the milk of lactating rats at concentrations above those in plasma.

8.4 Pediatric Use

SPIRIVA HANDIHALER is not indicated for use in children. The safety and effectiveness of SPIRIVA HANDIHALER in pediatric patients have not been established.

8.5 Geriatric Use

Based on available data, no adjustment of SPIRIVA HANDIHALER dosage in geriatric patients is warranted *[see Clinical Pharmacology (12.3)]*.

Of the total number of patients who received SPIRIVA HANDIHALER in the 1-year clinical trials, 426 were <65 years, 375 were 65 to 74 years, and 105 were ≥75 years of age. Within each age subgroup, there were no differences between the proportion of patients with adverse events in the SPIRIVA HANDIHALER and the comparator groups for most events. Dry mouth increased with age in the SPIRIVA HANDIHALER group (differences from placebo were 9.0%, 17.1%, and 16.2% in the aforementioned age subgroups). A higher frequency of constipation and urinary tract infections with increasing age was observed in the SPIRIVA HANDIHALER group in the placebo-controlled studies. The differences from placebo for constipation were 0%, 1.8%, and 7.8% for each of the age groups. The differences from placebo for urinary tract infections were –0.6%, 4.6%, and 4.5%. No overall differences in effectiveness were observed among these groups.

8.6 Renal Impairment

Patients with moderate to severe renal impairment (creatinine clearance of <60 mL/min) treated with SPIRIVA HANDIHALER should be monitored closely for anticholinergic side effects *[see Dosage and Administration (2), Warnings and Precautions (5.6), and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied.

10 OVERDOSAGE

High doses of tiotropium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 282 mcg tiotropium in 6 healthy volunteers. In a study of 12 healthy volunteers, bilateral conjunctivitis and dry mouth were seen following repeated once-daily inhalation of 141 mcg of tiotropium.

Treatment of overdosage consists of discontinuation of SPIRIVA HANDIHALER together with institution of appropriate symptomatic and/or supportive therapy.

Accidental Ingestion

Acute intoxication by inadvertent oral ingestion of SPIRIVA capsules is unlikely since it is not well-absorbed systemically.

A case of overdose has been reported from postmarketing experience. A female patient was reported to have inhaled 30 capsules over a 2.5 day period, and developed altered mental status, tremors, abdominal pain, and severe constipation. The patient was hospitalized, SPIRIVA HANDIHALER was discontinued, and the constipation was treated with an enema. The patient recovered and was discharged on the same day.

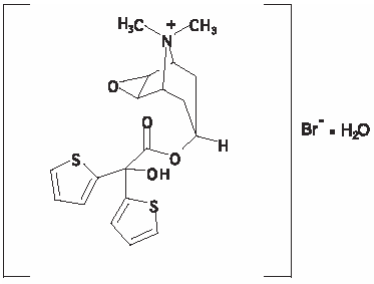
11 DESCRIPTION

SPIRIVA HANDIHALER consists of SPIRIVA capsules and a HANDIHALER device. Each light green, hard gelatin SPIRIVA capsule contains a dry powder consisting of 18 mcg tiotropium (equivalent to 22.5 mcg tiotropium bromide monohydrate) blended with lactose monohydrate (which may contain milk proteins).

The contents of SPIRIVA capsules are intended for oral inhalation only, and are intended for administration only with the HANDIHALER device.

The active component of SPIRIVA HANDIHALER is tiotropium. The drug substance, tiotropium bromide monohydrate, is an anticholinergic with specificity for muscarinic receptors. It is chemically described as (1α, 2β, 4β, 5α, 7β)-7-[(Hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane bromide monohydrate. It is a synthetic, non-chiral, quaternary ammonium compound. Tiotropium bromide is a white or yellowish white powder. It is sparingly soluble in water and soluble in methanol.

The structural formula is:



Tiotropium bromide (monohydrate) has a molecular mass of 490.4 and a molecular formula of $C_{19}H_{22}NO_4S_2Br \bullet H_2O$.

The HANDIHALER device is an inhalation device used to inhale the dry powder contained in the SPIRIVA capsule. The dry powder is delivered from the HANDIHALER device at flow rates as low as 20 L/min. Under standardized *in vitro* testing, the HANDIHALER device delivers a mean of 10.4 mcg tiotropium when tested at a flow rate of 39 L/min for 3.1 seconds (2 L total). In a study of 26 adult patients with COPD and severely compromised lung function [mean FEV_1 1.02 L (range 0.45 to 2.24 L); 37.6% of predicted (range 16% to 65%)], the median peak inspiratory flow (PIF) through the HANDIHALER device was 30.0 L/min (range 20.4 to 45.6 L/min). The amount of drug delivered to the lungs will vary depending on patient factors such as inspiratory flow and peak inspiratory flow through the HANDIHALER device, which may vary from patient to patient, and may vary with the exposure time of the SPIRIVA capsule outside the blister pack.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tiotropium is a long-acting, antimuscarinic agent, which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors, M_1 to M_5. In the airways, it exhibits pharmacological effects through inhibition of M_3-receptors at the smooth muscle leading to bronchodilation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In preclinical *in vitro* as well as *in vivo* studies, prevention of methacholine-induced bronchoconstriction effects was dose-dependent and lasted longer than 24 hours. The bronchodilation following inhalation of tiotropium is predominantly a site-specific effect.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In a multicenter, randomized, double-blind trial using tiotropium dry powder for inhalation that enrolled 198 patients with COPD, the number of subjects with changes from baseline-corrected QT interval of 30 to 60 msec was higher in the SPIRIVA HANDIHALER group as compared with placebo. This difference was apparent using both the Bazett (QTcB) [20 (20%) patients vs. 12 (12%) patients] and Fredericia (QTcF) [16 (16%) patients vs. 1 (1%) patient] corrections of QT for heart rate. No patients in either group had either QTcB or QTcF of >500 msec. Other clinical studies with SPIRIVA HANDIHALER did not detect an effect of the drug on QTc intervals.

The effect of tiotropium dry powder for inhalation on QT interval was also evaluated in a randomized, placebo- and positive-controlled crossover study in 53 healthy volunteers. Subjects received tiotropium dry powder for inhalation 18 mcg, 54 mcg (3 times the recommended dose), or placebo for 12 days. ECG assessments were performed at baseline and throughout the dosing interval following the first and last dose of study medication. Relative to placebo, the maximum mean change from baseline in study-specific QTc interval was 3.2 msec and 0.8 msec for tiotropium dry powder for inhalation 18 mcg and 54 mcg, respectively. No subject showed a new onset of QTc >500 msec or QTc changes from baseline of ≥60 msec.

12.3 Pharmacokinetics

Tiotropium is administered by dry powder inhalation. Some of the pharmacokinetic data described below were obtained with higher doses than recommended for therapy. A dedicated pharmacokinetic study in patients with COPD evaluating once-daily tiotropium delivered from the RESPIMAT inhaler (5 mcg) and as inhalation powder (18 mcg) from the HANDIHALER device resulted in a similar systemic exposure between the two products.

Absorption

Following dry powder inhalation by young healthy volunteers, the absolute bioavailability of 19.5% suggests that the fraction reaching the lung is highly bioavailable. Oral solutions of tiotropium have an absolute bioavailability of 2-3%. Food is not expected to influence the absorption of tiotropium. Maximum tiotropium plasma concentrations were observed 7 minutes after inhalation.

Distribution

Tiotropium is 72% bound to plasma protein and had a volume of distribution of 32 L/kg after intravenous administration to young healthy volunteers. Local concentrations in the lung are not known, but the mode of administration suggests substantially higher concentrations in the lung. Studies in rats have shown that tiotropium does not readily penetrate the blood-brain barrier.

Elimination

The terminal half-life of tiotropium in COPD patients following once daily inhalation of 5 mcg tiotropium was approximately 25 hours. Total clearance was 880 mL/min after intravenous administration in young healthy volunteers. After chronic once-daily dry powder inhalation by COPD patients, pharmacokinetic steady state was reached by day 7 with no accumulation thereafter.

Metabolism

The extent of metabolism is small. This is evident from a urinary excretion of 74% of unchanged substance after an intravenous dose to young healthy volunteers. Tiotropium, an ester, is nonenzymatically cleaved to the alcohol N-methylscopine and dithienylglycolic acid, neither of which binds to muscarinic receptors.

In vitro experiments with human liver microsomes and human hepatocytes suggest that a fraction of the administered dose (74% of an intravenous dose is excreted unchanged in the urine, leaving 25% for metabolism) is metabolized by cytochrome P450-dependent oxidation and subsequent glutathione conjugation to a variety of Phase II metabolites. This enzymatic pathway can be inhibited by CYP450 2D6 and 3A4 inhibitors, such as quinidine, ketoconazole, and gestodene. Thus, CYP450 2D6 and 3A4 are involved in the metabolic pathway that is responsible for the elimination of a small part of the administered dose. *In vitro* studies using human liver microsomes showed that tiotropium in supra-therapeutic concentrations did not inhibit CYP450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4.

Excretion

Intravenously administered tiotropium bromide is mainly excreted unchanged in urine (74%). After dry powder inhalation to COPD patients at steady state, urinary excretion was 7% (1.3mcg) of the unchanged dose over 24 hours. The renal clearance of tiotropium exceeds the creatinine clearance, indicating secretion into the urine.

Specific Populations

Geriatric Patients

As expected for all predominantly renally excreted drugs, advancing age was associated with a decrease of tiotropium renal clearance (365 mL/min in COPD patients <65 years to 271 mL/min in COPD patients ≥65 years). This did not result in a corresponding increase in $AUC_{0\text{-}6,ss}$ and $C_{max,ss}$ values following administration via HANDIHALER device.

Renal Impairment

Following 4-week SPIRIVA HANDIHALER or SPIRIVA RESPIMAT once daily dosing in patients with COPD, mild renal impairment (creatinine clearance 60-<90 mL/min) resulted in 6-23% higher $AUC_{0\text{-}6,ss}$ and 6-17% higher $C_{max,ss}$ values; moderate renal impairment (creatinine clearance 30-<60 mL/min) resulted in 54-57%

higher $AUC_{0-6,ss}$ and 15-31% higher $C_{max,ss}$ values compared to COPD patients with normal renal function (creatinine clearance ≥90 mL/min). There is insufficient data for tiotropium exposure in patients with severe renal impairment (creatinine clearance <30 mL/min) following inhalation of SPIRIVA HANDIHALER or SPIRIVA RESPIMAT. However AUC_{0-4} and C_{max} were 94% and 52% higher, respectively, in patients with severe renal impairment following intravenous infusion of tiotropium bromide.

Hepatic Impairment

The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied.

Drug Interactions

An interaction study with tiotropium (14.4 mcg intravenous infusion over 15 minutes) and cimetidine 400 mg three times daily or ranitidine 300 mg once daily was conducted. Concomitant administration of cimetidine with tiotropium resulted in a 20% increase in the AUC_{0-4h}, a 28% decrease in the renal clearance of tiotropium and no significant change in the C_{max} and amount excreted in urine over 96 hours. Co-administration of tiotropium with ranitidine did not affect the pharmacokinetics of tiotropium.

Common concomitant medications (long-acting $beta_2$-adrenergic agonists (LABA), inhaled corticosteroids (ICS)) used by patients with COPD were not found to alter the exposure to tiotropium.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of tumorigenicity was observed in a 104-week inhalation study in rats at tiotropium doses up to 59 mcg/kg/day, in an 83-week inhalation study in female mice at doses up to 145 mcg/kg/day, and in a 101-week inhalation study in male mice at doses up to 2 mcg/kg/day. These doses correspond to approximately 30, 40, and 0.5 times the recommended human daily inhalation dose (MRHDID) on a mcg/m^2 basis, respectively.

Tiotropium bromide demonstrated no evidence of mutagenicity or clastogenicity in the following assays: the bacterial gene mutation assay, the V79 Chinese hamster cell mutagenesis assay, the chromosomal aberration assays in human lymphocytes *in vitro* and mouse micronucleus formation *in vivo*, and the unscheduled DNA synthesis in primary rat hepatocytes *in vitro* assay.

In rats, decreases in the number of corpora lutea and the percentage of implants were noted at inhalation tiotropium doses of 78 mcg/kg/day or greater (approximately 40 times the MRHDID on a mcg/m^2 basis). No such effects were observed at 9 mcg/kg/day (approximately 5 times the MRHDID on a mcg/m^2 basis). The fertility index, however, was not affected at inhalation doses up to 1689 mcg/kg/day (approximately 910 times the MRHDID on a mcg/m^2 basis).

14 CLINICAL STUDIES

The SPIRIVA HANDIHALER (tiotropium bromide inhalation powder) clinical development program consisted of six Phase 3 studies in 2663 patients with COPD (1308 receiving SPIRIVA HANDIHALER): two 1-year, placebo-controlled studies, two 6-month, placebo-controlled studies and two 1-year, ipratropium-controlled studies. These studies enrolled patients who had a clinical diagnosis of COPD, were 40 years of age or older, had a history of smoking greater than 10 pack-years, had a forced expiratory volume in one second (FEV_1) less than or equal to 60% or 65% of predicted, and a ratio of FEV_1/FVC of less than or equal to 0.7.

In these studies, SPIRIVA HANDIHALER, administered once-daily in the morning, provided improvement in lung function (FEV_1), with peak effect occurring within 3 hours following the first dose.

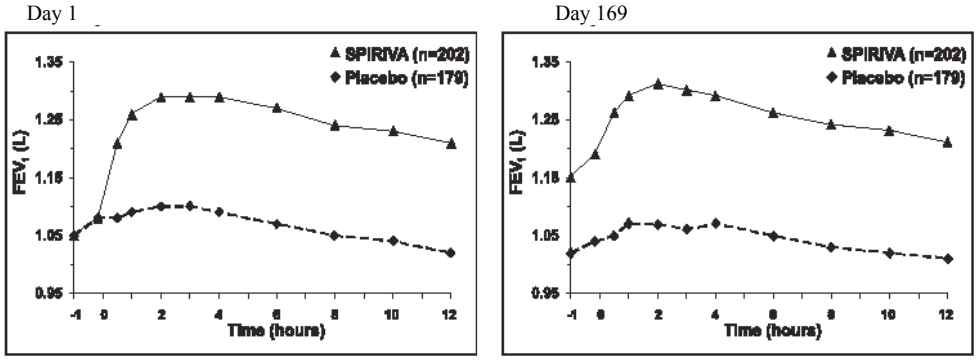
Two additional trials evaluated exacerbations: a 6-month, randomized, double-blind, placebo-controlled, multicenter clinical trial of 1829 COPD patients in a US Veterans Affairs setting and a 4-year, randomized, double-blind, placebo-controlled, multicenter, clinical trial of 5992 COPD patients. Long-term effects on lung function and other outcomes, were also evaluated in the 4-year multicenter trial.

6-Month to 1-Year Effects on Lung Function

In the 1-year, placebo-controlled trials, the mean improvement in FEV_1 at 30 minutes was 0.13 liters (13%) with a peak improvement of 0.24 liters (24%) relative to baseline after the first dose (Day 1). Further improvements in FEV_1 and forced vital capacity (FVC) were observed with pharmacodynamic steady state reached by Day 8 with once-daily treatment. The mean peak improvement in FEV_1, relative to baseline, was 0.28 to 0.31 liters (28% to 31%), after 1 week (Day 8) of once-daily treatment. Improvement of lung function was maintained for 24 hours after a single dose and consistently maintained over the 1-year treatment period with no evidence of tolerance.

In the two 6-month, placebo-controlled trials, serial spirometric evaluations were performed throughout daytime hours in Trial A (12 hours) and limited to 3 hours in Trial B. The serial FEV_1 values over 12 hours (Trial A) are displayed in Figure 1. These trials further support the improvement in pulmonary function (FEV_1) with SPIRIVA HANDIHALER, which persisted over the spirometric observational period. Effectiveness was maintained for 24 hours after administration over the 6-month treatment period.

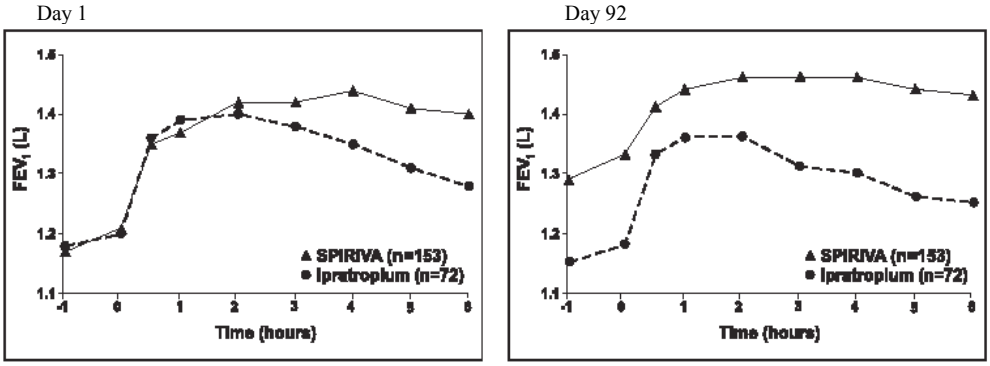
Figure 1 Mean FEV_1 Over Time (prior to and after administration of study drug) on Days 1 and 169 for Trial A (a Six-Month Placebo-Controlled Study)*



*Means adjusted for center, treatment, and baseline effect. On Day 169, a total of 183 and 149 patients in the SPIRIVA HANDIHALER and placebo groups, respectively, completed the trial. The data for the remaining patients were imputed using the last observation or least favorable observation carried forward.

Results of each of the 1-year ipratropium-controlled trials were similar to the results of the 1-year placebo-controlled trials. The results of one of these trials are shown in Figure 2.

Figure 2 Mean FEV_1 Over Time (0 to 6 hours post-dose) on Days 1 and 92, Respectively for One of the Two Ipratropium-Controlled Studies*



*Means adjusted for center, treatment, and baseline effect. On Day 92 (primary endpoint), a total of 151 and 69 patients in the SPIRIVA HANDIHALER and ipratropium groups, respectively, completed through 3 months of observation. The data for the remaining patients were imputed using the last observation or least favorable observation carried forward.

A randomized, placebo-controlled clinical study in 105 patients with COPD demonstrated that bronchodilation was maintained throughout the 24-hour dosing interval in comparison to placebo, regardless of whether SPIRIVA HANDIHALER was administered in the morning or in the evening.

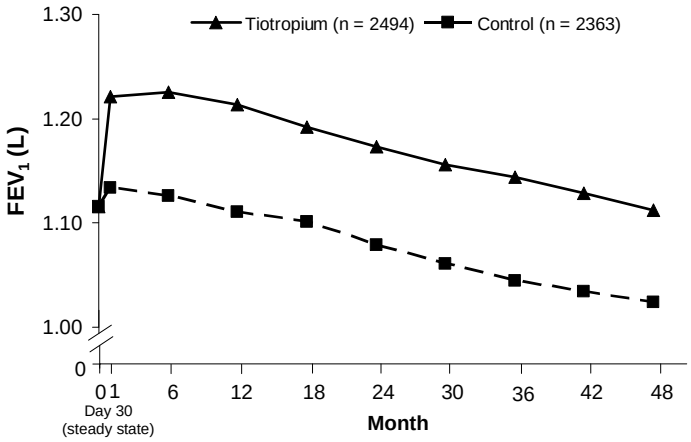
Throughout each week of the 1-year treatment period in the two placebo-controlled trials, patients taking SPIRIVA HANDIHALER had a reduced requirement for the use of rescue short-acting $beta_2$-agonists. Reduction in the use of rescue short-acting $beta_2$-agonists, as compared to placebo, was demonstrated in one of the two 6-month studies.

4-Year Effects on Lung Function

A 4-year, randomized, double-blind, placebo-controlled, multicenter clinical trial involving 5992 COPD patients was conducted to evaluate the long-term effects of SPIRIVA HANDIHALER on disease progression (rate of decline in FEV_1). Patients were permitted to use all respiratory medications (including short-acting and long-acting beta-agonists, inhaled and systemic steroids, and theophyllines) other than inhaled anticholinergics. The patients were 40 to 88 years of age, 75% male, and 90% Caucasian with a diagnosis of COPD and a mean pre-bronchodilator FEV_1 of 39% predicted (range = 9% to 76%) at study entry. There was no difference between the groups in either of the co-primary efficacy endpoints, yearly rate of decline in pre- and post-bronchodilator FEV_1, as demonstrated by similar slopes of FEV_1 decline over time (Figure 3).

SPIRIVA HANDIHALER maintained improvements in trough (pre-dose) FEV_1 (adjusted means over time: 87 to 103 mL) throughout the 4 years of the study (Figure 3).

Figure 3 Trough (pre-dose) FEV_1 Mean Values at Each Time Point



Repeated measure ANOVA was used to estimate means. Means are adjusted for baseline measurements. Baseline trough FEV_1 (observed mean) = 1.12. Patients with ≥3 acceptable pulmonary function tests after Day 30 and non-missing baseline value were included in the analysis.

Exacerbations

The effect of SPIRIVA HANDIHALER on COPD exacerbations was evaluated in two clinical trials: a 4-year clinical trial described above and a 6-month clinical trial of 1829 COPD patients in a Veterans Affairs setting. In the 6-month trial, COPD exacerbations were defined as a complex of respiratory symptoms (increase or new onset) of more than one of the following: cough, sputum, wheezing, dyspnea, or chest tightness with a duration of at least 3 days requiring treatment with antibiotics, systemic steroids, or hospitalization. The population had an age ranging from 40 to 90 years with 99% males, 91% Caucasian, and had COPD with a mean pre-bronchodilator FEV_1 percent predicted of 36% (range = 8% to 93%). Patients were permitted to use respiratory medications (including short-acting and long-acting beta-agonists, inhaled and systemic steroids, and theophyllines) other than inhaled anticholinergics. In the 6-month trial, the co-primary endpoints were the proportion of patients with COPD exacerbation and the proportion of patients with hospitalization due to COPD exacerbation. SPIRIVA HANDIHALER significantly reduced the proportion of COPD patients who experienced exacerbations compared to placebo (27.9% vs. 32.3%, respectively; Odds Ratio (OR) (tiotropium/placebo) = 0.81; 95% CI = 0.66, 0.99; p = 0.037). The proportion of patients with hospitalization due to COPD exacerbations in patients who used SPIRIVA HANDIHALER compared to placebo was 7.0% vs. 9.5%, respectively; OR = 0.72; 95% CI = 0.51, 1.01; p = 0.056.

Exacerbations were evaluated as a secondary outcome in the 4-year multicenter trial. In this trial, COPD exacerbations were defined as an increase or new onset of more than one of the following respiratory symptoms (cough, sputum, sputum purulence, wheezing, dyspnea) with a duration of three or more days requiring treatment with antibiotics and/or systemic (oral, intramuscular, or intravenous) steroids. SPIRIVA HANDIHALER significantly reduced the risk of an exacerbation by 14% (Hazard Ratio (HR) = 0.86; 95% CI = 0.81, 0.91; p<0.001) and reduced the risk of exacerbation-related hospitalization by 14% (HR = 0.86; 95% CI = 0.78, 0.95; p<0.002) compared to placebo. The median time to first exacerbation was delayed from 12.5 months (95% CI = 11.5, 13.8) in the placebo group to 16.7 months (95% CI = 14.9, 17.9) in the SPIRIVA HANDIHALER group.

All-Cause Mortality

In the 4-year placebo-controlled lung-function trial described above, all-cause mortality compared to placebo was assessed. There were no significant differences in all-cause mortality rates between SPIRIVA HANDIHALER and placebo.

The all-cause mortality of SPIRIVA HANDIHALER was also compared to tiotropium inhalation spray 5 mcg (SPIRIVA RESPIMAT 5 mcg) in an additional long-term, randomized, double-blind, double-dummy active-controlled study with an observation period up to 3 years. All-cause mortality was similar between SPIRIVA HANDIHALER and SPIRIVA RESPIMAT.

16 HOW SUPPLIED/STORAGE AND HANDLING

SPIRIVA HANDIHALER consists of SPIRIVA capsules and the HANDIHALER device. SPIRIVA capsules contain 18 mcg of tiotropium and are light green, with the Boehringer Ingelheim company logo on the SPIRIVA capsule cap and TI 01 on the SPIRIVA capsule body, or vice versa.

The HANDIHALER device is gray colored with a green piercing button. It is imprinted with SPIRIVA HANDIHALER (tiotropium bromide inhalation powder), the Boehringer Ingelheim company logo. It is also imprinted to indicate that SPIRIVA capsules should not be stored in the HANDIHALER device and that the HANDIHALER device is only to be used with SPIRIVA capsules.

SPIRIVA capsules are packaged in an aluminum/aluminum blister card and joined along a perforated-cut line. SPIRIVA capsules should always be stored in the blister and only removed immediately before use. The drug should be used immediately after the packaging over an individual SPIRIVA capsule is opened.

The following packages are available:

- carton containing 5 SPIRIVA capsules (1 unit-dose blister card) and 1 HANDIHALER inhalation device (NDC 0597-0075-75) (institutional pack)
- carton containing 30 SPIRIVA capsules (3 unit-dose blister cards) and 1 HANDIHALER inhalation device (NDC 0597-0075-41)
- carton containing 90 SPIRIVA capsules (9 unit-dose blister cards) and 1 HANDIHALER inhalation device (NDC 0597-0075-47)

Keep out of reach of children. Do not get powder into eyes.

Storage
Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

The SPIRIVA capsules should not be exposed to extreme temperature or moisture. Do not store SPIRIVA capsules in the HANDIHALER device.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Not for Acute Use:

Instruct patients that SPIRIVA HANDIHALER is a once-daily maintenance bronchodilator and should not be used for immediate relief of breathing problems (i.e., as a rescue medication).

Immediate Hypersensitivity Reactions:

Inform patients that anaphylaxis, angioedema (including swelling of the lips, tongue, or throat), urticaria, rash, bronchospasm, or itching, may occur after administration of SPIRIVA HANDIHALER. Advise patient to immediately discontinue treatment and consult a physician should any of these signs or symptoms develop.

Paradoxical Bronchospasm:

Inform patients that SPIRIVA HANDIHALER can produce paradoxical bronchospasm. Advise patients that if paradoxical bronchospasm occurs, patients should discontinue SPIRIVA HANDIHALER.

Worsening of Narrow-Angle Glaucoma:

Instruct patients to be alert for signs and symptoms of narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs and symptoms develop.

Inform patients that care must be taken not to allow the powder to enter into the eyes as this may cause blurring of vision and pupil dilation.

Since dizziness and blurred vision may occur with the use of SPIRIVA HANDIHALER, caution patients about engaging in activities such as driving a vehicle or operating appliances or machinery.

Worsening of Urinary Retention:

Instruct patients to be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Instructions for Administering SPIRIVA HANDIHALER:

Instruct patients on how to correctly administer SPIRIVA capsules using the HANDIHALER device *[see Patient Counseling Information (17)]*. Instruct patients that SPIRIVA capsules should only be administered via the HANDIHALER device and the HANDIHALER device should not be used for administering other medications. **Remind patients that the contents of SPIRIVA capsules are for oral inhalation only and must not be swallowed**.

Instruct patients always to store SPIRIVA capsules in sealed blisters and to remove only one SPIRIVA capsule immediately before use or its effectiveness may be reduced. Instruct patients to discard unused additional SPIRIVA capsules that are exposed to air (i.e., not intended for immediate use).

Distributed by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

Address medical inquiries to: (800) 542-6257 or (800) 459-9906 TTY.

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IT5300LA312018

Patient Information

SPIRIVA® (speh REE vah) HANDIHALER®
(tiotropium bromide inhalation powder)

	**Do NOT swallow SPIRIVA capsules.**

<u>Important Information:</u> Do not swallow SPIRIVA capsules. SPIRIVA capsules should only be used with the HANDIHALER device and inhaled through your mouth (oral inhalation).

Read the information that comes with your SPIRIVA HANDIHALER before you start using it and each time you refill your prescription. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or your treatment.

What is SPIRIVA HANDIHALER?

- SPIRIVA HANDIHALER is a prescription medicine used each day (a maintenance medicine) to control symptoms of chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.
- SPIRIVA HANDIHALER helps make your lungs work better for 24 hours. SPIRIVA HANDIHALER relaxes your airways and helps keep them open. You may start to feel like it is easier to breathe on the first day, but it may take longer for you to feel the full effects of the medicine. SPIRIVA HANDIHALER works best and may help make it easier to breathe when you use it every day.
- SPIRIVA HANDIHALER reduces the likelihood of flare-ups and worsening of COPD symptoms (COPD exacerbations). A COPD exacerbation is defined as an increase or new onset of more than one COPD symptom such as cough, mucus, shortness of breath, and wheezing that requires medicine beyond your rescue medicine.

SPIRIVA HANDIHALER is not a rescue medicine and should not be used for treating sudden breathing problems. Your doctor may give you other medicine to use for sudden breathing problems.

It is not known if SPIRIVA HANDIHALER is safe and effective in children.

Who should not take SPIRIVA HANDIHALER?

Do not use SPIRIVA HANDIHALER if you:

- are allergic to tiotropium, ipratropium (Atrovent®), or any of the ingredients in SPIRIVA HANDIHALER. See the end of this leaflet for a complete list of ingredients in SPIRIVA HANDIHALER.

Symptoms of a serious allergic reaction to SPIRIVA HANDIHALER may include:

- raised red patches on your skin (hives)
- itching
- rash
- swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing

If you have these symptoms of an allergic reaction, stop taking SPIRIVA HANDIHALER and call your doctor right away or go to the nearest hospital emergency room.

What should I tell my doctor before using SPIRIVA HANDIHALER?

Before taking SPIRIVA HANDIHALER, tell your doctor about all your medical conditions, including if you:

- have kidney problems.
- have glaucoma. SPIRIVA HANDIHALER may make your glaucoma worse.
- have an enlarged prostate, problems passing urine, or a blockage in your bladder. SPIRIVA HANDIHALER may make these problems worse.
- are pregnant or plan to become pregnant. It is not known if SPIRIVA HANDIHALER could harm your unborn baby.
- are breast-feeding or plan to breast-feed. It is not known if SPIRIVA HANDIHALER passes into breast milk. You and your doctor will decide if SPIRIVA HANDIHALER is right for you while you breast-feed.
- have a severe allergy to milk proteins. Ask your doctor if you are not sure.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines and eye drops, vitamins, and herbal supplements. Some of your other medicines or supplements may affect the way SPIRIVA HANDIHALER works. SPIRIVA HANDIHALER is an anticholinergic medicine. You should not take other anticholinergic medicines while using SPIRIVA HANDIHALER, including ipratropium. Ask your doctor or pharmacist if you are not sure if one of your medicines is an anticholinergic.

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist when you get a new medicine.

How should I take SPIRIVA HANDIHALER?

- Use SPIRIVA HANDIHALER exactly as prescribed. Use SPIRIVA HANDIHALER one time every day.
- Read the "Instructions for Use" at the end of this leaflet before you use SPIRIVA HANDIHALER. Talk with your doctor if you do not understand the instructions.
- **Do not swallow SPIRIVA capsules.**
- **Only use SPIRIVA capsules with the HANDIHALER device.**
- **Do not use the HANDIHALER device to take any other medicine**.
- SPIRIVA HANDIHALER comes as a powder in a SPIRIVA capsule that fits the HANDIHALER device. Each SPIRIVA capsule, containing only a small amount of SPIRIVA powder, is one full dose of medicine.
- Separate one blister from the blister card. Then take out one of the SPIRIVA capsules from the blister package right before you use it.
- After the capsule is pierced, take a complete dose of SPIRIVA HANDIHALER by breathing in the powder by mouth two times, using the HANDIHALER device (take 2 inhalations from one SPIRIVA capsule). See the "**Instructions for Use**" at the end of this leaflet.
- Throw away any SPIRIVA capsule that is not used right away after it is taken out of the blister package. Do not leave the SPIRIVA capsules open to air; they may not work as well.
- If you miss a dose, take it as soon as you remember. Do not use SPIRIVA HANDIHALER more than one time every 24 hours.
- If you use more than your prescribed dose of SPIRIVA HANDIHALER, call your doctor or a poison control center.

What should I avoid while using SPIRIVA HANDIHALER?

- Do not let the powder from the SPIRIVA capsule get into your eyes. Your vision may get blurry and the pupil in your eye may get larger (dilate). If this happens, call your doctor.
- SPIRIVA HANDIHALER can cause dizziness and blurred vision. Should you experience these symptoms you should use caution when engaging in activities such as driving a car or operating appliances or other machines.

What are the possible side effects of SPIRIVA HANDIHALER?

SPIRIVA HANDIHALER can cause serious side effects, including: Allergic reaction. Symptoms may include**:**

- raised red patches on your skin (hives)
- itching
- rash
- swelling of the lips, tongue, or throat that may cause difficulty in breathing or swallowing

If you have these symptoms of an allergic reaction, stop taking SPIRIVA HANDIHALER and call your doctor right away or

go to the nearest hospital emergency room.

- **Sudden narrowing and blockage of the airways into the lungs (bronchospasm).** Your breathing suddenly gets worse.

If you have these symptoms of bronchospasm, stop taking SPIRIVA HANDIHALER and call your doctor right away or go to the nearest hospital emergency room.

- **New or worsened increased pressure in the eyes (acute narrow-angle glaucoma).** Symptoms of acute narrow-angle glaucoma may include:
    - eye pain
    - blurred vision
    - seeing halos (visual halos) or colored images along with red eyes

Using only eye drops to treat these symptoms may not work. If you have these symptoms, stop taking SPIRIVA HANDIHALER and call your doctor right away.

- **New or worsened urinary retention.** Symptoms of blockage in your bladder and/or enlarged prostate may include: difficulty passing urine, painful urination.

If you have these symptoms of urinary retention, stop taking SPIRIVA HANDIHALER and call your doctor right away.

Other side effects with SPIRIVA HANDIHALER include:

- upper respiratory tract infection
- dry mouth
- sinus infection
- sore throat
- non-specific chest pain
- urinary tract infection
- indigestion
- runny nose
- constipation
- increased heart rate
- blurred vision

These are not all the possible side effects with SPIRIVA HANDIHALER. Tell your doctor if you have any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store SPIRIVA HANDIHALER?

- **Do not store SPIRIVA capsules in the HANDIHALER device.**
- Store SPIRIVA capsules in the sealed blister package at room temperature 68°F to 77°F (20°C to 25°C).
- Keep SPIRIVA capsules away from heat and cold (do not freeze).
- Store SPIRIVA capsules in a dry place. Throw away any unused SPIRIVA capsules that have been open to air.

Ask your doctor or pharmacist if you have any questions about storing your SPIRIVA capsules.

Keep SPIRIVA HANDIHALER, SPIRIVA capsules, and all medicines out of the reach of children.

General information about SPIRIVA HANDIHALER

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets. Do not use SPIRIVA HANDIHALER for a purpose for which it has not been prescribed. Do not give SPIRIVA HANDIHALER to other people even if they have the same symptoms that you have. It may harm them.

For more information about SPIRIVA HANDIHALER, talk with your doctor. You can ask your doctor or pharmacist for information about SPIRIVA HANDIHALER that is written for health professionals.

For more information about SPIRIVA HANDIHALER, go to www.SPIRIVA.com, or scan the code below, or call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257 or (TTY) 1-800-459-9906.

What are the ingredients in SPIRIVA HANDIHALER?

Active ingredient: tiotropium
Inactive ingredient: lactose monohydrate

What is COPD (Chronic Obstructive Pulmonary Disease)?

COPD is a serious lung disease that includes chronic bronchitis, emphysema, or both. Most COPD is caused by smoking. When you have COPD, your airways become narrow. So, air moves out of your lungs more slowly. This makes it hard to breathe.

This Patient Information has been approved by the U.S. Food and Drug Administration.

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Ridgefield, CT 06877 USA

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Instructions for Use

SPIRIVA® (speh REE vah) **HANDIHALER®**
(tiotropium bromide inhalation powder)

Do not swallow SPIRIVA capsules.

Important Information about using your SPIRIVA HANDIHALER

- **Do not swallow SPIRIVA capsules.**
- **SPIRIVA capsules should only be used with the HANDIHALER device and inhaled through your mouth (oral inhalation).**
- **Do not use your HANDIHALER device to take any other medicine.**

First read the Patient Information, then read these Instructions for Use before you start to use SPIRIVA HANDIHALER and each time you refill your prescription. There may be new information.

Becoming familiar with your HANDIHALER device and SPIRIVA capsules:

Your SPIRIVA HANDIHALER comes with SPIRIVA capsules in blister packaging and a HANDIHALER device. Use the new HANDIHALER device provided with your medicine.

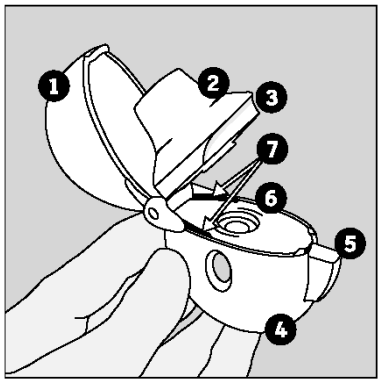

Figure A

The parts of your HANDIHALER device include:
(See Figure A)

1. dust cap (lid)
2. mouthpiece
3. mouthpiece ridge
4. base
5. green piercing button
6. center chamber
7. air intake vents

Figure B

Each SPIRIVA capsule is packaged in a blister. (See Figure B)

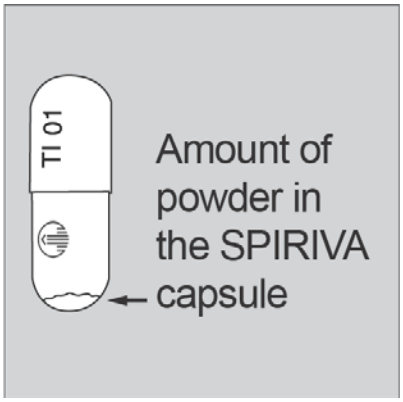

Figure C

- Each SPIRIVA capsule contains only a small amount of powder. (See Figure C) This is 1 full dose.
- **Do not open the SPIRIVA capsule** or it may not work.

Taking your full daily dose of medicine requires 4 main steps.

Step 1. Opening your HANDIHALER device:

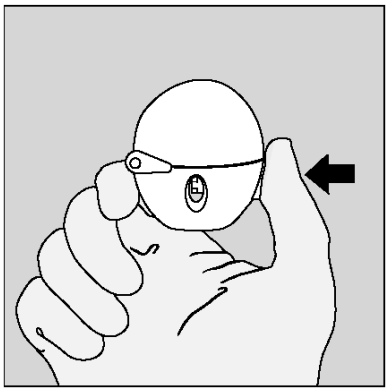

Figure D

After removing your HANDIHALER device from the pouch:

- Open the dust cap (lid) by pressing the green piercing button. (See Figure D)

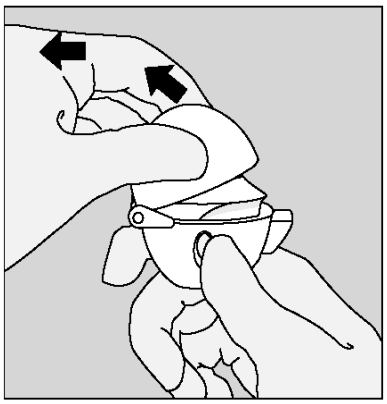

Figure E

- Pull the dust cap (lid) upwards away from the base to expose the mouthpiece. (See Figure E)

Figure F

- Open the mouthpiece by pulling the mouthpiece ridge up and away from the base so the center chamber is showing. (See Figure F)

Step 2. Inserting the SPIRIVA capsule into your HANDIHALER device:

Figure G

Each day, separate only 1 of the blisters from the blister card by tearing along the perforated line. (See Figure G)

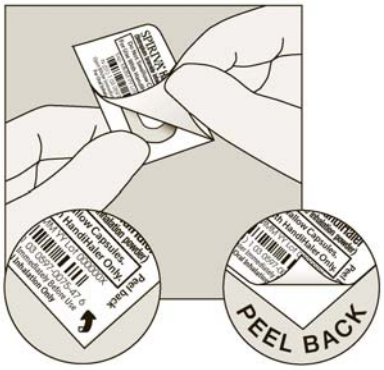

Figure H

Remove the SPIRIVA capsule from the blister:

- **Do not** cut the foil or use sharp instruments to take out the SPIRIVA capsule from the blister.
- Bend 1 of the blister corners with an arrow and separate the aluminum foil layers.
- Peel back the printed foil until you see the whole SPIRIVA capsule. (See Figure H)
- If you have opened more than 1 blister to the air, the extra SPIRIVA capsule should not be used and should be thrown away.

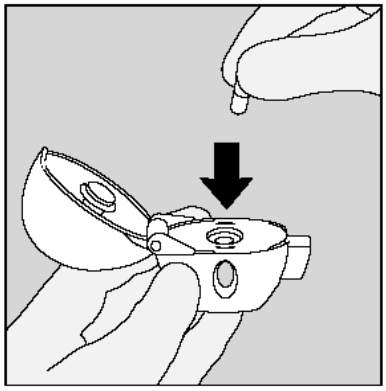

Figure I

Place the SPIRIVA capsule in the center chamber of your HANDIHALER device. (See Figure I)

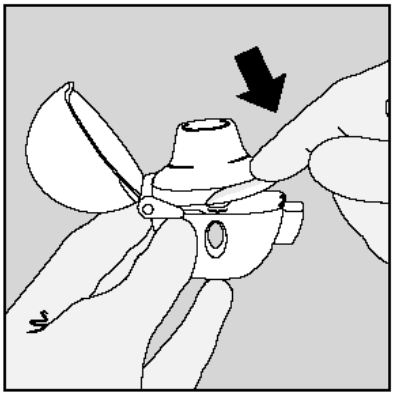

Figure J

Close the mouthpiece firmly against the gray base until you hear a click. Leave the dust cap (lid) open. (See Figure J)

Step 3. Piercing the SPIRIVA capsule:

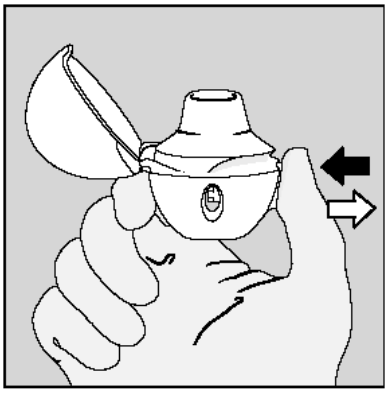

Figure K

- Hold your HANDIHALER device with the mouthpiece pointed up. (See Figure K)
- Press the green piercing button once until it is flat (flush) against the base, then release. This is how you make holes in the SPIRIVA capsule so that you get your medicine when you breathe in.
- **Do not** press the green button more than one time.
- **Do not** shake your HANDIHALER device.
- The piercing of the SPIRIVA capsule may produce small gelatin pieces. Some of these small pieces may pass through the screen of your HANDIHALER device into your mouth or throat when you breathe in your medicine. This is normal. The small pieces of gelatin should not harm you.

Step 4. Taking your full daily dose (2 inhalations from the same SPIRIVA capsule):

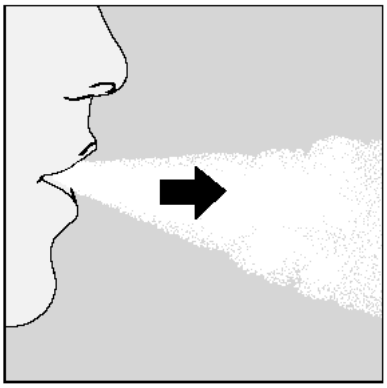

Figure L

Breathe out completely in 1 breath, emptying your lungs of any air. (See Figure L)

Important: Do not breathe into your HANDIHALER device.

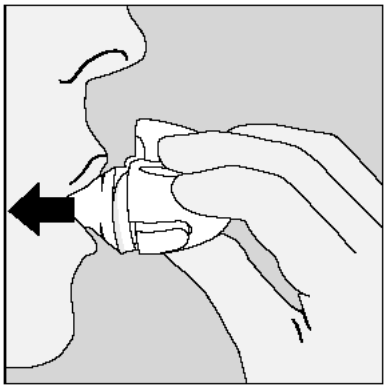

Figure M

With your next breath, take your medicine:

- **Hold your head in an upright position while you are looking straight ahead.** (See Figure M)
- Raise your HANDIHALER device to your mouth in a horizontal position. **Do not** block the air intake vents.
- Close your lips tightly around the mouthpiece.
- **Breathe in deeply** until your lungs are full. You should **hear or feel the SPIRIVA capsule vibrate** (rattle). (See Figure M)
- Hold your breath for a few seconds and, at the same time, take your HANDIHALER device out of your mouth.
- Breathe normally again.

The rattle tells you that you breathed in correctly. If you do not hear or feel a rattle, see the section, “If you do not hear or feel the SPIRIVA capsule rattle as you breathe in your medicine.”

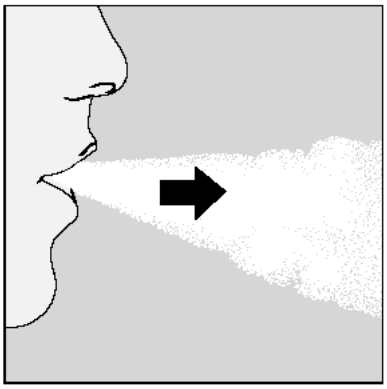

Figure N

To get your full daily dose, you must again, breathe out completely (See Figure N) and for a second time, breathe in (See Figure O) from the same SPIRIVA capsule.

Important: Do not press the green piercing button again.

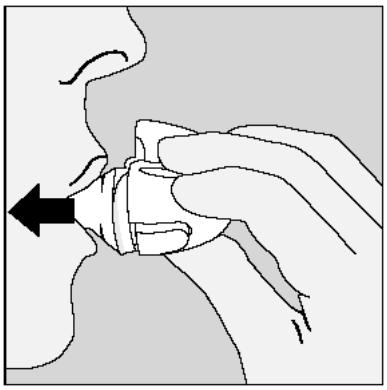

Figure O

Remember: To get your full medicine dose each day, you must breathe in 2 times from the same SPIRIVA capsule. Make sure you breathe out completely each time before you breathe in from your HANDIHALER device.

Caring for and storing your SPIRIVA HANDIHALER:

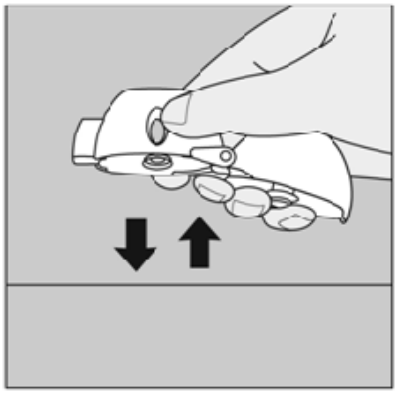

Figure P

- After taking your daily dose, open the mouthpiece and tip out the used SPIRIVA capsule into your trash can, without touching it.
- Remove any SPIRIVA capsule pieces or SPIRIVA powder buildup by turning your HANDIHALER device upside down and gently, but firmly, tapping it. (See Figure P) Then, close the mouthpiece and dustcap for storage.
- **Do not** store your HANDIHALER device and SPIRIVA capsules (blisters) in a damp moist place. Always store SPIRIVA capsules in the sealed blisters.

If you do not hear or feel the SPIRIVA capsule rattle as you breathe in your medicine:

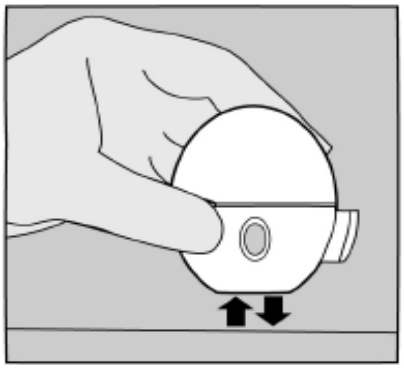

Figure Q

Do not press the green piercing button again.

Hold your HANDIHALER device with the mouthpiece pointed up and tap your HANDIHALER device gently on a table. (See Figure Q)

Check to see that the mouthpiece is completely closed. Breathe out completely before deeply breathing in again with the mouthpiece in your mouth. (See Figure O)

If you still do not hear or feel the SPIRIVA capsule rattle after repeating the above steps:

- Throw away the SPIRIVA capsule.
- Open the base by lifting the green piercing button and check the center chamber for pieces of the SPIRIVA capsule. SPIRIVA capsule pieces in the center chamber can cause a SPIRIVA capsule not to rattle.
- Turn your HANDIHALER device upside down and gently, but firmly, tap to remove the SPIRIVA capsule pieces. Call your doctor for instructions.

Cleaning your HANDIHALER device:

Figure R

Clean your HANDIHALER device as needed. (See Figure R)

- **It takes 24 hours to air dry your HANDIHALER device** after you clean it.
- **Do not** use cleaning agents or detergents.
- **Do not** place your HANDIHALER device in the dishwasher for cleaning.

Cleaning Steps:

- Open the dust cap and mouthpiece.
- Open the base by lifting the green piercing button.
- Look in the center chamber for SPIRIVA capsule pieces or powder buildup. If seen, tap out.
- Rinse your HANDIHALER device with warm water, pressing the green piercing button a few times so that the center chamber and the piercing needle is under the running water. Check that any powder buildup or SPIRIVA capsule pieces are removed.
- Dry your HANDIHALER device well by tipping the excess water out on a paper towel. Air-dry afterwards, leaving the dust cap, mouthpiece, and base open by fully spreading it out so that it dries completely.
- **Do not** use a hair dryer to dry your HANDIHALER device.
- **Do not** use your HANDIHALER device when it is wet. If needed, you may clean the outside of the mouthpiece with a clean damp cloth.

Helpful Hints to help ensure that you are properly taking your full daily dose of SPIRIVA HANDIHALER:

- **Press** the green piercing button **1 time; Breathe in 2 times; Breathe out completely** before each of the **2** inhalations.
- Always use the new HANDIHALER device provided with your medicine.
- Keep your HANDIHALER device with the mouthpiece pointed up when pressing the green piercing button.
- **Press the green piercing button 1 time** to pierce the SPIRIVA capsule.
- Do not breathe out into your HANDIHALER device.
- Keep your HANDIHALER device in a horizontal position and keep your head upright, looking straight ahead, when breathing in.
- Check the center chamber of your HANDIHALER device for SPIRIVA capsule pieces or powder build-up. If pieces or powder are seen, tap out before use.
- Clean your HANDIHALER as needed and dry thoroughly.

For more information, ask your doctor or pharmacist, or go to www.spiriva.com, or scan the code below, or call 1-800-542-6257 or (TTY) 1-800-459-9906.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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Revised: February 2018

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EXHIBIT B

US006777423B2

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

(10) **Patent No.: US 6,777,423 B2**
(45) **Date of Patent: Aug. 17, 2004**

(54) **CRYSTALLINE TIOTROPIUM BROMIDE MONOHYDRATE, PROCESSES FOR THE PREPARATION THEREOF, AND PHARMACEUTICAL COMPOSITIONS**

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(73) Assignee: **Boehringer Ingelheim Pharma KG**, Ingelheim (DE)

(*) 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.: **10/354,521**

(22) Filed: **Jan. 30, 2003**

(65) **Prior Publication Data**

US 2003/0171586 A1 Sep. 11, 2003

Related U.S. Application Data

(63) Continuation of application No. 09/961,822, filed on Sep. 24, 2001.
(60) Provisional application No. 60/249,349, filed on Nov. 16, 2000.

(30) **Foreign Application Priority Data**

Oct. 12, 2000 (DE) 100 50 621

(51) **Int. Cl.**[7] **A61K 31/439**; C07D 491/18
(52) **U.S. Cl.** **514/291**; 546/89; 546/91; 514/291; 514/304
(58) **Field of Search** 514/291, 304; 546/89, 91, 125

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Karl–Heinz Bozung et al; "New Medicament Compositions Based on Anticholinergically–effective Compounds and Betamimetics" U.S.S.N. 09/568,880; Filed May 9, 2000; Attorney Docket No. 1/1088; and divisional U.S.S.N. 09/695,581 Attorney Docket No. 1/1088–1–D1.
Accession No. (AN) : 1998:8089, USAN, Generic Name (CN) : Tiotropium Bromide, CAS Registry No. (RN) : 139404–48–1, printout ("the USAN reference") (1998).
U.S. patent application publication No. 2003/0087927–Crystalline Anticholinergic, Processes for Preparing It and Its use for Preparing a Pharmaceutical Composition published May 8, 2003.
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U.S. patent application HFA Suspension Formulations Containing Anticholinergic accorded Ser. No. 10/392,559 filed Mar. 20, 2003 for Docket No. 1/1316, Schmeizer, C.

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(74) *Attorney, Agent, or Firm*—Robert P. Raymond; Michael P. Morris; Andrea D. Small

(57) **ABSTRACT**

Crystalline monohydrate of (1α,2β,4β,5α,7β)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane bromide (tiotropium bromide monohydrate), processes for the preparation thereof, pharmaceutical compositions thereof, and their use.

16 Claims, 2 Drawing Sheets

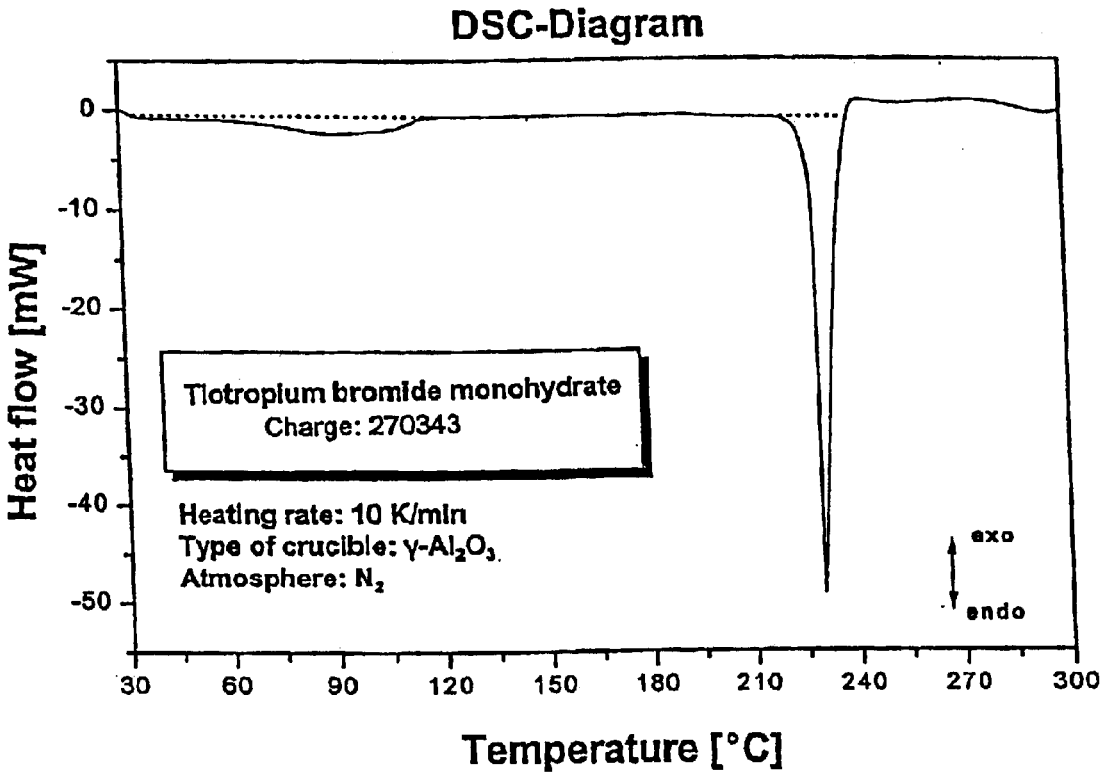

DSC-Diagram
Heat flow [mW]
0
-10
-20
-30
-40
-50
Tiotropium bromide monohydrate
Charge: 270343
Heating rate: 10 K/min
Type of crucible: γ-Al2O3
Atmosphere: N2
exo
endo
30
60
90
120
150
180
210
240
270
300
Temperature [°C]

Figure 1:

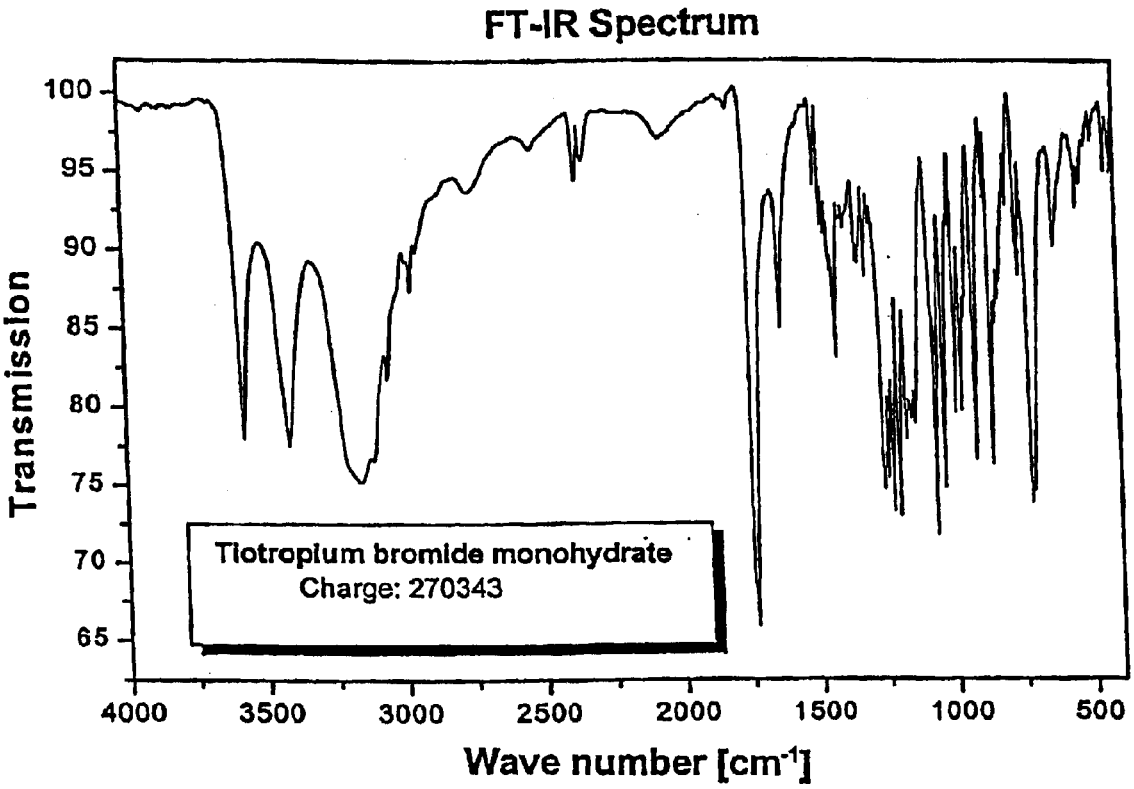

FT-IR Spectrum
Transmission
100
95
90
85
80
75
70
65
4000
3500
3000
2500
2000
1500
1000
500
Wave number [cm-1]
Tiotropium bromide monohydrate
Charge: 270343

Figure 2:

CRYSTALLINE TIOTROPIUM BROMIDE MONOHYDRATE, PROCESSES FOR THE PREPARATION THEREOF, AND PHARMACEUTICAL COMPOSITIONS

RELATED APPLICATIONS

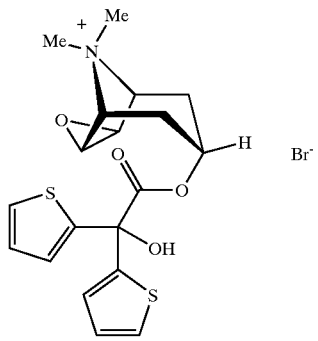
This application is a continuation of U.S. application Ser. No. 09/961,822, filed Sep. 24, 2001. Benefit under 35 U.S.C. § 119(e) of prior U.S. provisional application Serial No. 60/249,349, filed Nov. 16, 2000, is hereby claimed. Both of these applications are hereby incorporated by reference in their entireties.

BACKGROUND OF THE INVENTION

The invention relates to a crystalline monohydrate of (1α,2β,4β,5α,7β)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane bromide, processes for the preparation thereof, as well as the use thereof for preparing a pharmaceutical composition, particularly for preparing a pharmaceutical composition having an anticholinergic activity.

The compound (1α,2β,4β,5α,7β)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane bromide is known from European Patent Application EP 418 716 A1 and has the following chemical structure:

(I)



The compound has valuable pharmacological properties and is known by the name tiotropium bromide (BA679). Tiotropium bromide is a highly effective anticholinergic and can therefore provide therapeutic benefit in the treatment of asthma or chronic obstructive pulmonary disease (COPD).

Tiotropium bromide is preferably administered by inhalation. Suitable inhalable powders packed into appropriate capsules (inhalettes) may be used. Alternatively, it may be administered by the use of suitable inhalable aerosols. These also include powdered inhalable aerosols which contain, for example, HFA134a, HFA227 or mixtures thereof as propellant gas.

The correct manufacture of the abovementioned compositions which are suitable for use for the administration of a pharmaceutically active substance by inhalation is based on various parameters which are connected with the nature of the active substance itself. Without being restrictive, examples of these parameters are the stability of effect of the starting material under various environmental conditions, stability during production of the pharmaceutical formulation and stability in the final medicament compositions. The pharmaceutically active substance used for preparing the abovementioned pharmaceutical compositions should be as pure as possible and its stability in long-term storage must be guaranteed under various environmental conditions. This is absolutely essential to prevent the use of pharmaceutical compositions which contain, in addition to the actual active substance, breakdown products thereof, for example. In such cases the content of active substance in the capsules might be less than that specified.

The absorption of moisture reduces the content of pharmaceutically active substance on account of the weight gain caused by the uptake of water. Pharmaceutical compositions with a tendency to absorb moisture have to be protected from damp during storage, e.g., by the addition of suitable drying agents or by storing the medicament in a damp-proof environment. In addition, the uptake of moisture can reduce the content of pharmaceutically active substance during manufacture if the medicament is exposed to the environment without being protected from damp in any way.

Uniform distribution of the medicament in the formulation is a critical factor, particularly when the medicament has to be given in low doses. To ensure uniform distribution, the particle size of the active substance can be reduced to a suitable level, e.g., by grinding. Another aspect which is important in active substances to be administered by inhalation, e.g., by means of a powder, arises from the fact that only particles of a certain size can be taken into the lungs by inhalation. The particle size of these lung-bound particles (inhalable fraction) is in the sub-micron range. In order to obtain active substances of a corresponding particle size, a grinding process (so-called micronizing) is again required.

Since breakdown of the pharmaceutically active substance as a side effect of the grinding (or micronizing) has to be avoided as far as possible, in spite of the hard conditions required during the process, it is absolutely essential that the active substance should be highly stable throughout the grinding process. Only if the active substance is sufficiently stable during the grinding process is it possible to produce a homogeneous pharmaceutical formulation which always contains the specified amount of active substance in reproducible manner.

Another problem which may arise in the grinding process for preparing the desired pharmaceutical formulation is the input of energy caused by this process and the stress on the surface of the crystals. This may in certain circumstances lead to polymorphous changes, to a change in the amorphous configuration or to a change in the crystal lattice. Since the pharmaceutical quality of a pharmaceutical formulation requires that the active substance should always, have the same crystalline morphology, the stability and properties of the crystalline active substance are subject to stringent requirements from this point of view as well.

The stability of a pharmaceutically active substance is also important in pharmaceutical compositions for determining the shelf life of the particular medicament; the shelf life is the length of time during which the medicament can be administered without any risk. High stability of a medicament in the abovementioned pharmaceutical compositions under various storage conditions is therefore an additional advantage for both the patient and the manufacturer.

Apart from the requirements indicated above, it should be generally borne in mind that any change to the solid state of a pharmaceutical composition which is capable of improving its physical and chemical stability gives a significant advantage over less stable forms of the same medicament.

The aim of the invention is thus to provide a new, stable crystalline form of the compound tiotropium bromide which meets the stringent requirements imposed on pharmaceutically active substances as mentioned above.

DETAILED DESCRIPTION OF THE INVENTION

It has been found that, depending on the choice of conditions which can be used when purifying the crude

product obtained after industrial manufacture, tiotropium bromide occurs in various crystalline modifications.

It has been found that these different modifications can be deliberately produced by selecting the solvents used for the crystallization as well as by a suitable choice of the process conditions used in the crystallization process.

Surprisingly, it has been found that the monohydrate of tiotropium bromide, which can be obtained in crystalline form by choosing specific reaction conditions, meets the stringent requirements mentioned above and thus solves the problem on which the present invention is based. Accordingly the present invention relates to crystalline tiotropium bromide monohydrate.

According to another aspect, the present invention relates to a process for preparing crystalline hydrates of tiotropium bromide. This preparation process is characterized in that tiotropium bromide, which has been obtained for example by the method disclosed in EP 418 716 A1, is taken up in water, the mixture obtained is heated and finally the hydrates of tiotropium bromide are crystallized while cooling slowly.

The present invention further relates to crystalline hydrates of tiotropium bromide which may be obtained by the above method.

One aspect of the present invention relates to a process for preparing crystalline tiotropium bromide monohydrate which is described in more detail hereinafter.

In order to prepare the crystalline monohydrate according to the present invention, tiotropium bromide, which has been obtained for example according to the method disclosed in EP 418 716 A1, has to be taken up in water and heated, then purified with activated charcoal and, after removal of the activated charcoal, the tiotropium bromide monohydrate has to be crystallized out slowly while cooling gently.

The method described below is preferably used according to the invention.

In a suitably dimensioned reaction vessel the solvent is mixed with tiotropium bromide, which has been obtained, for example, according to the method disclosed in EP 418 716 A1. 0.4 kg to 1.5 kg, preferably 0.6 kg to 1 kg, most preferably about 0.8 kg of water are used as solvent per mole of tiotropium bromide used. The mixture obtained is heated with stirring, preferably to more than 50° C., most preferably to more than 60° C. The maximum temperature which can be selected will be determined by the boiling point of the solvent used, i.e., water. Preferably the mixture is heated to a range from 80° C.–90° C.

Activated charcoal, dry or moistened with water, is added to this solution. 10 g to 50 g, more preferably 15 g to 35 g, most preferably about 25 g of activated charcoal are put in per mole of tiotropium bromide used. If desired, the activated charcoal is suspended in water before being added to the solution containing the tiotropium bromide. 70 g to 200 g, preferably 100 g to 160 g, most preferably about 135 g water are used to suspend the activated charcoal, per mole of tiotropium bromide used. If the activated charcoal is suspended in water prior to being added to the solution containing the tiotropium bromide, it is advisable to rinse with the same amount of water.

After the activated charcoal has been added, stirring is continued at constant temperature for between 5 and 60 minutes, preferably between 10 and 30 minutes, most preferably about 15 minutes, and the mixture obtained is filtered to remove the activated charcoal. The filter is then rinsed with water. 140 g to 400 g, preferably 200 g to 320 g, most preferably about 270 g of water are used for this, per mole of tiotropium bromide used.

The filtrate is then slowly cooled, preferably to a temperature of 20° C.–25° C. The cooling is preferably carried out at a cooling rate of 1° C. to 10° C. per 10 to 30 minutes, preferably 2° C. to 8° C. per 10 to 30 minutes, more preferably 3° C. to 5° C. per 10 to 20 minutes, most preferably 3° C. to 5° C. roughly per 20 minutes. If desired, the cooling to 20° C. to 25° C. may be followed by further cooling to below 20° C., most preferably to 10° C. to 15° C.

Once the filtrate has cooled, it is stirred for between 20 minutes and 3 hours, preferably between 40 minutes and 2 hours, most preferably about one hour, to complete the crystallization.

The crystals formed are finally isolated by filtering or suction filtering the solvent. If it proves necessary to subject the crystals obtained to another washing step, it is advisable to use water or acetone as the washing solvent. 0.1 l to 1.0 l, preferably 0.2 l to 0.5 l, most preferably about 0.3 l solvent are used, per mole of tiotropium bromide, to wash the tiotropium bromide monohydrate crystals obtained. If desired the washing step may be repeated.

The product obtained is dried in vacuo or using circulating hot air until a water content of 2.5%–4.0% is obtained.

One aspect of the present invention relates to crystalline tiotropium bromide monohydrate which can be obtained using the method described above.

The tiotropium bromide monohydrate obtainable using the method described above was investigated by Differential Scanning Calorimetry (DSC). The DSC diagram shows two characteristic signals. The first, relatively broad, endothermic signal between 50–120° C. can be attributed to the dehydration of the tiotropium bromide monohydrate into the anhydrous form. The second, relatively sharp, endothermic peak at 230° C.±5° C. can be put down to the melting of the substance (FIG. **1**). This data was obtained using a Mettler DSC 821 and evaluated using the Mettler STAR software package. The data was recorded at a heating rate of 10 K/min.

Since the substance melts with decomposition (i.e., incongruent melting process), the melting point observed depends to a great extent on the heating rate. At lower heating rates, the melting/decomposition process is observed at significantly lower temperatures, e.g., at 220° C.±5° C. with a heating rate of 3 K/min. It is also possible that the melting peak may be split. The split is all the more apparent the lower the heating rate in the DSC experiment.

The present invention is therefore directed to crystalline tiotropium bromide monohydrate which is characterized, according to FIG. **1**, by an endothermic peak at 230° C. (±5° C.) at a heating rate of 10 K/min.

The tiotropium bromide monohydrate according to the invention was characterized by IR spectroscopy. The data was obtained using a Nicolet FTIR spectrometer and evaluated with the Nicolet OMNIC software package, version 3.1. The measurement was carried out with 2.5 μmol of tiotropium bromide monohydrate in 300 mg of KBr. The IR spectrum obtained is shown in FIG. **2**. Table 1 shows some of the essential bands of the IR spectrum.

TABLE 1

Attribution of Specific Bands

Wave number (cm^{-1})	Attribution	Type of Oscillation
3570, 410	O—H	elongated oscillation
3105	Aryl C—H	elongated oscillation
1730	C═O	elongated oscillation
1260	Epoxide C—O	elongated oscillation
1035	Ester C—OC	elongated oscillation
720	Thiophene	cyclic oscillation

Accordingly the present invention relates to crystalline tiotropium bromide monohydrate which is characterized

according to FIG. **2** by an IR spectrum which has bands at wave numbers 3570, 3410, 3105, 1730, 1260, 1035 and 720 cm^{-1}, inter alia.

The tiotropium bromide monohydrate according to the invention was characterized by X-ray structural analysis. The measurements of X-ray diffraction intensity were carried out on an AFC7R-4-circuit diffractometer (Rigaku) using monochromatic copper K_α radiation. The structural solution and refinement of the crystal structure were obtained by direct methods (SHELXS86 Program) and FMLQ-refinement (TeXsan Program). Experimental details of the crystalline structure, structural resolution and refinement are collected in Table 2.

TABLE 2

Experimental Data on the Analysis of the Crystalline Structure of Tiotropium Bromide Monohydrate

A. CRYSTAL DATA	
Empirical Formula	$[C_{19}H_{22}NO_4S_2]Br.H_2O$
Formula Weight	472.43 + 18.00
Color and shape of crystals	colorless, prismatic
Dimensions of crystals	0.2 × 0.3 × 0.3 mm
Crystal system	monoclinic
Lattice type	primitive
Space group	P $2_1/n$
Lattice constants	a = 18.0774 Å b = 11.9711 Å c = 9.9321 Å β = 102.691° V = 2096.96 Å^3
Formula units per elementary cell	4
B. MEASUREMENTS OF INTENSITY	
Diffractometer	Rigaku AFC7R
X-ray generator	Rigaku RU200
Wavelength	λ = 1.54178 Å (monochromatic copper $K_{\alpha 0}$-radiation)
Current, voltage	50 kV, 100 mA
Take-off angle	6° C.
Crystal assembly	steam-saturated capillary
Crystal-detector gap	235 mm
Detector opening	3.0 mm vertical and horizontal
Temperature	18° C.
Determining the lattice constants	25 reflexes (50.8° < 2Θ <56.2°)
Scan type	ω - 2Θ
Scan speed	8.0 32.0°/min in ω
Scan width	(0.58 + 0.30 tan Θ)°
$2\Theta_{max}$	120°
Measured	5193
Independent reflexes	3281 (R_{int} = 0.051)
Corrections	Lorentz polarization Absorption (Transmission factors 0.56–1.00) Crystal decay: 10.47% decay
C. REFINEMENT	
Reflections (I > 3σI)	1978
Variable	254
Ratio of reflections/ parameters	7.8
R-values: R, Rw	0.062, 0.066

The X-ray structural analysis carried out showed that crystalline tiotropium bromide hydrate has a simple monoclinic cell with the following dimensions: a=18.0774 Å, b=11.9711 Å, c=9.9321 Å, β=102.691°, V=2096.96 Å^3. Accordingly, the present invention relates to crystalline tiotropium bromide monohydrate which is characterized by the elementary cell described above.

The atomic coordinates described in Table 3 were determined by the above X-ray structural analysis.

TABLE 3

	Coordinates			
Atom	x	y	z	u(eq)
Br(1)	0.63938(7)	0.0490(1)	0.2651(1)	0.0696(4)
S(1)	0.2807(2)	0.8774(3)	0.1219(3)	0.086(1)
S(2)	0.4555(3)	0.6370(4)	0.4214(5)	0.141(2)
O(1)	0.2185(4)	0.7372(6)	0.4365(8)	0.079(3)
O(2)	0.3162(4)	0.6363(8)	0.5349(9)	0.106(3)
O(3)	0.3188(4)	0.9012(5)	0.4097(6)	0.058(2)
O(4)	0.0416(4)	0.9429(6)	0.3390(8)	0.085(3)
O(5)	0.8185(5)	0.0004(8)	0.2629(9)	0.106(3)
N(1)	0.0111(4)	0.7607(6)	0.4752(7)	0.052(2)
C(1)	0.2895(5)	0.7107(9)	0.4632(9)	0.048(3)
C(2)	0.3330(5)	0.7876(8)	0.3826(8)	0.048(3)
C(3)	0.3004(5)	0.7672(8)	0.2296(8)	0.046(3)
C(4)	0.4173(5)	0.7650(8)	0.4148(8)	0.052(3)
C(5)	0.1635(5)	0.6746(9)	0.497(1)	0.062(3)
C(6)	0.1435(5)	0.7488(9)	0.6085(9)	0.057(3)
C(7)	0.0989(6)	0.6415(8)	0.378(1)	0.059(3)
C(8)	0.0382(5)	0.7325(9)	0.3439(9)	0.056(3)
C(9)	0.0761(6)	0.840(1)	0.315(1)	0.064(3)
C(10)	0.1014(6)	0.8974(8)	0.443(1)	0.060(3)
C(11)	0.0785(5)	0.8286(8)	0.5540(9)	0.053(3)
C(12)	−0.0632(6)	0.826(1)	0.444(1)	0.086(4)
C(13)	−0.0063(6)	0.6595(9)	0.554(1)	0.062(3)
C(14)	0.4747(4)	0.8652(9)	0.430(1)	0.030(2)
C(15)	0.2839(5)	0.6644(9)	0.1629(9)	0.055(3)
C(16)	0.528(2)	0.818(2)	0.445(2)	0.22(1)
C(17)	0.5445(5)	0.702(2)	0.441(1)	0.144(6)
C(18)	0.2552(6)	0.684(1)	0.019(1)	0.079(4)
C(19)	0.2507(6)	0.792(1)	−0.016(1)	0.080(4)
H(1)	−0.0767	0.8453	0.5286	0.102
H(2)	−0.0572	0.8919	0.3949	0.102
H(3)	−0.1021	0.7810	0.3906	0.102
H(4)	−0.0210	0.6826	0.6359	0.073
H(5)	−0.0463	0.6178	0.4982	0.073
H(6)	0.0377	0.6134	0.5781	0.073
H(7)	0.1300	0.7026	0.6770	0.069
H(8)	0.1873	0.7915	0.6490	0.069
H(9)	0.1190	0.6284	0.2985	0.069
H(10)	0.0762	0.5750	0.4016	0.069
H(11)	0.1873	0.6082	0.5393	0.073
H(12)	−0.0025	0.7116	0.2699	0.066
H(13)	0.1084	0.8383	0.2506	0.075
H(14)	0.1498	0.9329	0.4626	0.071
H(15)	0.0658	0.8734	0.6250	0.063
H(16)	0.2906	0.5927	0.2065	0.065
H(17)	0.2406	0.6258	−0.0469	0.094
H(18)	0.2328	0.8191	−0.1075	0.097
H(19)	0.4649	0.9443	0.4254	0.037
H(20)	0.5729	0.8656	0.4660	0.268
H(21)	0.5930	0.6651	0.4477	0.165
H(22)	0.8192	−0.0610	0.1619	0.084
H(23)	0.7603	0.0105	0.2412	0.084

x, y, z: fractional coordinates; and u(eq): mean quadratic amplitude of atomic movement in the crystal

According to another aspect, the present invention relates to the use of tiotropium bromide monohydrate as a medicament in the light of the pharmaceutical efficacy of the hydrate according to the invention.

To prepare a medicament which can be inhaled, particularly an inhalable powder, which contains the crystalline tiotropium bromide monohydrate described by the present invention, methods known from the prior art may be used. In this respect, reference is made, for example, to the teaching of DE-A-179 22 07. Accordingly, a further aspect of the present invention relates to inhalable powders characterized in that they contain tiotropium bromide monohydrate.

In view of the anticholinergic effects of tiotropium bromide monohydrate a further aspect of the present invention relates to the use of tiotropium bromide monohydrate for preparing a pharmaceutical composition for treating diseases in which the use of an anticholinergic agent may have

a therapeutic benefit. It is preferably used for preparing a pharmaceutical composition for treating asthma or COPD.

The following example of synthesis serves to illustrate a method of preparing crystalline tiotropium bromide monohydrate carried out by way of example. It is to be regarded only as a possible method described by way of example, without restricting the invention to its contents.

EXAMPLE OF SYNTHESIS

In a suitable reaction vessel, 15.0 kg of tiotropium bromide are added to 25.7 kg of water. The mixture is heated to 80° C.–90° C. and stirred at constant temperature until a clear solution is formed. Activated charcoal (0.8 kg), moistened with water, is suspended in 4.4 kg of water, this mixture is added to the solution containing the tiotropium bromide and rinsed with 4.3 kg of water. The mixture thus obtained is stirred for at least 15 minutes at 80° C.–90° C. and then filtered through a heated filter into an apparatus which has been preheated to an outer temperature of 70° C. The filter is rinsed with 8.6 kg of water. The contents of the apparatus are cooled to a temperature of 20° C.–25° C. at a rate of 3° C.–5° C. per 20 minutes. The apparatus is further cooled to 10° C.–15° C. using cold water, and the crystallization is completed by stirring for at least one hour. The crystals are isolated using a suction filter drier, the crystal slurry isolated is washed with 9 l of cold water (10° C.–15° C.) and cold acetone (10° C.–15° C.). The crystals obtained are dried at 25° C. for 2 hours in a nitrogen current. Yield: 13.4 kg of tiotropium bromide monohydrate (86% of theory).

We claim:

1. Crystalline tiotropium bromide monohydrate having an endothermic peak at 230° C.±5° C. occurring during thermal analysis using DSC at a heating rate of 10 K/min.

2. Crystalline tiotropium bromide monohydrate having an IR spectrum comprising bands at wave numbers 3570, 3410, 3105, 1730, 1260, 1035, and 720 cm^{-1}.

3. Crystalline tiotropium bromide monohydrate according to claim **1**, having an IR spectrum comprising bands at wave numbers 3570, 3410, 3105, 1730, 1260, 1035, and 720 cm^{-1}.

4. Crystalline tiotropium bromide monohydrate according to claim **1**, having a single monoclinic cell having the following dimensions: a=18.0774 Å, b=11.9711 Å, c=9.9321 Å, β=102.691°, and V=2096.96 $Å^3$.

5. Crystalline tiotropium bromide monohydrate according to claim **2**, having a single monoclinic cell having the following dimensions: a=18.0774 Å, b=11.9711 Å, c=9.9321 Å, β=102.691°, and V=2096.96 $Å^3$.

6. Crystalline tiotropium bromide monohydrate according to claim **3**, having a single monoclinic cell having the following dimensions: a=18.0774 Å, b=11.9711 Å, c=9.9321 Å, β=102.6910°, and V=2096.96 $Å^3$.

7. A process for preparing crystalline tiotropium bromide monohydrate according to claim **1**, the process comprising:

(a) dissolving tiotropium bromide in water to obtain a solution;

(b) heating the resulting solution;

(c) adding activated charcoal to the heated solution;

(d) removing the activated charcoal; and

(e) allowing the solution to slowly cool to obtain crystalline tiotropium bromide monohydrate.

8. A process for preparing crystalline tiotropium bromide monohydrate according to claim **1**, the process comprising:

(a) dissolving tiotropium bromide in water to obtain a solution;

(b) heating the resulting solution to more than 50° C.;

(c) adding activated charcoal to the heated solution;

(d) removing the activated charcoal; and

(e) allowing the solution to slowly cool to obtain crystalline tiotropium bromide monohydrate.

9. The process according to claim **8**, wherein 0.4 to 1.5 kg of water are used per mole of tiotropium bromide in step (a).

10. The process according to claim **9**, wherein 10 g to 50 g of activated charcoal per mole of tiotropium bromide is added in step (c).

11. The process according to claim **10**, wherein the activated charcoal added in step (c) is stirred for between 5 and 60 minutes before it is removed in step (d).

12. The process according to claim **11**, wherein step (d) is performed by filtration of the solution.

13. The process according to claim **12**, wherein the solution of step (e) is cooled to a temperature of 20° C.–25° C. at a cooling rate of 1 to 10° C. per 10 to 30 minutes.

14. A process for preparing the crystalline tiotropium bromide monohydrate according to claim **1**, the process comprising:

(a) dissolving tiotropium bromide in water to obtain a solution;

(b) heating the resulting solution; and

(c) allowing the solution to slowly cool to obtain crystalline tiotropium bromide monohydrate.

15. A process for preparing crystalline tiotropium bromide monohydrate according to claim **1**, the process comprising:

(a) dissolving tiotropium bromide in water to obtain a solution;

(b) heating the solution of step (a);

(c) adding activated charcoal to the heated solution of step (b);

(d) removing the activated charcoal from the solution of step (c); and

(e) allowing the solution to slowly cool to obtain crystalline tiotropium bromide monohydrate.

16. The process of claim **15**, wherein the solution of step (a) is heated to more than 50° C.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,777,423 B2
DATED : August 17, 2004
INVENTOR(S) : Rolf Banholzer et al.

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

Column 2,
Line 63, before the "DETAILED DESCRIPTION OF THE INVENTION" section, insert the following:

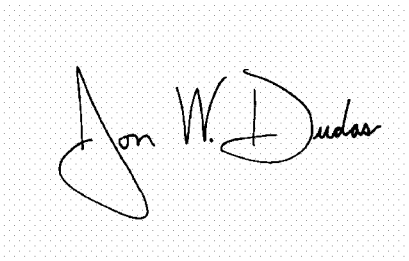
-- BRIEF DESCRIPTION OF DRAWINGS:

Figure 1 (FIG. 1): Characterization of crystalline tiotropium bromide monohydrate by Differential Scanning Calorimetry (DSC). The DSC diagram shows two characteristic signals. The first, relatively broad, endothermic signal between 50-120• C and the second, relatively sharp, endothermic peak at 230• C ±5• C .

Figure 2 (FIG.2): Characterization of crystalline tiotropium bromide monohydrate characterized by IR spectroscopy. The data was obtained using a Nicolet FTIR spectrometer and evaluated with Nicolet OMNIC software package, version 3.1. --.

Signed and Sealed this

Fourth Day of April, 2006



JON W. DUDAS
Director of the United States Patent and Trademark Office

EXHIBIT C

US006908928B2

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

(10) **Patent No.: US 6,908,928 B2**
(45) **Date of Patent: Jun. 21, 2005**

(54) **CRYSTALLINE TIOTROPIUM BROMIDE MONOHYDRATE, PROCESSES FOR THE PREPARATION THEREOF, AND PHARMACEUTICAL COMPOSITIONS**

(75) Inventors: **Rolf Banholzer**, Stuttgart (DE); **Peter Sieger**, Mittelbiberach (DE); **Christian Kulinna**, Mainz (DE); **Michael Trunk**, Ingelheim (DE); **Manfred Graulich**, Waldalgesheim (DE); **Peter Specht**, Ober-Hilbersheim (DE); **Helmut Meissner**, Ingelheim (DE); **Andreas Mathes**, Ockenheim (DE)

(73) Assignee: **BI Pharma KG.**, Ingelheim (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 427 days.

(21) Appl. No.: **09/961,822**

(22) Filed: **Sep. 24, 2001**

(65) **Prior Publication Data**

US 2002/0169321 A1 Nov. 14, 2002

Related U.S. Application Data

(60) Provisional application No. 60/249,349, filed on Nov. 16, 2000.

(30) **Foreign Application Priority Data**

Oct. 12, 2000 (DE) 100 50 621

(51) **Int. Cl.**[7] **A61K 31/438**; C07D 515/18

(52) **U.S. Cl.** **514/291**; 514/291; 514/304; 546/86; 546/89; 546/91

(58) **Field of Search** 546/89, 91, 127; 514/291, 304

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U.S. Patent Application No. 2003/0087927 –Crystalline Anticholinergic, Processes for Preparing it and its use for Preparing a Pharmaceutical Composition published May 8, 2003.

U.S. Patent Application, Crystlline Micronisate, Process for the Manufature thereof and use thereof for the Preparation of a Medicament, accorded Ser. No. 10/385,175, filed Mar. 5, 10, 2003, for Docket No. 1/1310, Bender, H. et al.

U.S. Patent Application HFA Suspension Formulations Containing Anticholinergic accorded Ser. No. 10/392,559 filed Mar. 20, 2003 for Docket No. 1/316, Schmelzer, C.

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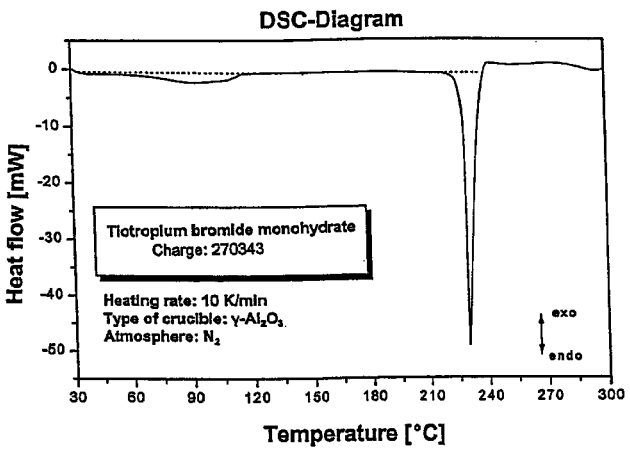
(74) *Attorney, Agent, or Firm*—Robert P. Raymond; Timothy X. Witkowski; Mary-Ellen Devlin

(57) **ABSTRACT**

Crystalline monohydrate of (1α,2β,4β,5α,7β)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane bromide (tiotropium bromide monohydrate), processes for the preparation thereof, pharmaceutical compositions thereof, and their use.

23 Claims, 2 Drawing Sheets



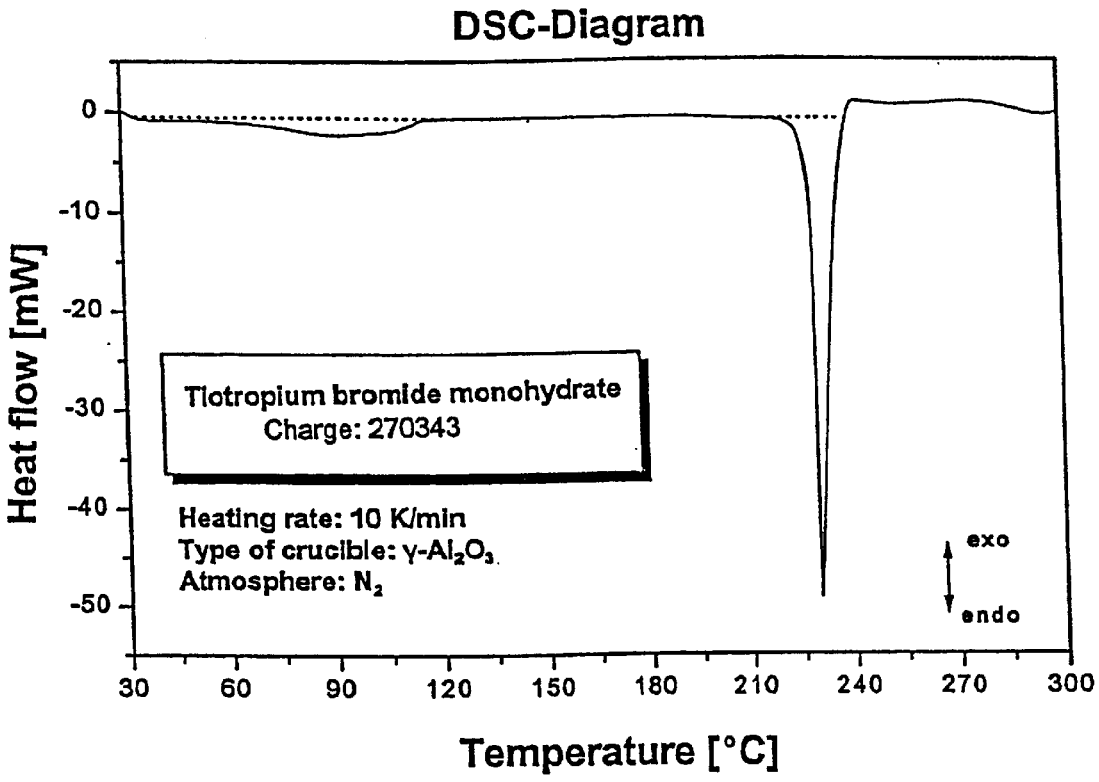

DSC-Diagram
Heat flow [mW]
0
-10
-20
-30
-40
-50
Tiotropium bromide monohydrate
Charge: 270343
Heating rate: 10 K/min
Type of crucible: γ-Al2O3
Atmosphere: N2
exo
endo
30
60
90
120
150
180
210
240
270
300
Temperature [°C]

Figure 1:

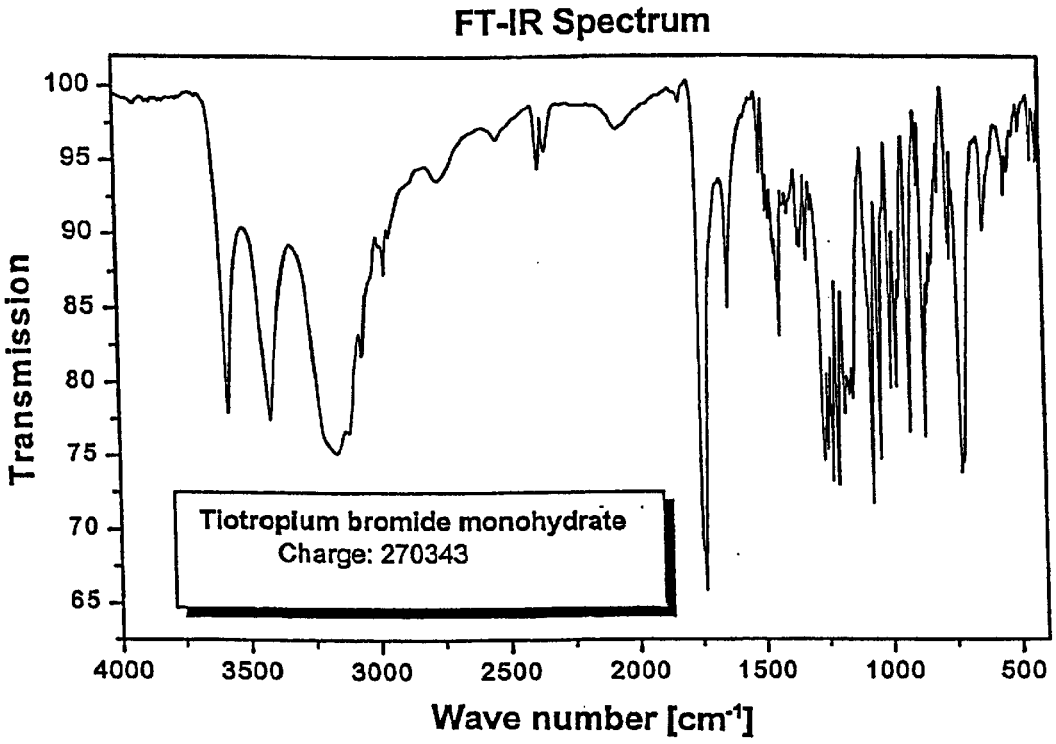

FT-IR Spectrum
Transmission
100
95
90
85
80
75
70
65
4000
3500
3000
2500
2000
1500
1000
500
Wave number [cm-1]
Tiotropium bromide monohydrate
Charge: 270343

Figure 2:

CRYSTALLINE TIOTROPIUM BROMIDE MONOHYDRATE, PROCESSES FOR THE PREPARATION THEREOF, AND PHARMACEUTICAL COMPOSITIONS

RELATED APPLICATIONS

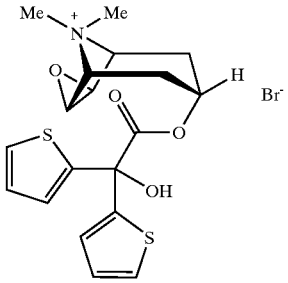
Benefit under 35 U.S.C. §119(e) of prior U.S. provisional application Ser. No. 60/249,349, filed Nov. 16, 2000, is hereby claimed.

BACKGROUND OF THE INVENTION

The invention relates to a crystalline monohydrate of (1α,2β,4β,5α,7β)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane bromide, processes for the preparation thereof, as well as the use thereof for preparing a pharmaceutical composition, particularly for preparing a pharmaceutical composition having an anticholinergic activity.

The compound (1α,2β,4β,5α,7β)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo [3.3.1.$0^{2,4}$]nonane bromide is known from European Patent Application EP 418 716 A1 and has the following chemical structure:

(I)



The compound has valuable pharmacological properties and is known by the name tiotropium bromide (BA679). Tiotropium bromide is a highly effective anticholinergic and can therefore provide therapeutic benefit in the treatment of asthma or chronic obstructive pulmonary disease (COPD).

Tiotropium bromide is preferably administered by inhalation. Suitable inhalable powders packed into appropriate capsules (inhalettes) may be used. Alternatively, it may be administered by the use of suitable inhalable aerosols. These also include powdered inhalable aerosols which contain, for example, HFA134a, HFA227 or mixtures thereof as propellant gas.

The correct manufacture of the abovementioned compositions which are suitable for use for the administration of a pharmaceutically active substance by inhalation is based on various parameters which are connected with the nature of the active substance itself. Without being restrictive, examples of these parameters are the stability of effect of the starting material under various environmental conditions, stability during production of the pharmaceutical formulation and stability in the final medicament compositions. The pharmaceutically active substance used for preparing the abovementioned pharmaceutical compositions should be as pure as possible and its stability in long-term storage must be guaranteed under various environmental conditions. This is absolutely essential to prevent the use of pharmaceutical compositions which contain, in addition to the actual active substance, breakdown products thereof, for example. In such cases the content of active substance in the capsules might be less than that specified.

The absorption of moisture reduces the content of pharmaceutically active substance on account of the weight gain caused by the uptake of water. Pharmaceutical compositions with a tendency to absorb moisture have to be protected from damp during storage, e.g., by the addition of suitable drying agents or by storing the medicament in a damp-proof environment. In addition, the uptake of moisture can reduce the content of pharmaceutically active substance during manufacture if the medicament is exposed to the environment without being protected from damp in any way.

Uniform distribution of the medicament in the formulation is a critical factor, particularly when the medicament has to be given in low doses. To ensure uniform distribution, the particle size of the active substance can be reduced to a suitable level, e.g., by grinding. Another aspect which is important in active substances to be administered by inhalation, e.g., by means of a powder, arises from the fact that only particles of a certain size can be taken into the lungs by inhalation. The particle size of these lung-bound particles (inhalable fraction) is in the sub-micron range. In order to obtain active substances of a corresponding particle size, a grinding process (so-called micronizing) is again required.

Since breakdown of the pharmaceutically active substance as a side effect of the grinding (or micronizing) has to be avoided as far as possible, in spite of the hard conditions required during the process, it is absolutely essential that the active substance should be highly stable throughout the grinding process. Only if the active substance is sufficiently stable during the grinding process is it possible to produce a homogeneous pharmaceutical formulation which always contains the specified amount of active substance in reproducible manner.

Another problem which may arise in the grinding process for preparing the desired pharmaceutical formulation is the input of energy caused by this process and the stress on the surface of the crystals. This may in certain circumstances lead to polymorphous changes, to a change in the amorphous configuration or to a change in the crystal lattice. Since the pharmaceutical quality of a pharmaceutical formulation requires that the active substance should always have the same crystalline morphology, the stability and properties of the crystalline active substance are subject to stringent requirements from this point of view as well.

The stability of a pharmaceutically active substance is also important in pharmaceutical compositions for determining the shelf life of the particular medicament; the shelf life is the length of time during which the medicament can be administered without any risk. High stability of a medicament in the abovementioned pharmaceutical compositions under various storage conditions is therefore an additional advantage for both the patient and the manufacturer.

Apart from the requirements indicated above, it should be generally borne in mind that any change to the solid state of a pharmaceutical composition which is capable of improving its physical and chemical stability gives a significant advantage over less stable forms of the same medicament.

The aim of the invention is thus to provide a new, stable crystalline form of the compound tiotropium bromide which meets the stringent requirements imposed on pharmaceutically active substances as mentioned above.

DETAILED DESCRIPTION OF THE INVENTION

It has been found that, depending on the choice of conditions which can be used when purifying the crude

product obtained after industrial manufacture, tiotropium bromide occurs in various crystalline modifications.

It has been found that these different modifications can be deliberately produced by selecting the solvents used for the crystallization as well as by a suitable choice of the process conditions used in the crystallization process.

Surprisingly, it has been found that the monohydrate of tiotropium bromide, which can be obtained in crystalline form by choosing specific reaction conditions, meets the stringent requirements mentioned above and thus solves the problem on which the present invention is based. Accordingly the present invention relates to crystalline tiotropium bromide monohydrate.

According to another aspect, the present invention relates to a process for preparing crystalline hydrates of tiotropium bromide. This preparation process is characterized in that tiotropium bromide, which has been obtained for example by the method disclosed in EP 418 716 A1, is taken up in water, the mixture obtained is heated and finally the hydrates of tiotropium bromide are crystallized while cooling slowly.

The present invention further relates to crystalline hydrates of tiotropium bromide which may be obtained by the above method.

One aspect of the present invention relates to a process for preparing crystalline tiotropium bromide monohydrate which is described in more detail hereinafter.

In order to prepare the crystalline monohydrate according to the present invention, tiotropium bromide, which has been obtained for example according to the method disclosed in EP 418 716 A1, has to be taken up in water and heated, then purified with activated charcoal and, after removal of the activated charcoal, the tiotropium bromide monohydrate has to be crystallized out slowly while cooling gently.

The method described below is preferably used according to the invention.

In a suitably dimensioned reaction vessel the solvent is mixed with tiotropium bromide, which has been obtained, for example, according to the method disclosed in EP 418 716 A1. 0.4 kg to 1.5 kg, preferably 0.6 kg to 1 kg, most preferably about 0.8 kg of water are used as solvent per mole of tiotropium bromide used. The mixture obtained is heated with stirring, preferably to more than 50° C., most preferably to more than 60° C. The maximum temperature which can be selected will be determined by the boiling point of the solvent used, i.e., water. Preferably the mixture is heated to a range from 80° C.–90° C.

Activated charcoal, dry or moistened with water, is added to this solution. 10 g to 50 g, more preferably 15 g to 35 g, most preferably about 25 g of activated charcoal are put in per mole of tiotropium bromide used. If desired, the activated charcoal is suspended in water before being added to the solution containing the tiotropium bromide. 70 g to 200 g, preferably 100 g to 160 g, most preferably about 135 g water are used to suspend the activated charcoal, per mole of tiotropium bromide used. If the activated charcoal is suspended in water prior to being added to the solution containing the tiotropium bromide, it is advisable to rinse with the same amount of water.

After the activated charcoal has been added, stirring is continued at constant temperature for between 5 and 60 minutes, preferably between 10 and 30 minutes, most preferably about 15 minutes, and the mixture obtained is filtered to remove the activated charcoal. The filter is then rinsed with water. 140 g to 400 g, preferably 200 g to 320 g, most preferably about 270 g of water are used for this, per mole of tiotropium bromide used.

The filtrate is then slowly cooled, preferably to a temperature of 20° C.–25° C. The cooling is preferably carried out at a cooling rate of 1° C. to 10° C. per 10 to 30 minutes, preferably 2° C. to 8° C. per 10 to 30 minutes, more preferably 3° C. to 5° C. per 10 to 20 minutes, most preferably 3° C. to 5° C. roughly per 20 minutes. If desired, the cooling to 20° C. to 25° C. may be followed by further cooling to below 20° C., most preferably to 10° C. to 15° C.

Once the filtrate has cooled, it is stirred for between 20 minutes and 3 hours, preferably between 40 minutes and 2 hours, most preferably about one hour, to complete the crystallization.

The crystals formed are finally isolated by filtering or suction filtering the solvent. If it proves necessary to subject the crystals obtained to another washing step, it is advisable to use water or acetone as the washing solvent. 0.1 l to 1.0 l, preferably 0.2 l to 0.5 l, most preferably about 0.3 l solvent are used, per mole of tiotropium bromide, to wash the tiotropium bromide monohydrate crystals obtained. If desired the washing step may be repeated.

The product obtained is dried in vacuo or using circulating hot air until a water content of 2.5%–4.0% is obtained.

One aspect of the present invention relates to crystalline tiotropium bromide monohydrate which can be obtained using the method described above.

The tiotropium bromide monohydrate obtainable using the method described above was investigated by Differential Scanning Calorimetry (DSC). The DSC diagram shows two characteristic signals. The first, relatively broad, endothermic signal between 50–120° C. can be attributed to the dehydration of the tiotropium bromide monohydrate into the anhydrous form. The second, relatively sharp, endothermic peak at 230° C.±5° C. can be put down to the melting of the substance (FIG. **1**). This data was obtained using a Mettler DSC 821 and evaluated using the Mettler STAR software package. The data was recorded at a heating rate of 10 K/min.

Since the substance melts with decomposition (i.e., incongruent melting process), the melting point observed depends to a great extent on the heating rate. At lower heating rates, the melting/decomposition process is observed at significantly lower temperatures, e.g., at 220° C. ±5° C. with a heating rate of 3 K/min. It is also possible that the melting peak may be split. The split is all the more apparent the lower the heating rate in the DSC experiment.

The present invention is therefore directed to crystalline tiotropium bromide monohydrate which is characterized, according to FIG. **1**, by an endothermic peak at 230° C. (±5° C.) at a heating rate of 10 K/min.

The tiotropium bromide monohydrate according to the invention was characterized by IR spectroscopy. The data was obtained using a Nicolet FTIR spectrometer and evaluated with the Nicolet OMNIC software package, version 3.1. The measurement was carried out with 2.5 μmol of tiotropium bromide monohydrate in 300 mg of KBr. The IR spectrum obtained is shown in FIG. **2**. Table 1 shows some of the essential bands of the IR spectrum.

TABLE 1

Attribution of Specific Bands

Wave number (cm^{-1})	Attribution	Type of Oscillation
3570, 410	O—H	elongated oscillation
3105	Aryl C—H	elongated oscillation
1730	C=0	elongated oscillation
1260	Epoxide C—O	elongated oscillation
1035	Ester C—OC	elongated oscillation
720	Thiophene	cyclic oscillation

Accordingly, the present invention relates to crystalline tiotropium bromide monohydrate which is characterized

according to FIG. **2** by an IR spectrum which has bands at wave numbers 3570, 3410, 3105, 1730, 1260, 1035 and 720 cm^{-1}, inter alia.

The tiotropium bromide monohydrate according to the invention was characterized by X-ray structural analysis. The measurements of X-ray diffraction intensity were carried out on an AFC7R-4-circuit diffractometer (Rigaku) using monochromatic copper K_α radiation. The structural solution and refinement of the crystal structure were obtained by direct methods (SHELXS86 Program) and FMLQ-refinement (TeXsan Program). Experimental details of the crystalline structural resolution and refinement are collected in Table 2.

TABLE 2

Experimental Data on the Analysis of the Crystalline Structure of Tiotropium Bromide Monohydrate

A. CRYSTAL DATA	
Empirical Formula	$[C_{19}H_{22}NO_4S_2]Br.H_2O$
Formula Weight	472.43 + 18.00
Color and shape of crystals	colorless, prismatic
Dimensions of crystals	0.2 × 0.3 × 0.3 mm
Crystal system	monoclinic
Lattice type	primitive
Space group	P $2_1/n$
Lattice constants	a = 18.0774 Å b = 11.9711 Å c = 9.9321 Å β = 102.691° V = 2096.96 $Å^3$
Formula units per elementary cell	4
B. MEASUREMENTS OF INTENSITY	
Diffractometer	Rigaku AFC7R
X-ray generator	Rigaku RU200
Wavelength	λ = 1.54178 Å (monochromatic copper K_α-radiation)
Current, voltage	50 kV, 100 mA
Take-off angle	6° C.
Crystal assembly	steam-saturated capillary
Crystal-detector gap	235 mm
Detector opening	3.0 mm vertical and horizontal
Temperature	18° C.
Determining the lattice constants	25 reflexes (50.8° < 2Θ < 56.2°)
Scan type	ω-2Θ
Scan speed	8.0 32.0°/min in ω
Scan width	(0.58 + 0.30 tan Θ)°
$2\Theta_{max}$	120°
Measured	5193
Independent reflexes	3281 (R_{int} = 0.051)
Corrections	Lorentz polarization Absorption (Transmission factors 0.56–1.00) Crystal decay: 10.47% decay
C. REFINEMENT	
Reflections (I > 3σI)	1978
Variable	254
Ratio of reflections/ parameters	7.8
R-values: R, Rw	0.062, 0.066

The X-ray structural analysis carried out showed that crystalline tiotropium bromide hydrate has a simple monoclinic cell with the following dimensions: a=18.0774 Å, b=11.9711 Å, c=9.9321 Å, β=102.691°, V=2096.96 $Å^3$. Accordingly, the present invention relates to crystalline tiotropium bromide monohydrate which is characterized by the elementary cell described above.

The atomic coordinates described in Table 3 were determined by the above X-ray structural analysis.

TABLE 3

	Coordinates			
Atom	x	y	z	u (eq)
Br(1)	0.63938(7)	0.0490(1)	0.2651(1)	0.0696(4)
S(1)	0.2807(2)	0.8774(3)	0.1219(3)	0.086(1)
S(2)	0.4555(3)	0.6370(4)	0.4214(5)	0.141(2)
O(1)	0.2185(4)	0.7372(6)	0.4365(8)	0.079(3)
O(2)	0.3162(4)	0.6363(8)	0.5349(9)	0.106(3)
O(3)	0.3188(4)	0.9012(5)	0.4097(6)	0.058(2)
O(4)	0.0416(4)	0.9429(6)	0.3390(8)	0.085(3)
O(5)	0.8185(5)	0.0004(8)	0.2629(9)	0.106(3)
N(1)	0.0111(4)	0.7607(6)	0.4752(7)	0.052(2)
C(1)	0.2895(5)	0.7107(9)	0.4632(9)	0.048(3)
C(2)	0.3330(5)	0.7876(8)	0.3826(8)	0.048(3)
C(3)	0.3004(5)	0.7672(8)	0.2296(8)	0.046(3)
C(4)	0.4173(5)	0.7650(8)	0.4148(8)	0.052(3)
C(5)	0.1635(5)	0.6746(9)	0.497(1)	0.062(3)
C(6)	0.1435(5)	0.7488(9)	0.6085(9)	0.057(3)
C(7)	0.0989(6)	0.6415(8)	0.378(1)	0.059(3)
C(8)	0.0382(5)	0.7325(9)	0.3439(9)	0.056(3)
C(9)	0.0761(6)	0.840(1)	0.315(1)	0.064(3)
C(10)	0.1014(6)	0.8974(8)	0.443(1)	0.060(3)
C(11)	0.0785(5)	0.8286(8)	0.5540(9)	0.053(3)
C(12)	−0.0632(6)	0.826(1)	0.444(1)	0.086(4)
C(13)	−0.0063(6)	0.6595(9)	0.554(1)	0.062(3)
C(14)	0.4747(4)	0.8652(9)	0.430(1)	0.030(2)
C(15)	0.2839(5)	0.6644(9)	0.1629(9)	0.055(3)
C(16)	0.528(2)	0.818(2)	0.445(2)	0.22(1)
C(17)	0.5445(5)	0.702(2)	0.441(1)	0.144(6)
C(18)	0.2552(6)	0.684(1)	0.019(1)	0.079(4)
C(19)	0.2507(6)	0.792(1)	−0.016(1)	0.080(4)
H(1)	−0.0767	0.8453	0.5286	0.102
H(2)	−0.0572	0.8919	0.3949	0.102
H(3)	−0.1021	0.7810	0.3906	0.102
H(4)	−0.0210	0.6826	0.6359	0.073
H(5)	−0.0463	0.6178	0.4982	0.073
H(6)	0.0377	0.6134	0.5781	0.073
H(7)	0.1300	0.7026	0.6770	0.069
H(8)	0.1873	0.7915	0.6490	0.069
H(9)	0.1190	0.6284	0.2985	0.069
H(10)	0.0762	0.5750	0.4016	0.069
H(11)	0.1873	0.6082	0.5393	0.073
H(12)	−0.0025	0.7116	0.2699	0.066
H(13)	0.1084	0.8383	0.2506	0.075
H(14)	0.1498	0.9329	0.4626	0.071
H(15)	0.0658	0.8734	0.6250	0.063
H(16)	0.2906	0.5927	0.2065	0.065
H(17)	0.2406	0.6258	−0.0469	0.094
H(18)	0.2328	0.8191	−0.1075	0.097
H(19)	0.4649	0.9443	0.4254	0.037
H(20)	0.5729	0.8656	0.4660	0.268
H(21)	0.5930	0.6651	0.4477	0.165
H(22)	0.8192	−0.0610	0.1619	0.084
H(23)	0.7603	0.0105	0.2412	0.084

x, y, z: fractional coordinates; and
u (eq): mean quadratic amplitude of atomic movement in the crystal

According to another aspect, the present invention relates to the use of tiotropium bromide monohydrate as a medicament in the light of the pharmaceutical efficacy of the hydrate according to the invention.

To prepare a medicament which can be inhaled, particularly an inhalable powder, which contains the crystalline tiotropium bromide monohydrate described by the present invention, methods known from the prior art may be used. In this respect, reference is made, for example, to the teaching of DE-A-179 22 07. Accordingly, a further aspect of the present invention relates to inhalable powders characterized in that they contain tiotropium bromide monohydrate.

In view of the anticholinergic effects of tiotropium bromide monohydrate a further aspect of the present invention relates to the use of tiotropium bromide monohydrate for preparing a pharmaceutical composition for treating dis-

eases in which the use of an anticholinergic agent may have a therapeutic benefit. It is preferably used for preparing a pharmaceutical composition for treating asthma or COPD.

The following example of synthesis serves to illustrate a method of preparing crystalline tiotropium bromide monohydrate carried out by way of example. It is to be regarded only as a possible method described by way of example, without restricting the invention to its contents.

Example of Synthesis

In a suitable reaction vessel, 15.0 kg of tiotropium bromide are added to 25.7 kg of water. The mixture is heated to 80° C.–90° C. and stirred at constant temperature until a clear solution is formed. Activated charcoal (0.8 kg), moistened with water, is suspended in 4.4 kg of water, this mixture is added to the solution containing the tiotropium bromide and rinsed with 4.3 kg of water. The mixture thus obtained is stirred for at least 15 minutes at 80° C.–90° C. and then filtered through a heated filter into an apparatus which has been preheated to an outer temperature of 70° C. The filter is rinsed with 8.6 kg of water. The contents of the apparatus are cooled to a temperature of 20° C.–25° C. at a rate of 3° C.–5° C. per 20 minutes. The apparatus is further cooled to 10° C.–15° C. using cold water, and the crystallization is completed by stirring for at least one hour. The crystals are isolated using a suction filter drier, the crystal slurry isolated is washed with 9 l of cold water (10° C.–15° C.) and cold acetone (10° C.–15° C.). The crystals obtained are dried at 25° C. for 2 hours in a nitrogen current. Yield: 13.4 kg of tiotropium bromide monohydrate (86% of theory).

We claim:

1. A pharmaceutical composition comprising:

(a) an effective amount of crystalline tiotropium bromide monohydrate having an endothermic peak at 230° C.±5° C. occurring during thermal analysis using DSC at a heating rate of 10 K/mm; and

(b) a pharmaceutically acceptable excipient.

2. A pharmaceutical composition comprising:

(a) an effective amount of crystalline tiotropium bromide monohydrate having an JR spectrum comprising bands at wave numbers 3570, 3410, 3105, 1730, 1260, 1035, and 720 cm^{-1}; and

(b) a pharmaceutically acceptable excipient.

3. A pharmaceutical composition comprising:

(a) an effective amount of crystalline tiotropium bromide monohydrate having (i) an endothermic peak at 230° C.±5° C. occurring during thermal analysis using DSC at a heating rate of 10 K/mm, and (ii) an JR spectrum comprising bands at wave numbers 3570, 3410,3105, 1730, 1260, 1035, and 720 cm^{-1}; and

(b) a pharmaceutically acceptable excipient.

4. A pharmaceutical composition comprising:

(a) an effective amount of crystalline tiotropium bromide monohydrate having a single monoclinic cell having the following dimensions: a=18.0774 Å, b=11.9711 Å, c=9.9321 Å, β=102.691°, and V=2096.96 $Å^3$; and

(b) a pharmaceutically acceptable excipient.

5. A pharmaceutical composition comprising:

(a) an effective amount of crystalline tiotropium bromide monohydrate having (i) an endothermic peak at 230° C.±5° C. occurring during thermal analysis using DSC at a heating rate of 10 K/mm, and (ii) a single monoclinic cell having the following dimensions: a=18.0774 Å, b=11.9711 Å, c=9.9321 Å, β=102.691°, and V=2096.96 $Å^3$; and

(b) a pharmaceutically acceptable excipient.

6. A pharmaceutical composition comprising:

(a) an effective amount of crystalline tiotropium bromide monohydrate having (i) an IR spectrum comprising bands at wave numbers 3570, 3410, 3105, 1730, 1260, 1035, and 720 cm^{-1}, and (ii) a single monoclinic cell having the following dimensions: a=18.0774 Å, b=11.9711 Å, c=9.9321 Å, β=102.691°, and V=2096.96 $Å^3$; and

(b) a pharmaceutically acceptable excipient.

7. A pharmaceutical composition comprising:

(a) an effective amount of crystalline tiotropium bromide monohydrate having (i) an endothermic peak at 230° C.±5° C. occurring during thermal analysis using DSC at a heating rate of 10 K/min, (ii) an JR spectrum comprising bands at wave numbers 3570, 3410, 3105, 1730, 1260, 1035, and 720 cm^{-1}, and (iii) a single monoclinic cell having the following dimensions: a=18.0774 Å, b=11.9711 Å, c=9.9321 Å, 13.102.691°, and V=2096.96 |^3; and

(b) a pharmaceutically acceptable excipient.

8. The pharmaceutical composition according to claim **1**, wherein the pharmaceutical composition is an inhalable powder.

9. The pharmaceutical composition according to claim **2**, wherein the pharmaceutical composition is an inhalable powder.

10. The pharmaceutical composition according to claim **3**, wherein the pharmaceutical composition is an inhalable powder.

11. The pharmaceutical composition according to claim **4**, wherein the pharmaceutical composition is an inhalable powder.

12. The pharmaceutical composition according to claim **5**, wherein the pharmaceutical composition is an inhalable powder.

13. The pharmaceutical composition according to claim **6**, wherein the pharmaceutical composition is an inhalable powder.

14. The pharmaceutical composition according to claim **7**, wherein the pharmaceutical composition is an inhalable powder.

15. A method for treatment of diseases in which the administration of an anticholinergic agent may have a therapeutic benefit, in a patient in need of such treatment, which method comprises administering the patient an effective amount of crystalline tiotropium bromide monohydrate having an endothermic peak at 230° C.±5° C. occurring during thermal analysis using DSC at a heating rate of 10 K/mm.

16. A method for treatment of diseases in which the administration of an anticholinergic agent may have a therapeutic benefit, in a patient in need of such treatment, which method comprises administering the patient an effective amount of crystalline tiotropium bromide monohydrate having an JR spectrum comprising bands at wave numbers 3570, 3410, 3105, 1730, 1260, 1035, and 720 cm^{-1}.

17. A method for treatment of diseases in which the administration of an anticholinergic agent may have a therapeutic benefit, in a patient in need of such treatment, which method comprises administering the patient an effective amount of crystalline tiotropium bromide monohydrate having (i) an endothermic peak at 230° C.±5° C. occurring during thermal analysis using DSC at a heating rate of 10 K/min, and (ii) an JR spectrum comprising bands at wave numbers 3570, 3410, 3105, 1730, 1260, 1035, and 720 cm^{-1}.

18. A method for treatment of diseases in which the administration of an anticholinergic agent may have a thera-

peutic benefit, in a patient in need of such treatment, which method comprises administering the patient an effective amount of crystalline tiotropium bromide monohydrate having a single monoclinic cell having the following dimensions: a=18.0774 Å, b=11.9711 Å, c=9.9321 Å, β=102.6910, and V=2096.96 Å^3.

19. Crystalline hydrates of tiotropium bromide obtained by a process comprising:

(a) dissolving tiotropium bromide in water to obtain a solution;

(b) heating the solution of step (a);

(c) adding activated charcoal to the heated solution of step (b);

(d) removing the activated charcoal from the solution of step (c); and

(e) allowing the solution to slowly cool to obtain crystalline hydrates of tiotropium bromide.

20. Crystalline hydrates of tiotropium bromide according to claim **19**, wherein the solution of step (a) is heated to more than 50° C.

21. A method for treatment of diseases in which the administration of an anticholinergic agent may have a therapeutic benefit, in a patient in need of such treatment, which method comprises administering the patient an effective amount of crystalline tiotropium bromide monohydrate having (i) an endothermic peak at 230° C.±5° C. occurring during thermal analysis using DSC at a heating rate of 10 K/mm, and (ii) a single monoclinic cell having the following dimensions: a=18.0774 Å, b=11.9711 Å, c=9.9321 Å, β=102.691°, and V=2096.96 |^3.

22. A method for treatment of diseases in which the administration of an anticholinergic agent may have a therapeutic benefit, in a patient in need of such treatment, which method comprises administering the patient an effective amount of crystalline tiotropium bromide monohydrate having (i) an IR spectrum comprising bands at wave numbers 3570, 3410, 3105, 1730, 1260, 1035, and 720 cm^{-1}, and (ii) a single monoclinic cell having the following dimensions: a=18.0774 Å, b=11.9711 Å, c=9.9321 Å, β=102.691°, and V=2096.96 Å^3.

23. A method for treatment of diseases in which the administration of an anticholinergic agent may have a therapeutic benefit, in a patient in need of such treatment, which method comprises administering the patient an effective amount of crystalline tiotropium bromide monohydrate having (i) an endothermic peak at 230° C. ±5° C. occurring during thermal analysis using DSC at a heating rate of 10 K/mm, (ii) an IR spectrum comprising bands at wave numbers 3570, 3410, 3105, 1730, 1260, 1035, and 720 cm^{-1}, and (iii) a single monoclinic cell having the following dimensions: a=18.0774 Å, b=11.9711 Å, c=9.9321 Å, β=102.691°, and V=2096.96 Å^3.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,908,928 B2
APPLICATION NO. : 09/961822
DATED : June 21, 2005
INVENTOR(S) : Banholzer 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 7, line 41 (Claim 2):
"JR spectrum" should read
--IR spectrum--

In Column 7, line 49 (Claim 3):
"JR spectrum" should read
--IR spectrum--

In Column 8, line 15 (Claim 7):
"JR spectrum" should read
--IR spectrum--

In Column 8, line 19 (Claim 7):
"13.102.691°" should read
--β =102.691°--

In Column 8, line 20 (Claim 7):
"V=2096.96 | ^{3}" should read
--V=2096.96 Å^3--

In Column 8, line 43 (Claim 15):
"A method for treatment of diseases in which the administration...." should read
--A method for treatment of the diseases asthma or COPD in which the administration....--

In Column 8, line 49 (Claim 15):
"K/mm." should read
--K/min.--

In Column 8, line 50 (Claim 16):
"A method for treatment of diseases in which the administration...." should read
--A method for treatment of the diseases asthma or COPD in which the administration....--

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CERTIFICATE OF CORRECTION

PATENT NO. : 6,908,928 B2
APPLICATION NO. : 09/961822
DATED : June 21, 2005
INVENTOR(S) : Banholzer 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 8, line 55 (Claim 16):
"JR spectrum" should read
--IR spectrum--

In Column 8, line 57 (Claim 17):
"A method for treatment of diseases in which the administration...." should read
--A method for treatment of the diseases asthma or COPD in which the administration....--

In Column 8, line 64 (Claim 17):
"JR spectrum" should read
--IR spectrum--

In Column 8, line 66 (Claim 18):
"A method for treatment of diseases in which the administration...." should read
--A method for treatment of the diseases asthma or COPD in which the administration....--

In Column 9, line 5 (Claim 18):
"β=102.6910" should read
--β=102.691°--

In Column 9, line 22 (Claim 21):
"A method for treatment of diseases in which the administration...." should read
--A method for treatment of the diseases asthma or COPD in which the administration....--

In Column 10, line 1 (Claim 21):
"K/mm" should read
--K/min--

In Column 10, line 3 (Claim 21):
"V=2096.96 | ^{3}" should read
--V=2096.96 Å^3--

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,908,928 B2
APPLICATION NO. : 09/961822
DATED : June 21, 2005
INVENTOR(S) : Banholzer 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 10, line 4 (Claim 22):
"A method for treatment of diseases in which the administration...." should read
--A method for treatment of the diseases asthma or COPD in which the administration....--

In Column 10, line 15 (Claim 23):
"A method for treatment of diseases in which the administration...." should read
--A method for treatment of the diseases asthma or COPD in which the administration....--

In Column 10, line 22 (Claim 23):
"K/mm" should read
--K/min--

Signed and Sealed this

Fifth Day of May, 2009

John Doll

JOHN DOLL
Acting Director of the United States Patent and Trademark Office

EXHIBIT D

US007309707B2

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

(10) **Patent No.: US 7,309,707 B2**
(45) **Date of Patent: Dec. 18, 2007**

(54) **CRYSTALLINE MICRONISATE, PROCESS FOR THE MANUFACTURE THEREOF AND USE THEREOF FOR THE PREPARATION OF A MEDICAMENT**

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(30) **Foreign Application Priority Data**

Mar. 20, 2002 (DE) 102 12 264

(51) **Int. Cl.**
C07D 491/00 (2006.01)

(52) **U.S. Cl.** **514/291**; 546/91

(58) **Field of Classification Search** 546/91; 514/291

See application file for complete search history.

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(57) **ABSTRACT**

The invention relates to a crystalline micronisate of (1α,2β,4β,5α,7β)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane-bromide, processes for preparing it and its use for preparing a pharmaceutical composition, particularly for preparing a pharmaceutical composition with an anticholinergic activity.

9 Claims, No Drawings

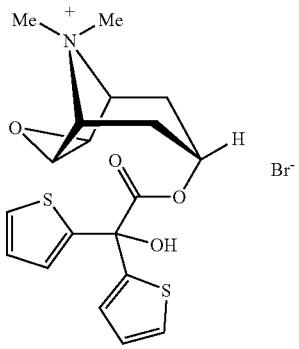
CRYSTALLINE MICRONISATE, PROCESS FOR THE MANUFACTURE THEREOF AND USE THEREOF FOR THE PREPARATION OF A MEDICAMENT

The invention relates to a crystalline micronisate of (1α,2β,4β,5α,7β)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane-bromide, processes for preparing it and its use for preparing a pharmaceutical composition, particularly for preparing a pharmaceutical composition with an anticholinergic activity.

BACKGROUND OF THE INVENTION

The compound (1α,2β,4β,5α,7β)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane-bromide, is known from European Patent Application EP 418 716 A1 and has the following chemical structure:

(I)



The compound has valuable pharmacological properties and is known by the name tiotropium bromide (BA679). Tiotropium bromide is a highly effective anticholinergic and can therefore provide therapeutic benefit in the treatment of asthma or COPD (chronic obstructive pulmonary disease).

Tiotropium bromide is preferably administered by inhalation. Suitable inhalable powders packed into appropriate capsules and administered by suitable powder inhalers may be used. Alternatively, it may be administered by the use of suitable inhalable aerosols. These also include powdered inhalable aerosols which contain, for example, HFA134a, HFA227 or mixtures thereof as propellant gas.

In view of the administration of tiotropium bromide by inhalation it is necessary to provide the active substance in a finely divided (or micronised) form. Preferably, the active substance has an average particles size of 0.5 to 10 μm, preferably from 1 to 6 μm, most preferably from 1.5 to 5 μm.

The above particles sizes are generally achieved by grinding (so-called micronisation) of the active substance. As breakdown of the pharmaceutically active substance must be prevented as far as possible as a side-effect of the micronisation, in spite of the hard conditions required for the process, high stability of the active substance during the grinding process is absolutely essential. It should be borne in mind that in some cases, during the grinding process, changes may occur to the solid properties of the active substance, which may influence the pharmacological properties of the formulation which is to be inhaled.

Methods of micronising pharmaceutically active substances are known as such in the prior art. The aim of the present invention is to provide a method which makes micronised tiotropium bromide available in a form which satisfies the stringent requirements imposed on an active substance intended for inhalation and thus takes account of the specific properties of tiotropium bromide.

DETAILED DESCRIPTION OF THE INVENTION

It has been found that, depending on the choice of conditions which can be used when purifying the crude product obtained after industrial manufacture, tiotropium bromide occurs in various crystalline modifications, so-called polymorphs.

It has also been found that these different modifications can be deliberately produced by selecting the solvents used for the crystallisation as well as by a suitable choice of the process conditions used in the crystallisation process.

For the purposes of the present invention, namely to provide tiotropium bromide in a micronised form suitable for inhalation, it has proved suitable to use the crystalline monohydrate of tiotropium bromide, which can be obtained in crystalline form by choosing specific reaction conditions.

In order to prepare this crystalline monohydrate, it is necessary to take up tiotropium bromide which has been obtained, for example, according to the instructions disclosed in EP 418 716 A1, in water, heat it, purify it with activated charcoal and after removing the activated charcoal slowly crystallise out the tiotropium bromide monohydrate by slow cooling. The method described below is preferably used according to the invention.

In a suitably dimensioned reaction vessel the solvent is mixed with tiotropium bromide, which has been obtained for example according to the method disclosed in EP 418 716 A1.

0.4 to 1.5 kg, preferably 0.6 to 1 kg, most preferably about 0.8 kg of water are used as solvent per mole of tiotropium bromide used. The mixture obtained is heated with stirring, preferably to more than 50° C., most preferably to more than 60° C. The maximum temperature which can be selected will be determined by the boiling point of the solvent used, i.e. water. Preferably the mixture is heated to a range from 80–90° C.

Activated charcoal, dry or moistened with water, is added to this solution. Preferably, 10 to 50 g, more preferably 15 to 35 g, most preferably about 25 g of activated charcoal are put in per mole of tiotropium bromide used. If desired, the activated charcoal is suspended in water before being added to the solution containing the tiotropium bromide. 70 to 200 g, preferably 100 to 160 g, most preferably about 135 g water are used to suspend the activated charcoal, per mole of tiotropium bromide used. If the activated charcoal is suspended in water prior to being added to the solution containing the tiotropium bromide, it is advisable to rinse with the same amount of water.

After the activated charcoal has been added, stirring is continued at constant temperature for between 5 and 60 minutes, preferably between 10 and 30 minutes, most preferably about 15 minutes, and the mixture obtained is filtered to remove the activated charcoal. The filter is then rinsed with water. 140 to 400 g, preferably 200 to 320 g, most preferably about 270 g of water are used for this, per mole of tiotropium bromide used.

The filtrate is then slowly cooled, preferably to a temperature of 20–25° C. The cooling is preferably carried out at a cooling rate of 1 to 10° C. per 10 to 30 minutes, preferably 2 to 8° C. per 10 to 30 minutes, more preferably

3 to 5° C. per 10 to 20 minutes, most preferably 3 to 5° C. roughly per 20 minutes. If desired, the cooling to 20 to 25° C. may be followed by further cooling to below 20° C., most preferably to 10 to 15° C.

Once the filtrate has cooled, it is stirred for between 20 minutes and 3 hours, preferably between 40 minutes and 2 hours, most preferably about one hour, to complete the crystallisation.

The crystals formed are finally isolated by filtering or suction filtering the solvent. If it proves necessary to subject the crystals obtained to another washing step, it is advisable to use water or acetone as the washing solvent. 0.1 to 1.0 l, preferably 0.2 to 0.5 l, most preferably about 0.3 l solvent are used, per mole of tiotropium bromide, to wash the tiotropium bromide monohydrate crystals obtained. If desired the washing step may be repeated.

The product obtained is dried in vacuo or using circulating hot air until a water content of 2.5–4.0% is obtained.

The resulting crystalline tiotropium bromide monohydrate is used in the grinding process (micronisation) described below. This process may be carried out using conventional mills. Preferably, the micronisation is carried out with the exclusion of moisture, more preferably, using a corresponding inert gas such as nitrogen, for example. It has proved particularly preferable to use air jet mills in which the material is comminuted by the impact of the particles on one another and on the walls of the grinding container. According to the invention, nitrogen is preferably used as the grinding gas. The material for grinding is conveyed by the grinding gas under specific pressures (grinding pressure). Within the scope of the present invention, the grinding pressure is usually set to a value between about 2 and 8 bar, preferably between about 3 and 7 bar, most preferably between about 3.5 and 6.5 bar. The material for grinding is fed into the air jet mill by means of the feed gas under specific pressures (feed pressure). Within the scope of the present invention a feed pressure of between about 2 and 8 bar, preferably between about 3 and 7 bar and most preferably between about 3.5 and 6 bar has proved satisfactory. The feed gas used is also preferably an inert gas, most preferably nitrogen again. The material to be ground (crystalline tiotropium bromide monohydrate) may be fed in at a rate of about 5–35 g/min, preferably at about 10–30 g/min.

For example, without restricting the subject of the invention thereto, the following apparatus has proved suitable as a possible embodiment of an air jet mill: a 2-inch Microniser with grinding ring, 0.8 mm bore, made by Messrs Sturtevant Inc., 348 Circuit Street, Hanover, Mass. 02239, USA. Using the apparatus, the grinding process is preferably carried out with the following grinding parameters: grinding pressure: about 4.5–6.5 bar; feed pressure: about 4.5–6.5 bar; supply of grinding material: about 17–21 g/min.

The ground material thus obtained is then further processed under the following specific conditions. The micronisate is exposed to a water vapour at a relative humidity of at least 40% at a temperature of 15–40° C., preferably 20–35° C., most preferably 25–30° C. Preferably, the humidity is set to a value of 50–95% r. h., preferably 60–90% r.h., most preferably 70–80% r.h. By relative humidity (r.h.) is meant, within the scope of the present invention, the quotient of the partial steam pressure and the steam pressure of the water at the temperature in question. Preferably, the micronisate obtained from the grinding process described above is subjected to the chamber conditions mentioned above for a period of at least 6 hours. Preferably, however, the micronisate is subjected to the chamber conditions mentioned above for about 12 to 48 hours, preferably about 18 to 36 hours, more preferably about 20 to 28 hours.

In one aspect the invention relates to tiotropium bromide micronisate which may be obtained by the process described above.

The micronisate of tiotropium bromide obtainable by the above method has a characteristic particle size X_{50} of between 1.0 μm and 3.5 μm, preferably between 1.1 μm and 3.3 μm, most preferably between 1.2 μm and 3.0 μm and $Q_{(5.8)}$ of more than 60%, preferably more than 70%, most preferably more than 80%. The characteristic value X_{50} denotes the median value of the particle size below which 50% of the particles fall, with regard to the distribution by volume of the individual particles. The characteristic value $Q_{(5.8)}$ corresponds to the quantity of particles below 5.8 μm , based on the volume distribution of the particles. The particle sizes were determined within the scope of the present invention by laser diffraction (Fraunhofer diffraction). More detailed information on this subject can be found in the experimental descriptions of the invention.

Also characteristic of the tiotropium micronisate according to the invention which was prepared by the above process are Specific Surface Area values in the range between 2 m^2/g and 5 m^2/g, more particularly between 2.5 m^2/g and 4.5 m^2/g and most outstandingly between 3.0 m^2/g and 4.0 m^2/g.

Carrying out the process according to the invention leads to the micronisate of tiotropium bromide according to the invention which is characterised by specific enthalpies of solution. These preferably have a value of more than 65 Ws/g, preferably more than 71 Ws/g. Most preferably the heat of solution of the micronisate according to the invention is in excess of 74 Ws/g.

Detailed information on determining the enthalpies of solution can be found in the experimental descriptions of the invention.

The tiotropium bromide micronisate which may be obtained using the above process is further characterised in that the water content of the micronisate is between about 1% and about 4.5%, preferably between about 1.4% and 4.2%, more preferably between about 2.4% and 4.1%. Particularly preferred tiotropium bromide micronisate according to the invention is characterised in that the water content of the micronisate is between about 2.6% and about 4.0%, most preferably between about 2.8% and 3.9%, particularly between about 2.9% and 3.8%.

One aspect of the present invention therefore relates to tiotropium bromide micronisate which has the above characteristics.

Within the scope of the present invention, unless otherwise stated, any reference to tiotropium bromide micronisate is to be taken as a reference to the crystalline micronisate of tiotropium bromide which has the above characteristics and which can be obtained by the method according to the invention as described above (micronisation followed by further treatment in accordance with the parameters described above).

In another aspect the present invention relates to the use of the tiotropium bromide micronisate according to the invention as a pharmaceutical composition in view of the pharmaceutical efficacy of the micronisate according to the invention.

In another aspect the present invention relates to inhalable powders characterised in that they contain tiotropium bromide micronisate according to the invention.

In view of the anticholinergic effects of tiotropium bromide a further aspect of the present invention relates to the

use of the tiotropium bromide micronisate according to the invention for preparing a pharmaceutical composition for treating diseases in which the use of an anticholinergic agent may have a therapeutic benefit. It is preferably used for preparing a pharmaceutical composition for treating asthma or COPD.

The tiotropium bromide micronisate which may be obtained by the process according to the invention is exceptionally suitable for the preparation of pharmaceutical formulations. It may be used particularly for preparing inhalable powders.

Accordingly, the present invention relates to inhalable powders containing at least about 0.03%, preferably less than 5%, more preferably less than 3% of the tiotropium bromide micronisate obtainable by the process described above in admixture with a physiologically acceptable excipient, characterised in that the excipient consists of a mixture of coarser excipient with an average particle size of 15 to 80 μm and finer excipient with an average particle size of 1 to 9 μm, the proportion of finer excipient in the total amount of excipient being from 1 to 20%.

The percentages specified are percent by weight.

According to the invention, inhalable powders are preferred which contain about 0.05 to about 1%, preferably about 0.1 to about 0.8%, more preferably about 0.2 to about 0.5% tiotropium bromide micronisate, which may be obtained by the method described above and has the characteristics of the micronisate which may be obtained according to the invention.

The inhalable powders containing the micronisate according to the invention are preferably characterised in that the excipient consists of a mixture of coarser excipient with an average particle size of 17 to 50 μm, more preferably 20 to 30 μm and finer excipient with an average particle size of 2 to 8 μm, more preferably 3 to 7 μm. The average particle size here denotes the 50% value from the volume distribution measured by laser diffraction by the dry dispersion method. Preferred powders for inhalation are those wherein the proportion of finer excipient in the total amount of excipient is from 3 to 15%, more preferably 5 to 10%.

Where the present invention refers to a mixture, this always means a mixture obtained by mixing together components which have previously been clearly defined. Accordingly an excipient mixture of coarser and finer ingredients can only refer to mixtures obtained by mixing a coarser excipient component with a finer one.

The coarser and finer excipient fractions may consist of the same chemical substance or chemically different substances, while inhalable powders in which the coarser excipient fraction and the finer excipient fraction consist of the same chemical compound are preferred.

Examples of physiologically acceptable excipients which may be used to prepare the inhalable powders according to the invention include, for example, monosaccharides (e.g. glucose or arabinose), disaccharides (e.g. lactose, saccharose, maltose or trehalose), oligo- and polysaccharides (e.g. dextrane), polyalcohols (e.g. sorbitol, mannitol, xylitol), salts (e.g. sodium chloride, calcium carbonate) or mixtures of these excipients with one another. Preferably, mono- or disaccharides are used, while the use of lactose, glucose or trehalose is preferred, preferably lactose or glucose, particularly, but not exclusively, in the form of their hydrates. For the purposes of the invention, lactose is the particularly preferred excipient, while lactose monohydrate is most particularly preferred.

The inhalable powders containing the micronisate according to the invention may for example be administered using inhalers which meter a single dose from a reservoir by means of a measuring chamber (e.g. according to U.S. Pat. No. 4,570,630A) or by other means (e.g. according to DE 36 25 685 A). Preferably, however, the inhalable powders are packed into capsules, which are used in inhalers such as those described in WO 94/28958, for example. If the inhalable powder according to the invention is to be packed into capsules or other packages which provide single doses in accordance with the preferred application mentioned above, it is advisable to fill the capsules with amounts of from 1 to 15 mg, preferably 3 to 10 mg, most preferably from 4 to 6 mg of inhalable powder per capsule.

The inhalable powders containing the tiotropium bromide micronisate according to the invention are characterised by a high degree of homogeneity in terms of the accuracy of measuring a single dose. This is in the range from <8%, preferably <6%, most preferably <4%.

The inhalable powders containing the tiotropium bromide micronisate according to the invention may be obtained by the method described below.

After the starting materials have been weighed out, first of all the excipient mixture is prepared from the defined fractions of coarser excipient and finer excipient. Then the inhalable powders according to the invention are prepared from the excipient mixture and the active substance. If the inhalable powder is to be administered using capsules containing powders in suitable inhalers the preparation of the inhalable powder is followed by the manufacture of the capsules containing the powder.

In the preparation methods described below, the abovementioned components are used in the proportions by weight described in the abovementioned compositions of the inhalable powders according to the invention. The inhalable powders according to the invention are prepared by mixing the coarser excipient fractions with the finer excipient fractions and then mixing the resulting excipient mixture with the active substance. To prepare the excipient mixture the coarser and finer excipient fractions are placed in a suitable mixing container. The two components are preferably added through a screening granulator with a mesh size of 0.1 to 2 mm, most preferably 0.3 to 1 mm, even more preferably 0.3 to 0.6 mm. Preferably, the coarser excipient is put in first, and then the finer and coarser excipient are added alternately. It is particularly preferred when preparing the excipient mixture to screen in the two components in alternate layers. Preferably, the two components are screened alternately, in 15 to 45, most preferably 20 to 40 layers each. The two excipients may be mixed while the two components are being added. Preferably, however, the two ingredients are not mixed until after they have been screened in layers.

After the preparation of the excipient mixture, this and the active substance, the tiotropium bromide micronisate according to the invention, are placed in a suitable mixing container. The active substance used has an average particle size of 0.5 to 10 μm, preferably 1 to 6 μm, more preferably 1.5 to 5 μm. The two components are preferably added through a screening granulator with a mesh size of 0.1 to 2 mm, most preferably 0.3 to 1 mm, even more preferably 0.3 to 0.6 mm.

Preferably, the excipient mixture is put in and then the active substance is added to the mixing container. Preferably, in this mixing process, the two components are added in batches. In the preparation of the excipient mixture it is particularly preferred to screen in the two components alternately in 25 to 65, preferably 30 to 60 layers each. The

operation of mixing the excipient mixture with the active substance may be carried out while the two components are being added.

Preferably, however, the two ingredients are not mixed until after they have been screened in layers.

The powder mixture obtained by if desired by passed through a screening granulator once more or repeatedly and then subjected to another mixing process.

In another aspect the present invention relates to an inhalable powder which contains the tiotropium bromide micronisate according to the invention and may be obtained by the methods described above.

The following detailed experimental descriptions serve to illustrate the present invention more fully without restricting the scope of the invention to the embodiments described by way of example hereinafter.

Experimental Section

A) Preparation of Crystalline Tiotropium Bromide Monohydrate

15.0 kg of tiotropium bromide, which may be prepared by the experimental procedure disclosed in European Patent Application EP 418 716 A1, are added to 25.7 kg of water in a suitable reaction vessel. The mixture is heated to 80–90° C. and stirred at constant temperature until a clear solution is formed. Activated charcoal (0.8 kg), moistened with water, is suspended in 4.4 kg of water, this mixture is added to the solution containing the tiotropium bromide and rinsed with 4.3 kg of water. The mixture thus obtained is stirred for at least 15 min at 80–90° C. and then filtered through a heated filter into an apparatus which has been preheated to an outer temperature of 70° C. The filter is rinsed with 8.6 kg of water. The contents of the apparatus are cooled at 3–5° C. every 20 minutes to a temperature of 20–25° C. The apparatus is further cooled to 10–15° C. using cold water and crystallisation is completed by stirring for at least one hour. The crystals are isolated using a suction drier, the crystal slurry isolated is washed with 9 litres of cold water (10–15° C.) and cold acetone (10–15° C.). The crystals obtained are dried in a nitrogen current at 25° C. over 2 hours.

Yield: 13.4 kg of tiotropium bromide monohydrate (86% of theory)

Characterisation of Crystalline Tiotropium Bromide Monohydrate

The tiotropium bromide monohydrate obtainable using the method described above was investigated by DSC (Differential Scanning Calorimetry). The DSC diagram shows two characteristic signals. The first, relatively broad, endothermic signal between 50–120° C. can be attributed to the dehydration of the tiotropium bromide monohydrate into the anhydrous form. The second, relatively sharp, endothermic peak at 230±5° C. can be put down to the melting of the substance. This data was obtained using a Mettler DSC 821 and evaluated using the Mettler STAR software package. The data was recorded at a heating rate of 10 K/min.

Since the substance melts with decomposition (=incongruent melting process), the melting point observed depends to a great extent on the heating rate. At lower heating rates, the melting/decomposition process is observed at significantly lower temperatures, e.g. at 220±5° C. at a heating rate of 3 K/min. It is also possible that the melting peak may be split. The split is all the more apparent the lower the heating rate in the DSC experiment.

The crystalline tiotropium bromide monohydrate was characterised by IR spectroscopy. The data was obtained using a Nicolet FTIR spectrometer and evaluated with the Nicolet OMNIC software package, version 3.1. The measurement was carried out with 2.5 μmol of tiotropium bromide monohydrate in 300 mg of KBr. Table 1 shows some of the essential bands of the IR spectrum.

TABLE 1

Attribution of specific bands

Wave number (cm^{-1})	Attribution	Type of oscillation
3570, 3410	O—H	elongated oscillation
3105	Aryl C—H	elongated oscillation
1730	C═O	elongated oscillation
1260	Epoxide C—O	elongated oscillation
1035	Ester C—OC	elongated oscillation
720	Thiophene	cyclic oscillation

The crystalline tiotropium bromide monohydrate was characterised by X-ray structural analysis. The measurements of X-ray diffraction intensity were carried out on an AFC7R-4-circuit diffractometer (Rigaku) using monochromatic copper K_α radiation. The structural resolution and refinement of the crystal structure were obtained by direct methods (SHELXS86 Program) and FMLQ-refinement (TeXsan Program). Experimental details of the crystalline structure, structural resolution and refinement are collected in Table 2.

TABLE 2

Experimental data on the analysis of the crystalline structure of tiotropium bromide monohydrate.

A. Crystal data	
Empirical formula	$[C_{19}H_{22}NO_4S_2]$ $Br.H_2O$
Weight of formula	472.43 + 18.00
colour and shape of crystals	colourless, prismatic
dimensions of crystals	0.2 × 0.3 × 0.3 mm
crystal system	monoclinic
lattice type	primitive
space group	P $2_1/n$
lattice constants	a = 18.0774 Å, b = 11.9711 Å c = 9.9321 Å β = 102.691° V = 2096.96 $Å^3$
formula units per elementary cell	4
B. Measurements of intensity	
Diffractometer	Rigaku AFC7R
X-ray generator	Rigaku RU200
wavelength	λ = 1.54178Å (monochromatic copper K_α-radiation)
current, voltage	50 kV, 100 mA
take-off angle	6°
crystal assembly	steam-saturated capillary
crystal-detector gap	235 mm
detector opening	3.0 mm vertical and horizontal
temperature	18°
determining the lattice constants	25 reflexes (50.8° < 2Θ < 56.2°)
Scan Type	ω - 2Θ
Scan speed	8.0 32.0°/min in ω
Scan width	(0.58 + 0.30 tan Θ)°
2Θ max	120°
measured	5193
independent reflexes	3281 (R_{int} = 0.051)
corrections	Lorentz polarisation Absorption (Transmission factors 0.56–1.00) crystal decay 10.47% decay

TABLE 2-continued

Experimental data on the analysis of the crystalline structure of tiotropium bromide monohydrate.

C. Refinement	
Reflections (I > 3σI)	1978
Variable	254
ratio of reflections/parameters	7.8
R-values: R, Rw	0.062, 0.066

The X-ray structural analysis carried out showed that crystalline tiotropium bromide hydrate has a simple monoclinic cell with the following dimensions: a=18.0774 Å, b=11.9711 Å, c=9.9321 Å, β=102.691°, V=2096.96 Å^3.

The atomic coordinates described in Table 3 were determined by the above X-ray structural analysis:

TABLE 3

	Coordinates			
Atom	x	y	z	u (eq)
Br(1)	0.63938(7)	0.0490(1)	0.2651(1)	0.0696(4)
S(1)	0.2807(2)	0.8774(3)	0.1219(3)	0.086(1)
S(2)	0.4555(3)	0.6370(4)	0.4214(5)	0.141(2)
O(1)	0.2185(4)	0.7372(6)	0.4365(8)	0.079(3)
O(2)	0.3162(4)	0.6363(8)	0.5349(9)	0.106(3)
O(3)	0.3188(4)	0.9012(5)	0.4097(6)	0.058(2)
O(4)	0.0416(4)	0.9429(6)	0.3390(8)	0.085(3)
O(5)	0.8185(5)	0.0004(8)	0.2629(9)	0.106(3)
N(1)	0.0111(4)	0.7607(6)	0.4752(7)	0.052(2)
C(1)	0.2895(5)	0.7107(9)	0.4632(9)	0.048(3)
C(2)	0.3330(5)	0.7876(8)	0.3826(8)	0.048(3)
C(3)	0.3004(5)	0.7672(8)	0.2296(8)	0.046(3)
C(4)	0.4173(5)	0.7650(8)	0.4148(8)	0.052(3)
C(5)	0.1635(5)	0.6746(9)	0.497(1)	0.062(3)
C(6)	0.1435(5)	0.7488(9)	0.6085(9)	0.057(3)
C(7)	0.0989(6)	0.6415(8)	0.378(1)	0.059(3)
C(8)	0.0382(5)	0.7325(9)	0.3439(9)	0.056(3)
C(9)	0.0761(6)	0.840(1)	0.315(1)	0.064(3)
C(10)	0.1014(6)	0.8974(8)	0.443(1)	0.060(3)
C(11)	0.0785(5)	0.8286(8)	0.5540(9)	0.053(3)
C(12)	−0.0632(6)	0.826(1)	0.444(1)	0.086(4)
C(13)	−0.0063(6)	0.6595(9)	0.554(1)	0.062(3)
C(14)	0.4747(4)	0.8652(9)	0.430(1)	0.030(2)
C(15)	0.2839(5)	0.6644(9)	0.1629(9)	0.055(3)
C(16)	0.528(2)	0.818(2)	0.445(2)	0.22(1)
C(17)	0.5445(5)	0.702(2)	0.441(1)	0.144(6)
C(18)	0.2552(6)	0.684(1)	0.019(1)	0.079(4)
C(19)	0.2507(6)	0.792(1)	−0.016(1)	0.080(4)
H(1)	−0.0767	0.8453	0.5286	0.102
H(2)	−0.0572	0.8919	0.3949	0.102
H(3)	−0.1021	0.7810	0.3906	0.102
H(4)	−0.0210	0.6826	0.6359	0.073
H(5)	−0.0463	0.6178	0.4982	0.073
H(6)	0.0377	0.6134	0.5781	0.073
H(7)	0.1300	0.7026	0.6770	0.069
H(8)	0.1873	0.7915	0.6490	0.069
H(9)	0.1190	0.6284	0.2985	0.069
H(10)	0.0762	0.5750	0.4016	0.069
H(11)	0.1873	0.6082	0.5393	0.073
H(12)	−0.0025	0.7116	0.2699	0.066
H(13)	0.1084	0.8383	0.2506	0.075
H(14)	0.1498	0.9329	0.4626	0.071
H(15)	0.0658	0.8734	0.6250	0.063
H(16)	0.2906	0.5927	0.2065	0.065
H(17)	0.2406	0.6258	−0.0469	0.094
H(18)	0.2328	0.8191	−0.1075	0.097
H(19)	0.4649	0.9443	0.4254	0.037
H(20)	0.5729	0.8656	0.4660	0.268
H(21)	0.5930	0.6651	0.4477	0.165
H(22)	0.8192	−0.0610	0.1619	0.084
H(23)	0.7603	0.0105	0.2412	0.084

x, y, z: fractional coordinates;
U (eq) mean quadratic amplitude of atomic movement in the crystal

C) Preparation of the Tiotropium Bromide Micronisate According to the Invention

The tiotropium bromide monohydrate obtainable by the process described above is micronised with an air jet mill of the 2-inch microniser type with grinding ring, 0.8 mm bore, made by Messrs Sturtevant Inc., 348 Circuit Street, Hanover, Mass. 02239, USA. Using nitrogen as the grinding gas the following grinding parameters are set, for example:

grinding pressure: 5.5 bar; feed pressure: 5.5 bar; supply (of crystalline monohydrate) or flow speed: 19 g/min.

The ground material obtained is then spread out on sheet metal racks in a layer thickness of about 1 cm and subjected to the following climatic conditions for 24–24.5 hours: temperature: 25–30° C.; relative humidity: 70–80%.

D) Measuring Techniques for Characterizing the Tiotropium Bromide Micronisate According to the Invention

The parameters mentioned in the description which characterise the tiotropium bromide micronisate according to the invention were obtained by the measuring techniques and methods described below:

D.1) Determining the Water Content According to Karl-Fischer (Tiotropium Bromide):

Titrator	Type Mettler DL 18 with
Calibrating substance:	disodium tartrate dihydrate
Titrant:	Hydranal-Titrant 5 (Riedel-deHaen)
Solvent:	Hydranal Solvent (Riedel-deHaen)
Measuring method:	
Sample amount:	50–100 mg
Stirring time:	60 s

The stirring time before the start of titration ensures that the sample is fully dissolved.

The water content of the sample is calculated by the apparatus in percent and indicated.

D.2) Determining Particle Size by Laser Diffraction (Fraunhofer Diffraction)

Measuring Method:

To determine the particle size the powder is fed into a laser diffraction spectrometer by means of a dispersing unit.

Measuring equipment:	Laser diffraction spectrometer (HELOS), Messrs. Sympatec
Software:	WINDOX Version 3.3/REL 1
Dispersing unit:	RODOS/Dispersing pressure: 3 bar
Equipment parameters:	
Detector:	Multielement detector (31 semicircular rings)
Method:	Air dispersal
Focal length:	100 mm
Measuring range:	RS 0.5/0.9–175 µm
Evaluation mode:	HRLD-Mode
Rodos Dry Disperser:	
Injector:	4 mm
Pressure:	3 bar
Injector vacuum:	maximum (~100 mbar)
Suction:	Nilfilsk (advance 5 s)
Metering device:	Vibri
Feed rate:	40% (manually increased to 100%)
Bed height:	2 mm
Speed of rotation:	0

D.3) Determining the Specific Surface Area (1-Bundle B.E.T. Method):

Measuring Method:

The specific surface is determined by exposing the powder sample to a nitrogen/helium atmosphere at different pressures. Cooling the sample causes the nitrogen molecules to be condensed on the surface of the particles. The quantity of condensed nitrogen is determined by means of the change in the thermal heat conductivity of the nitrogen/helium mixture and the surface of the sample is calculated by means of the surface nitrogen requirement. Using this value and the weight of the sample, the specific surface is calculated.

Equipment and materials:	
Measuring equipment:	Monosorb, Messrs Quantachrome
Heater:	Monotektor, Messrs Quantachrome
Measuring and drying gas:	nitrogen (5.0)/helium (4.6) 70/30, Messer Griesheim
Adsorbate:	30% nitrogen in helium
Coolant:	liquid nitrogen
Measuring cell:	with capillary tube, Messrs. W. Pabisch GmbH&Co.KG
Calibration peak;	1000 µl, Fa. Precision Sampling Corp.
Analytical scale:	R 160 P, Fa. Satorius

Calculating the Specific Surface:

The measured values are indicated by the equipment in [m^2] and are usually converted into [cm^2/g] on weighing (dry mass):

$$A_{spez} = \frac{MW * 10000}{m_{tr}}$$

A_{spez} =	specific surface [cm^2/g]
MW =	Measured value [m^2]
m_{tr} =	dry mass [g]
10000 =	conversion factor [cm^2/m^2]

D.4) Determining the Heat of Solution (Enthalpy of Solution) E_c:

The solution enthalpy is determined using a solution calorimeter 2225 Precision Solution Calorimeter made by Messrs. Thermometric.

The heat of solution is calculated by means of the change in temperature occurring (as a result of the dissolving process) and the system-related change in temperature calculated from the base line.

Before and after the ampoule is broken, electrical calibration is carried out with an integrated heating resistor of a precisely known power. A known heat output is delivered to the system over a set period and the jump in temperature is determined.

Method and equipment parameters:	
Solution calorimeter:	2225 Precision Solution Calorimeter, Messrs Thermometric
Reaction cell:	100 ml
Thermistor resistance:	30.0 kΩ (at 25° C.)
Speed of stirrer:	600 U/min
Thermostat:	Thermostat of 2277 Thermal Activity Monitor TAM, Messrs Thermometric

-continued

Method and equipment parameters:	
Temperature:	25° C. ± 0.0001° C. (over 24 h)
Measuring ampoules:	Crushing ampoules 1 ml, Messrs Thermometric
Seal:	Silicon stopper and beeswax, Messrs. Thermometric
Weight:	40 to 50 mg
Solvent:	Chemically pure water
Volume of solvent:	100 ml
Bath temperature:	25° C.
Temperature resolution:	High
Starting temperature:	−40 mK (± 10 mK) temperature-offset
Interface:	2280-002 TAM accessory interface 50 Hz, Messrs Thermometric
Software:	SolCal V 1.1 for WINDOWS
Evaluation:	Automatic evaluation with Menu point CALCULATION/ANALYSE EXPERIMENT. (Dynamics of base line; calibration after breakage of ampoule).

Electrical Calibration:

The electrical calibration takes place during the measurement, once before and once after the breakage of the ampoule. The calibration after the breakage of the ampoule is used for the evaluation.

Amount of heat:	2.5 Ws
Heating power:	250 mW
Heating time:	10 s
Duration of base lines:	5 min (before and after heating)

Evaluation for Tiotropium Bromide Micronisate:

As the mass of the tiotropium bromide micronisate weighed out has to be corrected by the water content of the material, the unsealed ampoules together with about 1 g of the test substance are left to stand open for at least 4 hours. After this equilibration time the ampoules are sealed with the silicon stoppers and the water content of the bulk sample is determined by Karl-Fischer titration. The filled and sealed ampoule is weighed on the scale again. The sample mass is corrected according to the following formula:

$$m_c = \left(\frac{100\% - x}{100\%}\right) \cdot m_w$$

where:

m_c is the corrected mass

m_w is the sample mass weighed into the ampoule

x is the water content in percent (determined in parallel by Karl-Fischer titration)

The corrected mass m_c determined by this calculation is used as the input value (=weight) to calculate the solution enthalpy measured.

E) Preparation of the Powder Formulation Containing the Tiotropium Bromide Micronisate According to the Invention

In the Examples which follow, lactose-monohydrate (200M) is used as the coarser excipient. It may be obtained,

for example, from Messrs DMV International, 5460 Veghel/NL under the product name Pharmatose 200M.

In the Examples which follow, lactose-monohydrate (5μ) is used as the finer excipient. It may be obtained from lactose-monohydrate 200M by conventional methods (micronising). Lactose-monohydrate 200M may be obtained, for example, from Messrs DMV International, 5460 Veghel/NL under the product name Pharmatose 200M.

Apparatus

The following machines and equipment, for example, may be used to prepare the inhalable powders containing the tiotropium bromide micronisate according to the invention:

Mixing container or powder mixer: Gyrowheel mixer 200 L; type: DFW80N-4; made by: Messrs Engelsmann, D-67059 Ludwigshafen.

Granulating sieve: Quadro Comil; type: 197-S; made by: Messrs Joisten & Kettenbaum, D-51429 Bergisch-Gladbach.

E.1) Preparation of the Excipient Mixture:

31.82 kg of lactose monohydrate for inhalation (200M) are used as the coarser excipient component. 1.68 kg of lactose monohydrate (5 μm) are used as the finer excipient component. In the resulting 33.5 kg of excipient mixture the proportion of the finer excipient component is 5%.

About 0.8 to 1.2 kg of lactose monohydrate for inhalation (200M) are added to a suitable mixing container through a suitable granulating sieve with a mesh size of 0.5 mm. Then alternate layers of lactose monohydrate (5 μm) in batches of about 0.05 to 0.07 kg and lactose monohydrate for inhalation (200M) in batches of 0.8 to 1.2 kg are sieved in. Lactose monohydrate for inhalation (200M) and lactose monohydrate (5 μm) are added in 31 and 30 layers, respectively (tolerance: ±6 layers).

The ingredients sieved in are then mixed together (mixing at 900 rpm).

E.2) Preparation of the Final Mixture

To prepare the final mixture, 32.87 kg of the excipient mixture (1.1) and about 0.13 kg of the tiotropium bromide micronisate according to the invention are used. The content of active substance in the resulting 33.0 kg of inhalable powder is 0.4%.

About 1.1 to 1.7 kg of excipient mixture (E.1) are added to a suitable mixing container through a suitable granulating sieve with a mesh size of 0.5 mm. Then alternate layers of tiotropium bromide micronisate in batches of about 0.003 kg and excipient mixture (E.1) in batches of 0.6 to 0.8 kg are sieved in. The excipient mixture and the active substance are added in 46 and 45 layers, respectively (tolerance: ±9 layers).

The ingredients are sieved and then mixed together.

The final mixture is passed twice more through a granulating sieve and then mixed (mixing at 900 rpm).

E.3) Inhalation Capsules:

Inhalation capsules having the following composition were produced using the mixture obtained according to E.2:

tiotropium bromide monohydrate:	0.0225 mg
lactose monohydrate (200 M):	5.2025 mg
lactose monohydrate (5 μm):	0.2750 mg
hard gelatine capsule:	49.0 mg
Total:	54.5 mg

Analogously to the method described in E.2 inhalation capsules of the following composition are obtained:

a)	tiotropium bromide monohydrate:	0.0225 mg
	lactose monohydrate (200 M):	4.9275 mg
	lactose monohydrate (5 μm):	0.5500 mg
	hard gelatine capsule:	49.0 mg
	Total:	54.5 mg
b)	tiotropium bromide monohydrate:	0.0225 mg
	lactose monohydrate (200 M):	5.2025 mg
	lactose monohydrate (5 μm):	0.2750 mg
	polyethylene capsule:	100.0 mg
	Total:	105.50 mg

F) Measuring Techniques for Determining the Particle Sizes of the Excipient Components used in E)

The average particle size of the various excipient ingredients of the formulation containing the tiotropium bromide micronisate according to the invention which may be prepared according to E) was determined as follows:

F.1) Determining the Particle Size of Finely Divided Lactose:

Measuring Equipment and Settings:

The equipment is operated according to the manufacturer's instructions.

Measuring equipment:	HELOS Laser-diffraction spectrometer, (SympaTec)
Dispersing unit:	RODOS dry disperser with suction funnel, (SympaTec)
Sample quantity:	from 100 mg
Product feed:	Vibri Vibrating channel, Messrs. Sympatec
Frequency of vibrating channel:	40 rising to 100%
Duration of sample feed:	1 to 15 sec. (in the case of 100 mg)
Focal length:	100 mm (measuring range: 0.9–175 μm)
Measuring time:	about 15 s (in the case of 100 mg)
Cycle time:	20 ms
Start/stop at:	1% on channel 28
Dispersing gas:	compressed air
Pressure:	3 bar
Vacuum:	maximum
Evaluation method:	HRLD

Sample Preparation/Product Feed:

At least 100 mg of the test substance are weighed onto a piece of card. Using another piece of card all the larger lumps are broken up. The powder is then sprinkled finely over the front half of the vibrating channel (starting about 1 cm from the front edge). After the start of the measurement the frequency of the vibrating channel is varied from about 40% up to 100% (towards the end of the measurement). The time taken to feed in the entire sample is 10 to 15 sec.

F.2) Determining the Particle Size of Lactose 200M:

Measuring Equipment and Settings:

The equipment is operated according to the manufacturer's instructions.

Measuring equipment:	Laser diffraction spectrometer (HELOS), Sympatec
Dispersing unit:	RODOS dry disperser with suction funnel, Sympatec

-continued

Sample quantity:	500 mg
Product feed:	VIBRI Vibrating channel, Messrs. Sympatec
Frequency of vibrating channel:	18 rising to 100%
Focal length (1):	200 mm (measuring range: 1.8–350 µm)
Focal length (2):	500 mm (measuring range: 4.5–875 µm)
Measuring time:	10 s
Cycle time:	10 ms
Start/stop at:	1% on channel 19
Pressure:	3 bar
Vacuum:	maximum
Evaluation method:	HRLD

Sample Preparation/Product Feed:

About 500 mg of the test substance are weighed onto a piece of card. Using another piece of card all the larger lumps are broken up. The powder is then transferred into the funnel of the vibrating channel. A gap of 1.2 to 1.4 mm is set between the vibrating channel and funnel. After the start of the measurement the amplitude setting of the vibrating channel is increased from 0 to 40% until a continuous flow of product is obtained. Then it is reduced to an amplitude of about 18%. Towards the end of the measurement the amplitude is increased to 100%.

What is claimed is:

1. Crystalline tiotropium bromide micronisate, characterised by a particle size X_{50} of between 1.0 µm and 3.5 µm at a $Q_{(5.8)}$ value of more than 60%, by a specific surface value in the range between 2 m^2/g and 5 m^2/g, by a specific heat of solution of more than 65 Ws/g and by a water content from about 1% to about 4.5%, wherein the crystalline tiotropium bromide micronisate is obtained from crystalline tiotropium bromide monohydrate, which crystalline tiotropium bromide monohydrate when thermally analysed by DSC has an endothermic maximum at 230±5° C. at a heating rate of 10K/min, has an IR spectrum which has bands inter alia at wavelengths 3570, 3410, 3105, 1730, 1260, 1035 and 720 cm^{-1} and which is characterised by a simple monoclinic cell with the following dimensions: a=18.0774 Å, b=11.9711 Å, c=9.9321 Å, β=102.691°, V=2096.96 $Å^3$.

2. The crystalline tiotropium bromide micronisate according to claim **1**, characterised in that the particle size X_{50} has a value of 1.1 µm to 3.3 µm, at a $Q_{(5.8)}$ value of more than 70%.

3. The crystalline tiotropium bromide micronisate according to one of claims **1** or **2**, characterised in that it has a specific surface value in the range from 2.5 m^2/g to 4.5 m^2/g.

4. The crystalline tiotropium bromide micronisate according claim **1**, characterised by a specific heat of solution of more than 71 Ws/g.

5. The crystalline tiotropium bromide micronisate according to claim **1**, characterised by a water content from about 1.4% to about 4.2%.

6. A process for preparing crystalline tiotropium bromide micronisate which comprises the steps of:

a) obtaining crystalline tiotropium bromide monohydrate, which crystalline tiotropium bromide monohydrate when thermally analysed by DSC has an endothermic maximum at 230±5° C. at a heating rate of 10K/min, has bands inter alia at wavelengths 3570, 3410, 3105, 1730, 1260, 1035 and 720 cm^{-1} and which is characterised by a simple monoclinic cell with the following dimensions: a=18.0774 Å, b=11.9711 Å, c=9.9321 Å, β=102.691°, V=2096.96 $Å^3$,

b) micronizing the crystalline tiotropium bromide monohydrate so obtained and,

c) exposing the resulting micronized crystalline tiotropium bromide at a temperature of about 15 to about 40° C. to water with a relative humidity of at least about 40% for a period of at least about 6 hours.

7. The process according to claim **6**, characterised in that the tiotropium bromide monohydrate is micronized under inert gas.

8. The process according to claim **6**, characterised in that the tiotropium bromide monohydrate is micronized using an air jet mill with the following grinding parameters:

grinding pressure:	about 2–about 8 bar;
feed pressure:	about 2–about 8 bar;
grinding gas/feed gas:	nitrogen;
product supply:	about 5–about 35 g/min.

9. The process according to claim **8**, characterised in that the micronized tiotropium bromide is exposed at a temperature of about 20—about 35° C. is exposed to water vapour at a relative humidity of about 50—about 95% for a period of about 12 to 48 hours.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,309,707 B2
APPLICATION NO. : 10/385175
DATED : December 17, 2007
INVENTOR(S) : Helmut Bender 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 15, Line 30:

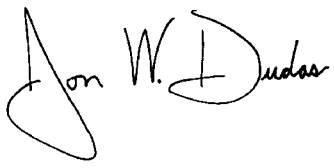
"Crystalline tiotropium bromide micronisate, characterized by a particle size X50 of between 1.0 µm and 3.5 µm at a Q(5.8) value of more than 60%,....."

Should read:

--Crystalline tiotropium bromide micronisate, characterized by a particle size X50 of between 1.0 µm and 3.5 µm, at a Q(5.8) value of more than 60%,.....--

Signed and Sealed this

Thirteenth Day of May, 2008



JON W. DUDAS
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,309,707 B2
APPLICATION NO. : 10/385175
DATED : December 18, 2007
INVENTOR(S) : Helmut Bender et al.

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In Column 15, Line 30:

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Should read:

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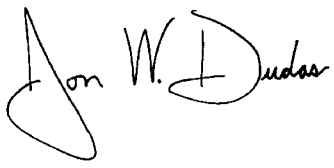
This certificate supersedes the Certificate of Correction issued May 13, 2008.

Signed and Sealed this

Seventeenth Day of June, 2008



JON W. DUDAS
Director of the United States Patent and Trademark Office

EXHIBIT E

US007642268B2

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

(10) **Patent No.: US 7,642,268 B2**
(45) **Date of Patent: *Jan. 5, 2010**

(54) **CRYSTALLINE MICRONISATE, PROCESS FOR THE MANUFACTURE THEREOF AND USE THEREOF FOR THE PREPARATION OF A MEDICAMENT**

(75) Inventors: **Helmut Bender**, Wiesbaden (DE); **Hagen Graebner**, Ingelheim (DE); **Konrad Schindler**, Ingelheim am Rhein (DE); **Michael Trunk**, Ingelheim (DE); **Michael Walz**, Bingen am Rhein (DE)

(73) Assignee: **Boehringer Ingelheim Pharma GmbH & Co. KG**, Ingelheim am Rhein (DE)

(*) 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.: **11/532,716**

(22) Filed: **Sep. 18, 2006**

(65) **Prior Publication Data**

US 2007/0015785 A1 Jan. 18, 2007

Related U.S. Application Data

(63) Continuation of application No. 10/385,175, filed on Mar. 10, 2003, now Pat. No. 7,309,707.

(60) Provisional application No. 60/413,129, filed on Sep. 24, 2002.

(30) **Foreign Application Priority Data**

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(51) **Int. Cl.**
C07D 491/08 (2006.01)
A61K 31/4745 (2006.01)

(52) **U.S. Cl.** **514/291**; 546/91

(58) **Field of Classification Search** 546/91; 514/291

See application file for complete search history.

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(57) **ABSTRACT**

The invention relates to a crystalline micronisate of (1 α,2β,4β,5α,7β)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane-bromide, processes for preparing it and its use for preparing a pharmaceutical composition, particularly for preparing a pharmaceutical composition with an anticholinergic activity.

9 Claims, No Drawings

CRYSTALLINE MICRONISATE, PROCESS FOR THE MANUFACTURE THEREOF AND USE THEREOF FOR THE PREPARATION OF A MEDICAMENT

RELATED APPLICATIONS

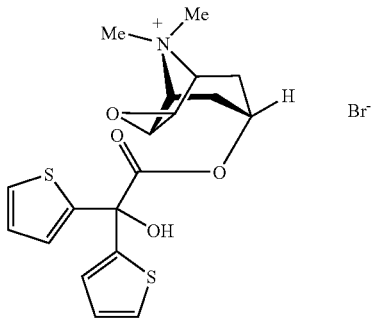
This application is a continuation of U.S. patent application Ser. No. 10/385,175, filed Mar. 10, 2003, now U.S. Pat. No. 7,309,707, which claims priority to U.S. Provisional Patent Application No. 60/413,129, filed Sep. 24, 2002, which claims priority to German Patent Application No. 102 12 264, filed Mar. 20, 2002, the contents of which are incorporated herein by reference in their entirety.

The invention relates to a crystalline micronisate of (1α, 2β,4β,5α,7β)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane-bromide, processes for preparing it and its use for preparing a pharmaceutical composition, particularly for preparing a pharmaceutical composition with an anticholinergic activity.

BACKGROUND OF THE INVENTION

The compound (1α,2β, 4β,5α,7β)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo [3.3.1.$0^{2,4}$]nonane-bromide, is known from European Patent Application EP 418 716 A1 and has the following chemical structure:

(I)



The compound has valuable pharmacological properties and is known by the name tiotropium bromide (BA679). Tiotropium bromide is a highly effective anticholinergic and can therefore provide therapeutic benefit in the treatment of asthma or COPD (chronic obstructive pulmonary disease).

Tiotropium bromide is preferably administered by inhalation. Suitable inhalable powders packed into appropriate capsules and administered by suitable powder inhalers may be used. Alternatively, it may be administered by the use of suitable inhalable aerosols. These also include powdered inhalable aerosols which contain, for example, HFA134a, HFA227 or mixtures thereof as propellant gas.

In view of the administration of tiotropium bromide by inhalation it is necessary to provide the active substance in a finely divided (or micronised) form. Preferably, the active substance has an average particles size of 0.5 to 10 μm, preferably from 1 to 6 μm, most preferably from 1.5 to 5 μm.

The above particles sizes are generally achieved by grinding (so-called micronisation) of the active substance. As breakdown of the pharmaceutically active substance must be prevented as far as possible as a side-effect of the micronisation, in spite of the hard conditions required for the process, high stability of the active substance during the grinding process is absolutely essential. It should be borne in mind that in some cases, during the grinding process, changes may occur to the solid properties of the active substance, which may influence the pharmacological properties of the formulation which is to be inhaled.

Methods of micronising pharmaceutically active substances are known as such in the prior art. The aim of the present invention is to provide a method which makes micronised tiotropium bromide available in a form which satisfies the stringent requirements imposed on an active substance intended for inhalation and thus takes account of the specific properties of tiotropium bromide.

DETAILED DESCRIPTION OF THE INVENTION

It has been found that, depending on the choice of conditions which can be used when purifying the crude product obtained after industrial manufacture, tiotropium bromide occurs in various crystalline modifications, so-called polymorphs.

It has also been found that these different modifications can be deliberately produced by selecting the solvents used for the crystallisation as well as by a suitable choice of the process conditions used in the crystallisation process.

For the purposes of the present invention, namely to provide tiotropium bromide in a micronised form suitable for inhalation, it has proved suitable to use the crystalline monohydrate of tiotropium bromide, which can be obtained in crystalline form by choosing specific reaction conditions.

In order to prepare this crystalline monohydrate, it is necessary to take up tiotropium bromide which has been obtained, for example, according to the instructions disclosed in EP 418 716 A1, in water, heat it, purify it with activated charcoal and after removing the activated charcoal slowly crystallise out the tiotropium bromide monohydrate by slow cooling. The method described below is preferably used according to the invention.

In a suitably dimensioned reaction vessel the solvent is mixed with tiotropium bromide, which has been obtained for example according to the method disclosed in EP 418 716 A1.

0.4 to 1.5 kg, preferably 0.6 to 1 kg, most preferably about 0.8 kg of water are used as solvent per mole of tiotropium bromide used. The mixture obtained is heated with stirring, preferably to more than 50° C., most preferably to more than 60° C. The maximum temperature which can be selected will be determined by the boiling point of the solvent used, i.e. water. Preferably the mixture is heated to a range from 80-90° C.

Activated charcoal, dry or moistened with water, is added to this solution. Preferably, 10 to 50 g, more preferably 15 to 35 g, most preferably about 25 g of activated charcoal are put in per mole of tiotropium bromide used. If desired, the activated charcoal is suspended in water before being added to the solution containing the tiotropium bromide. 70 to 200 g, preferably 100 to 160 g, most preferably about 135 g water are used to suspend the activated charcoal, per mole of tiotropium bromide used. If the activated charcoal is suspended in water prior to being added to the solution containing the tiotropium bromide, it is advisable to rinse with the same amount of water.

After the activated charcoal has been added, stirring is continued at constant temperature for between 5 and 60 minutes, preferably between 10 and 30 minutes, most preferably about 15 minutes, and the mixture obtained is filtered to remove the activated charcoal. The filter is then rinsed with

water. 140 to 400 g, preferably 200 to 320 g, most preferably about 270 g of water are used for this, per mole of tiotropium bromide used.

The filtrate is then slowly cooled, preferably to a temperature of 20-25° C. The cooling is preferably carried out at a cooling rate of 1 to 10° C. per 10 to 30 minutes, preferably 2 to 8° C. per 10 to 30 minutes, more preferably 3 to 5° C. per 10 to 20 minutes, most preferably 3 to 5° C. roughly per 20 minutes. If desired, the cooling to 20 to 25° C. may be followed by further cooling to below 20° C., most preferably to 10 to 15° C.

Once the filtrate has cooled, it is stirred for between 20 minutes and 3 hours, preferably between 40 minutes and 2 hours, most preferably about one hour, to complete the crystallisation.

The crystals formed are finally isolated by filtering or suction filtering the solvent. If it proves necessary to subject the crystals obtained to another washing step, it is advisable to use water or acetone as the washing solvent. 0.1 to 1.0 l, preferably 0.2 to 0.5 l, most preferably about 0.3 l solvent are used, per mole of tiotropium bromide, to wash the tiotropium bromide monohydrate crystals obtained. If desired the washing step may be repeated.

The product obtained is dried in vacuo or using circulating hot air until a water content of 2.5-4.0% is obtained.

The resulting crystalline tiotropium bromide monohydrate is used in the grinding process (micronisation) described below. This process may be carried out using conventional mills. Preferably, the micronisation is carried out with the exclusion of moisture, more preferably, using a corresponding inert gas such as nitrogen, for example. It has proved particularly preferable to use air jet mills in which the material is comminuted by the impact of the particles on one another and on the walls of the grinding container. According to the invention, nitrogen is preferably used as the grinding gas. The material for grinding is conveyed by the grinding gas under specific pressures (grinding pressure). Within the scope of the present invention, the grinding pressure is usually set to a value between about 2 and 8 bar, preferably between about 3 and 7 bar, most preferably between about 3.5 and 6.5 bar. The material for grinding is fed into the air jet mill by means of the feed gas under specific pressures (feed pressure). Within the scope of the present invention a feed pressure of between about 2 and 8 bar, preferably between about 3 and 7 bar and most preferably between about 3.5 and 6 bar has proved satisfactory. The feed gas used is also preferably an inert gas, most preferably nitrogen again. The material to be ground (crystalline tiotropium bromide monohydrate) may be fed in at a rate of about 5-35 g/min, preferably at about 10-30 g/min.

For example, without restricting the subject of the invention thereto, the following apparatus has proved suitable as a possible embodiment of an air jet mill: a 2-inch Microniser with grinding ring, 0.8 mm bore, made by Messrs Sturtevant Inc., 348 Circuit Street, Hanover, Mass. 02239, USA. Using the apparatus, the grinding process is preferably carried out with the following grinding parameters: grinding pressure: about 4.5-6.5 bar; feed pressure: about 4.5-6.5 bar; supply of grinding material: about 17-21 g/min.

The ground material thus obtained is then further processed under the following specific conditions. The micronisate is exposed to a water vapour at a relative humidity of at least 40% at a temperature of 15-40° C., preferably 20-35° C., most preferably 25-30° C. Preferably, the humidity is set to a value of 50-95% r.h., preferably 60-90% r.h., most preferably 70-80% r.h. By relative humidity (r.h.) is meant, within the scope of the present invention, the quotient of the partial steam pressure and the steam pressure of the water at the temperature in question. Preferably, the micronisate obtained from the grinding process described above is subjected to the chamber conditions mentioned above for a period of at least 6 hours. Preferably, however, the micronisate is subjected to the chamber conditions mentioned above for about 12 to 48 hours, preferably about 18 to 36 hours, more preferably about 20 to 28 hours.

In one aspect the invention relates to tiotropium bromide micronisate which may be obtained by the process described above.

The micronisate of tiotropium bromide obtainable by the above method has a characteristic particle size X_{50} of between 1.0 μm and 3.5 μm, preferably between 1.1 μm and 3.3 μm, most preferably between 1.2 μm and 3.0 μm and $Q_{(5.8)}$ of more than 60%, preferably more than 70%, most preferably more than 80%. The characteristic value X_{50} denotes the median value of the particle size below which 50% of the particles fall, with regard to the distribution by volume of the individual particles. The characteristic value $Q_{(5.8)}$ corresponds to the quantity of particles below 5.8 μm , based on the volume distribution of the particles. The particle sizes were determined within the scope of the present invention by laser diffraction (Fraunhofer diffraction). More detailed information on this subject can be found in the experimental descriptions of the invention.

Also characteristic of the tiotropium micronisate according to the invention which was prepared by the above process are Specific Surface Area values in the range between 2 m^2/g and 5 m^2/g, more particularly between 2.5 m^2/g and 4.5 m^2/g and most outstandingly between 3.0 m^2/g and 4.0 m^2/g.

Carrying out the process according to the invention leads to the micronisate of tiotropium bromide according to the invention which is characterised by specific enthalpies of solution. These preferably have a value of more than 65 Ws/g, preferably more than 71 Ws/g. Most preferably the heat of solution of the micronisate according to the invention is in excess of 74 Ws/g.

Detailed information on determining the enthalpies of solution can be found in the experimental descriptions of the invention.

The tiotropium bromide micronisate which may be obtained using the above process is further characterised in that the water content of the micronisate is between about 1% and about 4.5%, preferably between about 1.4% and 4.2%, more preferably between about 2.4% and 4.1%. Particularly preferred tiotropium bromide micronisate according to the invention is characterised in that the water content of the micronisate is between about 2.6% and about 4.0%, most preferably between about 2.8% and 3.9%, particularly between about 2.9% and 3.8%.

One aspect of the present invention therefore relates to tiotropium bromide micronisate which has the above characteristics.

Within the scope of the present invention, unless otherwise stated, any reference to tiotropium bromide micronisate is to be taken as a reference to the crystalline micronisate of tiotropium bromide which has the above characteristics and which can be obtained by the method according to the invention as described above (micronisation followed by further treatment in accordance with the parameters described above).

In another aspect the present invention relates to the use of the tiotropium bromide micronisate according to the invention as a pharmaceutical composition in view of the pharmaceutical efficacy of the micronisate according to the invention.

In another aspect the present invention relates to inhalable powders characterised in that they contain tiotropium bromide micronisate according to the invention.

In view of the anticholinergic effects of tiotropium bromide a further aspect of the present invention relates to the use of the tiotropium bromide micronisate according to the invention for preparing a pharmaceutical composition for treating diseases in which the use of an anticholinergic agent may have a therapeutic benefit. It is preferably used for preparing a pharmaceutical composition for treating asthma or COPD.

The tiotropium bromide micronisate which may be obtained by the process according to the invention is exceptionally suitable for the preparation of pharmaceutical formulations. It may be used particularly for preparing inhalable powders.

Accordingly, the present invention relates to inhalable powders containing at least about 0.03%, preferably less than 5%, more preferably less than 3% of the tiotropium bromide micronisate obtainable by the process described above in admixture with a physiologically acceptable excipient, characterised in that the excipient consists of a mixture of coarser excipient with an average particle size of 15 to 80 μm and finer excipient with an average particle size of 1 to 9 μm, the proportion of finer excipient in the total amount of excipient being from 1 to 20%.

The percentages specified are percent by weight.

According to the invention, inhalable powders are preferred which contain about 0.05 to about 1%, preferably about 0.1 to about 0.8%, more preferably about 0.2 to about 0.5% tiotropium bromide micronisate, which may be obtained by the method described above and has the characteristics of the micronisate which may be obtained according to the invention.

The inhalable powders containing the micronisate according to the invention are preferably characterised in that the excipient consists of a mixture of coarser excipient with an average particle size of 17 to 50 μm, more preferably 20 to 30 μm and finer excipient with an average particle size of 2 to 8 μm, more preferably 3 to 7 μm. The average particle size here denotes the 50% value from the volume distribution measured by laser diffraction by the dry dispersion method. Preferred powders for inhalation are those wherein the proportion of finer excipient in the total amount of excipient is from 3 to 15%, more preferably 5 to 10%.

Where the present invention refers to a mixture, this always means a mixture obtained by mixing together components which have previously been clearly defined. Accordingly an excipient mixture of coarser and finer ingredients can only refer to mixtures obtained by mixing a coarser excipient component with a finer one.

The coarser and finer excipient fractions may consist of the same chemical substance or chemically different substances, while inhalable powders in which the coarser excipient fraction and the finer excipient fraction consist of the same chemical compound are preferred.

Examples of physiologically acceptable excipients which may be used to prepare the inhalable powders according to the invention include, for example, monosaccharides (e.g. glucose or arabinose), disaccharides (e.g. lactose, saccharose, maltose or trehalose), oligo- and polysaccharides (e.g. dextrane), polyalcohols (e.g. sorbitol, mannitol, xylitol), salts (e.g. sodium chloride, calcium carbonate) or mixtures of these excipients with one another. Preferably, mono- or disaccharides are used, while the use of lactose, glucose or trehalose is preferred, preferably lactose or glucose, particularly, but not exclusively, in the form of their hydrates. For the purposes of the invention, lactose is the particularly preferred excipient, while lactose monohydrate is most particularly preferred.

The inhalable powders containing the micronisate according to the invention may for example be administered using inhalers which meter a single dose from a reservoir by means of a measuring chamber (e.g. according to US 4570630A) or by other means (e.g. according to DE 36 25 685 A). Preferably, however, the inhalable powders are packed into capsules, which are used in inhalers such as those described in WO 94/28958, for example. If the inhalable powder according to the invention is to be packed into capsules or other packages which provide single doses in accordance with the preferred application mentioned above, it is advisable to fill the capsules with amounts of from 1 to 15 mg, preferably 3 to 10 mg, most preferably from 4 to 6 mg of inhalable powder per capsule.

The inhalable powders containing the tiotropium bromide micronisate according to the invention are characterised by a high degree of homogeneity in terms of the accuracy of measuring a single dose. This is in the range from <8%, preferably <6%, most preferably <4%.

The inhalable powders containing the tiotropium bromide micronisate according to the invention may be obtained by the method described below.

After the starting materials have been weighed out, first of all the excipient mixture is prepared from the defined fractions of coarser excipient and finer excipient. Then the inhalable powders according to the invention are prepared from the excipient mixture and the active substance. If the inhalable powder is to be administered using capsules containing powders in suitable inhalers the preparation of the inhalable powder is followed by the manufacture of the capsules containing the powder.

In the preparation methods described below, the abovementioned components are used in the proportions by weight described in the abovementioned compositions of the inhalable powders according to the invention. The inhalable powders according to the invention are prepared by mixing the coarser excipient fractions with the finer excipient fractions and then mixing the resulting excipient mixture with the active substance. To prepare the excipient mixture the coarser and finer excipient fractions are placed in a suitable mixing container. The two components are preferably added through a screening granulator with a mesh size of 0.1 to 2 mm, most preferably 0.3 to 1 mm, even more preferably 0.3 to 0.6 mm. Preferably, the coarser excipient is put in first, and then the finer and coarser excipient are added alternately. It is particularly preferred when preparing the excipient mixture to screen in the two components in alternate layers. Preferably, the two components are screened alternately, in 15 to 45, most preferably 20 to 40 layers each. The two excipients may be mixed while the two components are being added. Preferably, however, the two ingredients are not mixed until after they have been screened in in layers.

After the preparation of the excipient mixture, this and the active substance, the tiotropium bromide micronisate according to the invention, are placed in a suitable mixing container. The active substance used has an average particle size of 0.5 to 10 μm, preferably 1 to 6 μm, more preferably 1.5 to 5 μm. The two components are preferably added through a screening granulator with a mesh size of 0.1 to 2 mm, most preferably 0.3 to 1 mm, even more preferably 0.3 to 0.6 mm. Preferably, the excipient mixture is put in and then the active substance is added to the mixing container. Preferably, in this mixing process, the two components are added in batches. In the preparation of the excipient mixture it is particularly

preferred to screen in the two components alternately in 25 to 65, preferably 30 to 60 layers each. The operation of mixing the excipient mixture with the active substance may be carried out while the two components are being added. Preferably, however, the two ingredients are not mixed until after they have been screened in in layers.

The powder mixture obtained by if desired by passed through a screening granulator once more or repeatedly and then subjected to another mixing process.

In another aspect the present invention relates to an inhalable powder which contains the tiotropium bromide micronisate according to the invention and may be obtained by the methods described above.

The following detailed experimental descriptions serve to illustrate the present invention more fully without restricting the scope of the invention to the embodiments described by way of example hereinafter.

Experimental Section

A) Preparation of Crystalline Tiotropium Bromide Monohydrate

15.0 kg of tiotropium bromide, which may be prepared by the experimental procedure disclosed in European Patent Application EP 418 716 A1, are added to 25.7 kg of water in a suitable reaction vessel. The mixture is heated to 80-90° C. and stirred at constant temperature until a clear solution is formed. Activated charcoal (0.8 kg), moistened with water, is suspended in 4.4 kg of water, this mixture is added to the solution containing the tiotropium bromide and rinsed with 4.3 kg of water. The mixture thus obtained is stirred for at least 15 min at 80-90° C. and then filtered through a heated filter into an apparatus which has been preheated to an outer temperature of 70° C. The filter is rinsed with 8.6 kg of water. The contents of the apparatus are cooled at 3-5° C. every 20 minutes to a temperature of 20-25° C. The apparatus is further cooled to 10-15° C. using cold water and crystallisation is completed by stirring for at least one hour. The crystals are isolated using a suction drier, the crystal slurry isolated is washed with 9 liters of cold water (10-15° C.) and cold acetone (10-15° C.). The crystals obtained are dried in a nitrogen current at 25° C. over 2 hours.

Yield: 13.4 kg of tiotropium bromide monohydrate (86% of theory)

Characterisation of Crystalline Tiotropium Bromide Monohydrate

The tiotropium bromide monohydrate obtainable using the method described above was investigated by DSC (Differential Scanning Calorimetry). The DSC diagram shows two characteristic signals. The first, relatively broad, endothermic signal between 50-120° C. can be attributed to the dehydration of the tiotropium bromide monohydrate into the anhydrous form. The second, relatively sharp, endothermic peak at 230±5° C. can be put down to the melting of the substance. This data was obtained using a Mettler DSC 821 and evaluated using the Mettler STAR software package. The data was recorded at a heating rate of 10 K/min.

Since the substance melts with decomposition (=incongruent melting process), the melting point observed depends to a great extent on the heating rate. At lower heating rates, the melting/decomposition process is observed at significantly lower temperatures, e.g. at 220±5 ° C. at a heating rate of 3 K/min. It is also possible that the melting peak may be split. The split is all the more apparent the lower the heating rate in the DSC experiment.

The crystalline tiotropium bromide monohydrate was characterised by IR spectroscopy. The data was obtained using a Nicolet FTIR spectrometer and evaluated with the Nicolet OMNIC software package, version 3.1. The measurement was carried out with 2.5 μmol of tiotropium bromide monohydrate in 300 mg of KBr. Table 1 shows some of the essential bands of the IR spectrum.

TABLE 1

Attribution of specific bands

Wave number (cm^{-1})	Attribution	Type of oscillation
3570, 3410	O—H	elongated oscillation
3105	Aryl C—H	elongated oscillation
1730	C═O	elongated oscillation
1260	Epoxide C—O	elongated oscillation
1035	Ester C—OC	elongated oscillation
720	Thiophene	cyclic oscillation

The crystalline tiotropium bromide monohydrate was characterised by X-ray structural analysis. The measurements of X-ray diffraction intensity were carried out on an AFC7R- 4-circuit diffractometer (Rigaku) using monochromatic copper K_α radiation. The structural resolution and refinement of the crystal structure were obtained by direct methods (SHELXS86 Program) and FMLQ-refinement (TeXsan Program). Experimental details of the crystalline structure, structural resolution and refinement are collected in Table 2.

TABLE 2

Experimental data on the analysis of the crystalline structure of tiotropium bromide monohydrate.

A. Crystal data	
Empirical formula	$[C_{19}H_{22}NO_4S_2]\ Br^{\bullet}H_2O$
Weight of formula	472.43 + 18.00
colour and shape of crystals	colourless, prismatic
dimensions of crystals	0.2 × 0.3 × 0.3 mm
crystal system	monoclinic
lattice type	primitive
space group	P $2_1/n$
lattice constants	a = 18.0774 Å, b = 11.9711 Å c = 9.9321 Å β = 102.691° V = 2096.96 $Å^3$
formula units per elementary cell	4
B. Measurements of intensity	
Diffractometer	Rigaku AFC7R
X-ray generator	Rigaku RU200
wavelength	λ = 1.54178 Å(monochromatic copper K_α-radiation)
current, voltage	50 kV, 100 mA
take-off angle	6°
crystal assembly	steam-saturated capillary
crystal-detector gap	235 mm
detector opening	3.0 mm vertical and horizontal
temperature	18°
determining the lattice constants	25 reflexes (50.8° < 2Θ < 56.2°)
Scan Type	ω - 2Θ
Scan speed	8.0 32.0°/min in ω
Scan width	(0.58 + 0.30 tan Θ) °
2Θmax	120°
measured	5193
independent reflexes	3281 (R_{int} = 0.051)
corrections	Lorentz polarisation Absorption (Transmission factors 0.56-1.00) crystal decay 10.47% decay
C. Refinement	
Reflections (I > 3σI)	1978
Variable	254
ratio of reflections/parameters	7.8
R-values: R, Rw	0.062, 0.066

The X-ray structural analysis carried out showed that crystalline tiotropium bromide hydrate has a simple monoclinic cell with the following dimensions: a=18.0774 Å, b=11.9711 Å, c=9.9321 Å, β=102.691°, V=2096.96 Å^3.

The atomic coordinates described in Table 3 were determined by the above X-ray structural analysis:

TABLE 3

	Coordinates			
Atom	x	y	z	u (eq)
Br(1)	0.63938(7)	0.0490(1)	0.2651(1)	0.0696(4)
S(1)	0.2807(2)	0.8774(3)	0.1219(3)	0.086(1)
S(2)	0.4555(3)	0.6370(4)	0.4214(5)	0.141(2)
O(1)	0.2185(4)	0.7372(6)	0.4365(8)	0.079(3)
O(2)	0.3162(4)	0.6363(8)	0.5349(9)	0.106(3)
O(3)	0.3188(4)	0.9012(5)	0.4097(6)	0.058(2)
O(4)	0.0416(4)	0.9429(6)	0.3390(8)	0.085(3)
O(5)	0.8185(5)	0.0004(8)	0.2629(9)	0.106(3)
N(1)	0.0111(4)	0.7607(6)	0.4752(7)	0.052(2)
C(1)	0.2895(5)	0.7107(9)	0.4632(9)	0.048(3)
C(2)	0.3330(5)	0.7876(8)	0.3826(8)	0.048(3)
C(3)	0.3004(5)	0.7672(8)	0.2296(8)	0.046(3)
C(4)	0.4173(5)	0.7650(8)	0.4148(8)	0.052(3)
C(5)	0.1635(5)	0.6746(9)	0.497(1)	0.062(3)
C(6)	0.1435(5)	0.7488(9)	0.6085(9)	0.057(3)
C(7)	0.0989(6)	0.6415(8)	0.378(1)	0.059(3)
C(8)	0.0382(5)	0.7325(9)	0.3439(9)	0.056(3)
C(9)	0.0761(6)	0.840(1)	0.315(1)	0.064(3)
C(10)	0.1014(6)	0.8974(8)	0.443(1)	0.060(3)
C(11)	0.0785(5)	0.8286(8)	0.5540(9)	0.053(3)
C(12)	−0.0632(6)	0.826(1)	0.444(1)	0.086(4)
C(13)	−0.0063(6)	0.6595(9)	0.554(1)	0.062(3)
C(14)	0.4747(4)	0.8652(9)	0.430(1)	0.030(2)
C(15)	0.2839(5)	0.6644(9)	0.1629(9)	0.055(3)
C(16)	0.528(2)	0.818(2)	0.445(2)	0.22(1)
C(17)	0.5445(5)	0.702(2)	0.441(1)	0.144(6)
C(18)	0.2552(6)	0.684(1)	0.019(1)	0.079(4)
C(19)	0.2507(6)	0.792(1)	−0.016(1)	0.080(4)
H(1)	−0.0767	0.8453	0.5286	0.102
H(2)	−0.0572	0.8919	0.3949	0.102
H(3)	−0.1021	0.7810	0.3906	0.102
H(4)	−0.0210	0.6826	0.6359	0.073
H(5)	−0.0463	0.6178	0.4982	0.073
H(6)	0.0377	0.6134	0.5781	0.073
H(7)	0.1300	0.7026	0.6770	0.069
H(8)	0.1873	0.7915	0.6490	0.069
H(9)	0.1190	0.6284	0.2985	0.069
H(10)	0.0762	0.5750	0.4016	0.069
H(11)	0.1873	0.6082	0.5393	0.073
H(12)	−0.0025	0.7116	0.2699	0.066
H(13)	0.1084	0.8383	0.2506	0.075
H(14)	0.1498	0.9329	0.4626	0.071
H(15)	0.0658	0.8734	0.6250	0.063
H(16)	0.2906	0.5927	0.2065	0.065
H(17)	0.2406	0.6258	−0.0469	0.094
H(18)	0.2328	0.8191	−0.1075	0.097
H(19)	0.4649	0.9443	0.4254	0.037
H(20)	0.5729	0.8656	0.4660	0.268
H(21)	0.5930	0.6651	0.4477	0.165
H(22)	0.8192	−0.0610	0.1619	0.084
H(23)	0.7603	0.0105	0.2412	0.084

x, y, z: fractional coordinates;
U(eq) mean quadratic amplitude of atomic movement in the crystal

C) Preparation of the Tiotropium Bromide Micronisate According to the Invention

The tiotropium bromide monohydrate obtainable by the process described above is micronised with an air jet mill of the 2-inch microniser type with grinding ring, 0.8 mm bore, made by Messrs Sturtevant Inc., 348 Circuit Street, Hanover, Mass. 02239, USA. Using nitrogen as the grinding gas the following grinding parameters are set, for example:

grinding pressure: 5.5 bar; feed pressure: 5.5 bar; supply (of crystalline monohydrate) or flow speed: 19 g/min.

The ground material obtained is then spread out on sheet metal racks in a layer thickness of about 1 cm and subjected to the following climatic conditions for 24-24.5 hours: temperature: 25-30° C.; relative humidity: 70-80%.

D) Measuring Techniques for Characterising the Tiotropium Bromide Micronisate According to the Invention

The parameters mentioned in the description which characterise the tiotropium bromide micronisate according to the invention were obtained by the measuring techniques and methods described below:

D.1) Determining the Water Content According to Karl-Fischer (Tiotropium Bromide):
Titrator Type Mettler DL 18 with
Calibrating substance: disodium tartrate dihydrate
Titrant: Hydranal-Titrant 5 (Riedel-deHaen)
Solvent: Hydranal Solvent (Riedel-deHaen)

Measuring Method:
Sample amount: 50-100 mg
Stirring time: 60 s

The stirring time before the start of titration ensures that the sample is fully dissolved.

The water content of the sample is calculated by the apparatus in percent and indicated.

D.2) Determining Particle Size by Laser Diffraction (Fraunhofer Diffraction)

Measuring Method:

To determine the particle size the powder is fed into a laser diffraction spectrometer by means of a dispersing unit.

Measuring equipment: Laser diffraction spectrometer (HELOS), Messrs. Sympatec
Software: WINDOX Version 3.3/REL 1
Dispersing unit: RODOS/Dispersing pressure: 3 bar

Equipment Parameters:
Detector: Multielement detector (31 semicircular rings)
Method: Air dispersal
Focal length: 100 mm
Measuring range: RS 0.5/0.9-175 μm
Evaluation mode: HRLD-Mode

Rodos Dry Disperser:
Injector: 4 mm
Pressure: 3 bar
Injector vacuum: maximum (~100 mbar)
Suction: Nilfilsk (advance 5 s)
Metering device: Vibri
Feed rate: 40% (manually increased to 100%)
Bed height: 2 mm
Speed of rotation: 0

D.3) Determining the Specific Surface Area (1-Bundle B.E.T. Method):

Measuring method:

The specific surface is determined by exposing the powder sample to a nitrogen/helium atmosphere at different pressures. Cooling the sample causes the nitrogen molecules to be condensed on the surface of the particles. The quantity of condensed nitrogen is determined by means of the change in the thermal heat conductivity of the nitrogen/helium mixture and the surface of the sample is calculated by means of the surface nitrogen requirement. Using this value and the weight of the sample, the specific surface is calculated.

Equipment And Materials:
Measuring equipment: Monosorb, Messrs Quantachrome
Heater: Monotektor, Messrs Quantachrome

Measuring and drying gas: nitrogen (5.0)/helium (4.6) 70/30, Messer Griesheim
Adsorbate: 30% nitrogen in helium
Coolant: liquid nitrogen
Measuring cell: with capillary tube, Messrs. W. Pabisch GmbH & Co. KG
Calibration peak; 1000 µ, Fa. Precision Sampling Corp.
Analytical scale: R 160 P, Fa. Satorius

Calculating the Specific Surface:

The measured values are indicated by the equipment in [m^2] and are usually converted into [cm^2/g] on weighing (dry mass):

$$A_{spez} = \frac{MW * 10000}{m_{tr}}$$

A_{spez} = specific surface [cm^2/g]
MW = Measured value [m^2]
m_{tr} = dry mass [g]
10000 = conversion factor [cm^2/m^2]

D.4) Determining the Heat of Solution (Enthalpy of Solution) E_c:

The solution enthalpy is determined using a solution calorimeter 2225 Precision Solution Calorimeter made by Messrs. Thermometric.

The heat of solution is calculated by means of the change in temperature occurring (as a result of the dissolving process) and the system-related change in temperature calculated from the base line.

Before and after the ampoule is broken, electrical calibration is carried out with an integrated heating resistor of a precisely known power. A known heat output is delivered to the system over a set period and the jump in temperature is determined.

Method And Equipment Parameters:
Solution calorimeter: 2225 Precision Solution Calorimeter, Messrs Thermometric
Reaction cell: 100 ml
Thermistor resistance: 30.0 kΩ(at 25° C.)
Speed of stirrer: 600 U/min
Thermostat: Thermostat of 2277 Thermal Activity Monitor TAM, Messrs Thermometric
Temperature: 25° C.±0.0001° C. (over 24 h)
Measuring ampoules: Crushing ampoules 1 ml, Messrs Thermometric
Seal: Silicon stopper and beeswax, Messrs. Thermometric
Weight: 40 to 50 mg
Solvent: Chemically pure water
Volume of solvent: 100 ml
Bath temperature: 25° C.
Temperature resolution: High
Starting temperature: −40mK (±10mK) temperature-offset
Interface: 2280-002 TAM accessory interface 50 Hz, Messrs Thermometric
Software: SolCal V 1.1 for WINDOWS
Evaluation: Automatic evaluation with Menu point CALCULATION/ANALYSE EXPERIMENT. (Dynamics of base line; calibration after breakage of ampoule).

Electrical Calibration:

The electrical calibration takes place during the measurement, once before and once after the breakage of the ampoule. The calibration after the breakage of the ampoule is used for the evaluation.

Amount of heat: 2.5 Ws
Heating power: 250 mW
Heating time: 10 s
Duration of base lines: 5 min (before and after heating)

Evaluation for Tiotropium Bromide Micronisate:

As the mass of the tiotropium bromide micronisate weighed out has to be corrected by the water content of the material, the unsealed ampoules together with about 1 g of the test substance are left to stand open for at least 4 hours. After this equilibration time the ampoules are sealed with the silicon stoppers and the water content of the bulk sample is determined by Karl-Fischer titration. The filled and sealed ampoule is weighed on the scale again. The sample mass is corrected according to the following formula:

$$m_c = \left(\frac{100\% - x}{100\%}\right) \cdot m_w$$

where: m_c is the corrected mass
m_w is the sample mass weighed into the ampoule
x is the water content in percent (determined in parallel by Karl-Fischer titration)

The corrected mass m_c determined by this calculation is used as the input value (=weight) to calculate the solution enthalpy measured.

E) Preparation of the Powder Formulation Containing the Tiotropium Bromide Micronisate According to the Invention

In the Examples which follow, lactose-monohydrate (200M) is used as the coarser excipient. It may be obtained, for example, from Messrs DMV International, 5460 Veghel/NL under the product name Pharmatose 200M.

In the Examples which follow, lactose-monohydrate (5µ) is used as the finer excipient. It may be obtained from lactose-monohydrate 200M by conventional methods (micronising). Lactose-monohydrate 200M may be obtained, for example, from Messrs DMV International, 5460 Veghel/NL under the product name Pharmatose 200M.

Apparatus

The following machines and equipment, for example, may be used to prepare the inhalable powders containing the tiotropium bromide micronisate according to the invention:

Mixing container or powder mixer: Gyrowheel mixer 200 L; type: DFW80N-4; made by: Messrs Engelsmann, D-67059 Ludwigshafen.

Granulating sieve: Quadro Comil; type: 197-S; made by: Messrs Joisten & Kettenbaum, D-51429 Bergisch-Gladbach.

E.1) Preparation of the Excipient Mixture:

31.82 kg of lactose monohydrate for inhalation (200M) are used as the coarser excipient component. 1.68 kg of lactose monohydrate (5 µm) are used as the finer excipient component. In the resulting 33.5 kg of excipient mixture the proportion of the finer excipient component is 5%.

About 0.8 to 1.2 kg of lactose monohydrate for inhalation (200M) are added to a suitable mixing container through a suitable granulating sieve with a mesh size of 0.5 mm. Then alternate layers of lactose monohydrate (5 μm) in batches of about 0.05 to 0.07 kg and lactose monohydrate for inhalation (200M) in batches of 0.8 to 1.2 kg are sieved in. Lactose monohydrate for inhalation (200M) and lactose monohydrate (5 μm) are added in 31 and 30 layers, respectively (tolerance: ±6 layers).

The ingredients sieved in are then mixed together (mixing at 900 rpm).

E.2) Preparation of the Final Mixture

To prepare the final mixture, 32.87 kg of the excipient mixture (1.1) and about 0.13 kg of the tiotropium bromide micronisate according to the invention are used. The content of active substance in the resulting 33.0 kg of inhalable powder is 0.4%.

About 1.1 to 1.7 kg of excipient mixture (E.1) are added to a suitable mixing container through a suitable granulating sieve with a mesh size of 0.5 mm. Then alternate layers of tiotropium bromide micronisate in batches of about 0.003 kg and excipient mixture (E.1) in batches of 0.6 to 0.8 kg are sieved in. The excipient mixture and the active substance are added in 46 and 45 layers, respectively (tolerance: ±9 layers).

The ingredients are sieved and then mixed together.

The final mixture is passed twice more through a granulating sieve and then mixed (mixing at 900 rpm).

E.3) Inhalation Capsules:

Inhalation capsules having the following composition were produced using the mixture obtained according to E.2:

tiotropium bromide monohydrate:	0.0225 mg
lactose monohydrate (200 M):	5.2025 mg
lactose monohydrate (5 μm):	0.2750 mg
hard gelatine capsule:	49.0 mg
Total:	54.5 mg

Analogously to the method described in E.2 inhalation capsules of the following composition are obtained:

a)	
tiotropium bromide monohydrate:	0.0225 mg
lactose monohydrate (200 M):	4.9275 mg
lactose monohydrate (5 μm):	0.5500 mg
hard gelatine capsule:	49.0 mg
Total:	54.5 mg
b)	
tiotropium bromide monohydrate:	0.0225 mg
lactose monohydrate (200 M):	5.2025 mg
lactose monohydrate (5 μm):	0.2750 mg
polyethylene capsule:	100.0 mg
Total:	105.50 mg

F) Measuring Techniques for Determining the Particle Sizes of the Excipient Components Used In E)

The average particle size of the various excipient ingredients of the formulation containing the tiotropium bromide micronisate according to the invention which may be prepared according to E) was determined as follows:

F.1) Determining the Particle Size of Finely Divided Lactose:

Measuring Equipment And Settings:
The equipment is operated according to the manufacturer's instructions.
Measuring equipment: HELOS Laser-diffraction spectrometer, (SympaTec)
Dispersing unit: RODOS dry disperser with suction funnel, (SympaTec)
Sample quantity: from 100 mg
Product feed: Vibri Vibrating channel, Messrs. Sympatec
Frequency of vibrating channel: 40 rising to 100%
Duration of sample feed: 1 to 15 sec. (in the case of 100 mg)
Focal length: 100 mm (measuring range: 0.9-175 μm)
Measuring time: about 15 s (in the case of 100 mg)
Cycle time: 20 ms
Start/stop at: 1% on channel 28
Dispersing gas: compressed air
Pressure: 3 bar
Vacuum: maximum
Evaluation method: HRLD

Sample Preparation/product Feed:

At least 100 mg of the test substance are weighed onto a piece of card.

Using another piece of card all the larger lumps are broken up. The powder is then sprinkled finely over the front half of the vibrating channel (starting about 1 cm from the front edge). After the start of the measurement the frequency of the vibrating channel is varied from about 40% up to 100% (towards the end of the measurement). The time taken to feed in the entire sample is 10 to 15 sec.

F.2) Determining the Particle Size of Lactose 200M:

Measuring Equipment And Settings:
The equipment is operated according to the manufacturer's instructions.
Measuring equipment: Laser diffraction spectrometer (HELOS), Sympatec
Dispersing unit: RODOS dry disperser with suction funnel, Sympatec
Sample quantity: 500 mg
Product feed: VIBRI Vibrating channel, Messrs. Sympatec
Frequency of vibrating channel: 18 rising to 100%
Focal length (1): 200 mm (measuring range: 1.8-350 μm)
Focal length (2): 500 mm (measuring range: 4.5-875 μm)
Measuring time: 10 s
Cycle time: 10 ms
Start/stop at: 1% on channel 19
Pressure: 3 bar
Vacuum: maximum
Evaluation method: HRLD

Sample Preparation/Product Feed:

About 500 mg of the test substance are weighed onto a piece of card.

Using another piece of card all the larger lumps are broken up. The powder is then transferred into the funnel of the vibrating channel. A gap of 1.2 to 1.4 mm is set between the vibrating channel and funnel. After the start of the measurement the amplitude setting of the vibrating channel is increased from 0 to 40% until a continuous flow of product is obtained. Then it is reduced to an amplitude of about 18%. Towards the end of the measurement the amplitude is increased to 100%.

What is claimed is:

1. A pharmaceutical composition, comprising crystalline tiotropium bromide micronisate characterised by a particle

size X_{50} of between 1.0 μm and 3.5 μm at a $Q_{(5.8)}$ value of more than 60%, by a specific surface value in the range between 2 m^2/g and 5 m^2/g, by a specific heat of solution of more than 65 Ws/g and by a water content from about 1% to about 4.5%, wherein the crystalline tiotropium bromide micronisate is obtained from crystalline tiotropium bromide monohydrate, which crystalline tiotropium bromide monohydrate when thermally analysed by DSC has an endothermic maximum at 230±5° C. at a heating rate of 10K/min, has an IR spectrum which has bands inter alia at wavelengths 3570, 3410, 3105, 1730, 1260, 1035 and 720 cm^{-1} and which is characterised by a simple monoclinic cell with the following dimensions: a=18.0774 Å, b=11.9711 Å, c=9.9321 Å, β=102.691°, V =2096.96 $Å^3$; in admixture with at least one physiologically acceptable excipient.

2. The pharmaceutical composition according to claim **1**, characterised in that it is an inhalable powder.

3. The pharmaceutical composition which is an inhalable powder according to claim **2**, characterised in that it contains at least about 0.03% of tiotropium bromide micronisate in admixture with the physiologically acceptable excipient and further characterised in that the excipient consists of a mixture of coarser excipient with an average particle size of 15 to 80 μm and finer excipient with an average particle size of 1 to 9 μm, wherein the proportion of finer excipient in the total quantity of excipient is from 1 to 20%.

4. The pharmaceutical composition which is an inhalable powder according to claim **3**, characterised in that it contains between about 0.05 and about 1%, of tiotropium bromide micronisate.

5. The pharmaceutical composition which is an inhalable powder according to claim **4**, characterised in that the excipient consists of a mixture of coarser excipient with an average particle size of 17 to 50 μm and finer excipient with an average particle size of 2 to 8μm.

6. The pharmaceutical composition which is an inhalable powder according to claim **3**, characterised in that the proportion of finer excipient in the total quantity of excipient is from about 3 to about 15%.

7. The pharmaceutical composition which is an inhalable powder according to claim **3**, characterised in that monosaccharides, disaccharides, oligo- and polysaccharides, polyalcohols, salts or mixtures of these excipients with one another may be used as excipients.

8. The pharmaceutical composition which is an inhalable powder according to claim **7**, characterised in that glucose, arabinose, lactose, saccharose, maltose, trehalose, dextrane, sorbitol, mannitol, xylitol, sodium chloride, calcium carbonate or mixtures of these excipients with one another may be used as excipients.

9. The pharmaceutical composition which is an inhalable powder according to claim **8**, characterised in that glucose or lactose or mixtures of these excipients with one another may be used as excipients.

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