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**UNITED STATES DISTRICT COURT  
DISTRICT OF NEW JERSEY**

SUCAMPO AG, SUCAMPO  
PHARMACEUTICALS, INC.,  
SUCAMPO PHARMA LLC, TAKEDA  
PHARMACEUTICAL COMPANY  
LIMITED, TAKEDA  
PHARMACEUTICALS USA, INC. and  
TAKEDA PHARMACEUTICALS  
AMERICA, INC.,

Plaintiffs,

v.

SUN PHARMACEUTICAL INDUSTRIES,  
LTD. and SUN PHARMACEUTICAL  
INDUSTRIES, INC.,

Defendants.

**Civil Action No.** \_\_\_\_\_

**COMPLAINT FOR  
PATENT INFRINGEMENT**

**(Filed Electronically)**

Plaintiffs Sucampo AG, Sucampo Pharmaceuticals, Inc., and Sucampo Pharma LLC (collectively, “Sucampo”) and Takeda Pharmaceutical Company Limited, Takeda Pharmaceuticals USA, Inc., and Takeda Pharmaceuticals America, Inc. (collectively, “Takeda”) (together with Sucampo, “Plaintiffs”), for their Complaint against Defendants Sun Pharmaceutical Industries, Ltd. (“Sun Ltd.”) and Sun Pharmaceutical Industries, Inc. (“Sun Inc.”) (collectively, “Sun” or “Defendants”), hereby allege as follows:

**THE PARTIES**

1. Sucampo AG is a Swiss corporation having a primary place of business at Baarerstrasse 22, CH-6300, Zug, Switzerland.
2. Sucampo Pharmaceuticals, Inc. is a corporation having a principal place of business at 1425 US Route 206, Bedminster, New Jersey 07921.
3. Sucampo Pharma LLC, which merged with a Japanese corporation previously known as R-Tech Ueno, Ltd., is a wholly-owned subsidiary of Sucampo Pharmaceuticals, Inc., having a principal place of business at 1-1-7 Uchisaiwaicho, Chiyoda-ku, Tokyo 100-0011, Japan.
4. Takeda Pharmaceutical Company Limited is a Japanese corporation having a principal place of business at 1-1, Doshomachi 4-chome, Chuo-ku, Osaka 540-8645, Japan.
5. Takeda Pharmaceuticals USA, Inc. is a corporation jointly owned by Takeda Pharmaceutical Company Limited and non-party Takeda Pharmaceuticals International AG, having a principal place of business at One Takeda Parkway, Deerfield, Illinois 60015.

6. Takeda Pharmaceuticals America, Inc. is a wholly-owned subsidiary of Takeda Pharmaceuticals USA, Inc., having a principal place of business at One Takeda Parkway, Deerfield, Illinois 60015.

7. Upon information and belief, Sun Ltd. is a corporation organized and existing under the laws of India, having a principal place of business at CTS No. 201 B/1, Western Express Highway, Goregaon (E), Mumbai, Maharashtra, India 400063.

8. In a Notice Letter dated September 18, 2018 (the “Sun Notice Letter”) sent to Sucampo, Sun Ltd. represented that it has “a principal place of business at 2 Independence Way, Princeton, NJ, 08540.”

9. Upon information and belief, Sun Inc. is a corporation organized and existing under the law of the State of Michigan, having principal places of business in the State of New Jersey, including, but not limited to, the following business addresses: (1) 270 Prospect Plains Road, Cranbury, New Jersey 08512 and (2) 2 Independence Way, Princeton, New Jersey 08540.

10. Upon information and belief, Sun Inc. is a wholly-owned subsidiary and agent of Sun Ltd.

11. Upon information and belief, Sun Inc. is registered with the State of New Jersey’s Division of Revenue and Enterprise Services as a business operating in New Jersey under Business ID Nos. 0100954087 and 0100970132.

12. Upon information and belief, Sun Inc. is registered with the State of New Jersey’s Department of Health as a drug manufacturer and wholesaler the under Registration No. 5003437.

13. Upon information and belief, Sun Inc. has appointed the Corporation Trust Company, 820 Bear Tavern Road, West Trenton, New Jersey 08628, as its registered agent for service of process.

14. Upon information and belief, Sun Inc. maintains several places of business in the State of New Jersey, including, but not limited to, the following business addresses: (1) 270 Prospect Plains Road, Cranbury, New Jersey 08512; (2) 1 Commerce Drive, Cranbury, New Jersey 08512; (3) 2 Independence Way, Princeton, New Jersey 08540; and (4) 6 Hollywood Court, South Plainfield, New Jersey 07080.

15. Upon information and belief, Sun Inc. develops, manufactures, and/or imports generic pharmaceutical versions of branded products for sale and use throughout the United States, including in this Judicial District. Upon information and belief, Sun Inc. markets, distributes, and/or sells generic pharmaceutical versions of branded products throughout the United States, including in this Judicial District.

16. Upon information and belief, Sun Ltd., either directly or through one or more of its wholly-owned subsidiaries and/or agents, develops, manufactures, and/or imports generic pharmaceutical versions of branded products for sale and use throughout the United States, including in this Judicial District. Upon information and belief, Sun Ltd., either directly or through one or more of its wholly-owned subsidiaries and/or agents, markets, distributes, and/or sells generic pharmaceutical versions of branded products throughout the United States, including in this Judicial District.

#### **JURISDICTION AND VENUE**

17. This is a civil action for infringement of United States Patent Nos. 7,795,312, 8,097,653, 8,389,542, 8,026,393, 8,338,639, 8,779,187, and 8,748,481 (collectively,

“the patents-in-suit”). This action arises under the Patent Laws of the United States, 35 U.S.C. § 100 *et seq.*

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

19. Venue is proper in this Court under 28 U.S.C. § 1400(b) because Sun has committed acts of infringement and has a regular and established place of business in this Judicial District.

20. This Court has personal jurisdiction over, and venue is proper as to, Sun Ltd. and Sun Inc. because, *inter alia*, Sun Ltd. and Sun Inc. have each committed, or aided, abetted, contributed to, or participated in the commission of, acts of patent infringement, including acts in the State of New Jersey, that have led to foreseeable harm and injury to Plaintiffs in the State of New Jersey.

21. Upon information and belief, Sun Ltd. and Sun Inc. are agents of each other with respect to formulating, manufacturing, packaging, marketing, and/or selling pharmaceutical products throughout the United States, and will do the same with respect to Sun’s proposed products that are the subject of Abbreviated New Drug Application (“ANDA”) No. 212292, for which Sun has sought approval from the United States Food and Drug Administration (“FDA”).

22. Upon information and belief, Sun Ltd. and Sun Inc. are acting in concert with each other with respect to formulating, manufacturing, packaging, marketing, and/or selling pharmaceutical products throughout the United States, and will do the same with respect to Sun’s proposed products that are the subject of ANDA No. 212292, for which Sun has sought approval from the FDA.

23. Upon information and belief, Sun Ltd., alone and/or together with its affiliate and agent Sun Inc., filed or caused to be filed ANDA No. 212292 with the FDA.

24. Upon information and belief, Sun Inc. acts at the direction, and for the benefit, of Sun Ltd., and is controlled and/or dominated by Sun Ltd.

25. Sun Ltd. sent the Sun Notice Letter, stating that the FDA has received ANDA No. 212292 seeking approval to commercially manufacture, use, market or sell generic lubiprostone capsules 8 mcg and 24 mcg (the “ANDA Products”) in the United States, including, upon information and belief, in the State of New Jersey, prior to the expiration of the patents-in-suit.

26. Upon information and belief, the actions of Sun Inc. of, *inter alia*, causing to be filed ANDA No. 212292 and maintaining its distribution channels including in the State of New Jersey, establish that if granted approval, Sun Inc. will commercially manufacture, use, offer to sell, sell, and/or import the ANDA Products throughout the United States, including in New Jersey.

27. This Court has personal jurisdiction over, and venue is proper as to, Sun Inc. because, *inter alia*, it: (1) has purposely availed itself of the privilege of doing business in New Jersey, including securing a New Jersey wholesale drug distributor’s license (Registration No. 5003437) and New Jersey Business Entity identification numbers (Registration Nos. 0100954087 and 0100970132); (2) develops, manufactures, and/or imports generic pharmaceutical versions of branded products for sale and use throughout the United States, including in the State of New Jersey; (3) directly or indirectly markets, distributes, and/or sells its generic pharmaceutical drugs in the State of New Jersey; (4) directly or indirectly maintains pervasive, continuous, and systematic contacts with the State of New Jersey, including through a

network of wholesalers and distributors, for the purposes of marketing, distribution, and/or sale of generic pharmaceutical drugs in New Jersey; (5) has employees and maintains several places of business located in New Jersey; and (6) enjoys substantial income from sales of its generic pharmaceutical drugs in the State of New Jersey.

28. Upon information and belief, Sun Inc. purposefully has conducted and continues to conduct business in this Judicial District. Upon information and belief, Sun Inc. works in concert with its agents with respect to the regulatory approval, manufacturing, marketing, sale, and distribution of its generic pharmaceutical products throughout the United States, including in this Judicial District.

29. Sun has not contested venue in at least seven actions brought in this Judicial District in the last five years. *See, e.g.*, Civil Action Nos. 18-11630, 17-8819, 17-5015, 15-8017, 14-6397, 14-4307.

30. Additionally, the business of Sun Inc. involves challenging patents held by branded pharmaceutical companies, including in this Judicial District. Sun Inc. has routinely consented to jurisdiction and venue in this Court, and availed itself of the protections afforded by this Court, including by asserting Counterclaims in this Court. *See, e.g., Celgene Corp. v. Sun Pharma Global FZE, et al.*, Civil Action No. 18-11630 (SDW)(LDW) (D.N.J.); *Boehringer Ingelheim Pharmaceuticals Inc., et al., v. Sun Pharmaceutical Industries, Ltd., et al.*, Civil Action No. 17-8819 (MAS)(LHG) (D.N.J.); *Otsuka Pharmaceutical Co. v. Sun Pharmaceutical Industries, Ltd.*, Civil Action No. 14-6397 (JBS)(KMW) (D.N.J.); *Otsuka Pharmaceutical Co. v. Sun Pharmaceutical Industries, Ltd., et al.*, Civil Action No. 14-4307 (JBS)(KMW) (D.N.J.).

31. Pursuant to 28 U.S.C. § 1391(c)(3), Sun Ltd. may be sued in any judicial district because it does not reside in the United States.

32. This Court has personal jurisdiction over, and venue is proper as to, Sun Ltd. because, *inter alia*, it: (1) holds Drug Master File No. 032472 for lubiprostone, the active pharmaceutical ingredient in the ANDA Products; (2) directs and/or controls Sun Inc.; (3) makes its generic pharmaceutical drugs available in the United States, including in New Jersey, through Sun Inc., which has at least two places of business in New Jersey; (4) directly or indirectly markets, distributes, and/or sells its generic pharmaceutical drugs in the State of New Jersey; (5) directly or indirectly maintains pervasive, continuous, and systematic contacts with the State of New Jersey, including through a network of wholesalers and distributors, for the purposes of marketing, distribution, and/or sale of generic pharmaceutical drugs in New Jersey; and (6) enjoys substantial income from sales of its generic pharmaceutical drugs in the State of New Jersey.

33. Upon information and belief, Sun Ltd. purposefully has conducted and continues to conduct business in this Judicial District. Upon information and belief, Sun Ltd. works in concert with its agents with respect to the regulatory approval, manufacturing, marketing, sale, and distribution of its generic pharmaceutical products throughout the United States, including in this Judicial District.

34. Additionally, the business of Sun Ltd. involves challenging patents held by branded pharmaceutical companies, including in this Judicial District. Sun Ltd. has routinely consented to jurisdiction and venue in this Court, and availed itself of the protections afforded by this Court, including by asserting Counterclaims in this Court. *See, e.g., Celgene Corp. v. Sun Pharma Global FZE, et al.*, Civil Action No. 18-11630 (SDW)(LDW) (D.N.J.); *Boehringer Ingelheim Pharmaceuticals Inc., et al. v. Sun Pharmaceutical Industries, Ltd., et al.*, Civil Action No. 17-8819 (MAS)(LHG) (D.N.J.); *Jazz Pharmaceuticals, Inc., et al. v. Sun*



*Pharmaceutical Industries, Ltd., et al.*, Civil Action No. 15-8229 (ES)(JAD) (D.N.J.); *Boehringer Ingelheim Pharmaceuticals, Inc., et al. v. Sun Pharmaceutical Industries Ltd., et al.*, Civil Action No. 15-5982 (PGS)(TJB) (D.N.J.); *Jazz Pharmaceuticals, Inc. v. Sun Pharmaceutical Industries, Ltd., et al.*, Civil Action No. 15-3217 (ES)(JAD) (D.N.J.); *Otsuka Pharmaceutical Co., Ltd. v. Sun Pharmaceutical Industries Ltd., et al.*, Civil Action No. 14-6397 (JBS)(KMW) (D.N.J.); *Otsuka Pharmaceutical Co., Ltd. v. Sun Pharmaceutical Industries, Inc., et al.*, Civil Action No. 14-4307 (JBS)(KMW) (D.N.J.). Sun Ltd. has further availed itself of the jurisdiction of this Court by previously initiating litigations in this Court. *See, e.g., Sun Pharmaceutical Industries Ltd., et al. v. Altana Pharma AG, et al.*, Civil Action No. 05-2391 (KSH) (D.N.J.).

35. Alternatively, to the extent the above facts do not establish personal jurisdiction over Sun Ltd., this Court may exercise jurisdiction over Sun Ltd. pursuant to Federal Rule of Civil Procedure 4(k)(2) because: (a) Plaintiffs' claims arise under federal law; (b) Sun Ltd. would be a foreign defendant not subject to personal jurisdiction in the courts of any state; and (c) Sun Ltd. has sufficient contacts with the United States as a whole, including, but not limited to, manufacturing and selling generic pharmaceutical products that are distributed throughout the United States, such that this Court's exercise of jurisdiction over Sun Ltd. satisfies due process.

**THE PATENTS-IN-SUIT**

36. Sucampo Pharmaceuticals, Inc. holds approved New Drug Application (“NDA”) No. 021908, under which the FDA granted approval on January 31, 2006 for 24 mcg lubiprostone capsules and on April 29, 2008 for 8 mcg lubiprostone capsules, both marketed in the United States under the trade name AMITIZA<sup>®</sup>.

37. AMITIZA<sup>®</sup> (lubiprostone) capsules approved in NDA No. 021908 are indicated for the treatment of chronic idiopathic constipation in adults and the treatment of opioid-induced constipation in adult patients with chronic, non-cancer pain. In addition, AMITIZA<sup>®</sup> (lubiprostone) capsules are indicated for the treatment of irritable bowel syndrome with constipation (“IBS-C”) in women  $\geq$  18 years old.

38. Sucampo AG owns United States Patent No. 7,795,312 (“the ’312 patent”) titled, “Method for Treating Abdominal Discomfort.” The ’312 patent was duly and legally issued on September 14, 2010. A copy of the ’312 patent is attached as Exhibit A.

39. Sucampo AG owns United States Patent No. 8,097,653 (“the ’653 patent”) titled, “Dosage Unit Comprising a Prostaglandin Analog for Treating Constipation.” The ’653 patent was duly and legally issued on January 17, 2012. A copy of the ’653 patent is attached as Exhibit B.

40. Sucampo AG owns United States Patent No. 8,389,542 (“the ’542 patent”) titled, “Dosage Unit Comprising a Prostaglandin Analog for Treating Constipation.” The ’542 patent was duly and legally issued on March 5, 2013. A copy of the ’542 patent is attached as Exhibit C.

41. Sucampo AG and Sucampo Pharma LLC co-own United States Patent No. 8,026,393 (“the ’393 patent”) titled, “Soft-Gelatin Capsule Formulation.” The ’393 patent was duly and legally issued on September 27, 2011. A copy of the ’393 patent is attached as Exhibit D.

42. Sucampo AG and Sucampo Pharma LLC co-own United States Patent No. 8,338,639 (“the ’639 patent”) titled, “Soft-Gelatin Capsule Formulation.” The ’639 patent was duly and legally issued on December 25, 2012. A copy of the ’639 patent is attached as Exhibit E.

43. Sucampo AG and Sucampo Pharma LLC co-own United States Patent No. 8,779,187 (“the ’187 patent”) titled, “Soft-Gelatin Capsule Formulation.” The ’187 patent was duly and legally issued on July 15, 2014. A copy of the ’187 patent is attached as Exhibit F.

44. Sucampo AG owns United States Patent No. 8,748,481 (“the ’481 patent”) titled, “Method for Treating Gastrointestinal Disorder.” The ’481 patent was duly and legally issued on June 10, 2014. A copy of the ’481 patent is attached as Exhibit G.

45. Takeda Pharmaceutical Company Limited is an exclusive licensee to the patents-in-suit. Takeda Pharmaceuticals USA, Inc. is a sublicensee of Takeda Pharmaceutical Company Limited. Takeda Pharmaceuticals America, Inc. is a sublicensee of Takeda Pharmaceuticals USA, Inc.

46. The patents-in-suit are listed in the FDA publication entitled *Approved Drug Products with Therapeutic Equivalence Evaluations* (“the Orange Book”) for AMITIZA<sup>®</sup>.

**SUN ANDA NO. 212292 AND NOTICE LETTER**

47. Upon information and belief, Sun Ltd. and Sun Inc. submitted or caused to be submitted ANDA No. 212292 to the FDA, including a certification with respect to the patents-in-suit under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355) (“Paragraph IV Certification”), seeking approval to engage in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of the ANDA Products prior to expiration of the patents-in-suit.

48. Upon information and belief, on or about September 18, 2018, Sun Ltd. sent the Sun Notice Letter to Sucampo. The Sun Notice Letter represented that ANDA No. 212292 contained Paragraph IV Certifications with respect to the ’312, ’393, ’639, ’653, ’542, ’187, and ’481 patents, and that Sun Ltd. sought approval of ANDA No. 212292 prior to the expiration of those patents.

49. Plaintiffs commenced this action within 45 days of the date of receipt of the Sun Notice Letter dated September 18, 2018.

**INFRINGEMENT OF THE PATENTS-IN-SUIT**

50. Plaintiffs repeat and re-allege paragraphs 1-49 as if fully set forth herein.

51. Sun Ltd. and Sun Inc. are jointly and severally liable for any infringement of the patents-in-suit because, upon information and belief, Sun Ltd. and Sun Inc. actively and knowingly caused to be submitted, assisted with, participated in, contributed to, and/or directed the submission of ANDA No. 212292 and the Paragraph IV Certification to the FDA.

52. By seeking approval of ANDA No. 212292 to engage in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of the ANDA Products prior to the expiration of the '312, '653, '542, '393, '639, '187, and '481 patents, Sun has infringed one or more claims of those patents under 35 U.S.C. § 271(e)(2)(A).

53. If Sun manufactures, uses, offers to sell, or sells within the United States, or imports into the United States, the ANDA Products prior to the expiration of the '312, '653, '542, '393, '639, '187, and '481 patents, Sun will infringe one or more claims of those patents under 35 U.S.C. § 271(a), (b) or (c).

54. Separate and apart from assertions of invalidity, the Sun Notice Letter does not deny or dispute infringement of Claims 7-12 and 18-22 of the '312 patent, Claims 1-13 of the '542 patent, Claims 1-9 and 11-21 of the '393 patent, Claims 1-8, 10, 12, 15, 17, 20-21, and 23 of the '639 patent, Claims 1-9, 11-13, 15, and 16 of the '187 patent, and Claims 1-13 and 15-17 of the '481 patent.

55. Plaintiffs are entitled to relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of the approval of Sun's ANDA be a date that is not earlier than the expiration date of the '312, '653, '542, '393, '639, '187, and '481 patents, or any later expiration of any patent term extension or exclusivity for these patents to which Plaintiffs are or become entitled.

56. Plaintiffs are entitled to a declaration that, if Sun commercially manufactures, uses, offers for sale, or sells the ANDA Products within the United States, imports the ANDA Products into the United States, or induces or contributes to such conduct, Sun will

infringe the '312, '653, '542, '393, '639, '187, and '481 patents under 35 U.S.C. § 271(a), (b), or (c).

57. Plaintiffs will be irreparably harmed by Sun's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

**PRAYER FOR RELIEF**

Plaintiffs request that the Court grant the following relief:

A. An Order adjudging and decreeing that Sun has infringed the '312, '653, '542, '393, '639, '187, and '481 patents by submitting ANDA No. 212292 to the FDA;

B. A permanent injunction pursuant to 35 U.S.C. § 271(e)(4)(B) or 35 U.S.C. § 283 restraining and enjoining Sun, its directors, officers, agents, attorneys, affiliates, divisions, successors and employees, and those acting in concert with Sun, from infringing the '312, '653, '542, '393, '639, '187, and '481 patents by the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of any drug product claimed in the aforementioned patents;

C. An Order pursuant to 35 U.S.C. § 271(e)(4)(A) decreeing that the effective date of any approval of ANDA No. 212292 be a date that is not earlier than the expiration date of the '312, '653, '542, '393, '639, '187, and '481 patents, or any later expiration of any patent term extension or exclusivity for the aforementioned patents to which Plaintiffs are or become entitled;

D. That Plaintiffs be awarded monetary relief to the extent Sun commercially manufactures, uses, offers for sale, or sells within the United States, or imports into the United States any product that infringes or induces or contributes to the infringement of the '312, '653, '542, '393, '639, '187, and '481 patents within the United States prior to the expiration of the

aforementioned patents, including any later expiration of any patent term extension or exclusivity for the patents to which Plaintiffs are or become entitled, and that any such monetary relief be awarded to Plaintiffs with prejudgment interest; and

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

Dated: October 30, 2018

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*Takeda Pharmaceuticals America, Inc.*



**CERTIFICATION PURSUANT TO LOCAL CIVIL RULES 11.2 & 40.1**

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

Dated: October 30, 2018

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Takeda Pharmaceuticals USA, Inc. and  
Takeda Pharmaceuticals America, Inc.*

# **EXHIBIT A**

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

(10) **Patent No.:** **US 7,795,312 B2**  
 (45) **Date of Patent:** **Sep. 14, 2010**

(54) **METHOD FOR TREATING ABDOMINAL DISCOMFORT**  
 (75) Inventors: **Ryuji Ueno**, Montgomery, MD (US);  
**Sachiko Kuno**, Montgomery, MD (US)  
 (73) Assignee: **Sucampo AG**, Zug (CH)

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(\* ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 263 days.

(21) Appl. No.: **10/745,689**

(22) Filed: **Dec. 29, 2003**

(65) **Prior Publication Data**  
 US 2004/0138308 A1 Jul. 15, 2004

**Related U.S. Application Data**

(60) Provisional application No. 60/436,462, filed on Dec. 27, 2002, provisional application No. 60/436,463, filed on Dec. 27, 2002.

(51) **Int. Cl.**  
**A61K 31/5575** (2006.01)

(52) **U.S. Cl.** ..... **514/573**

(58) **Field of Classification Search** ..... None  
 See application file for complete search history.

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(57) **ABSTRACT**

A method for treating irritable bowel syndrome in a mammalian subject includes administering an effective amount of 13,14-dihydro-15-keto-16,16-difluoro-18-methyl-prostaglandin E<sub>1</sub> or 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E<sub>1</sub>, or a salt, ether, ester or amide thereof, to the subject. A method for treating abdominal discomfort associated with irritable bowel syndrome in a mammalian subject includes administering an effective amount of 13,14-dihydro-15-keto-16,16-difluoro-18-methyl-prostaglandin E<sub>1</sub> or 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E<sub>1</sub>, or a salt, ether, ester or amide thereof, to the subject.

**22 Claims, No Drawings**

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**METHOD FOR TREATING ABDOMINAL DISCOMFORT****CROSS-REFERENCE TO RELATED APPLICATIONS**

This application claims the benefit of provisional application Nos. 60/436,462 and 60/436,463 both filed Dec. 27, 2002, the contents of which are incorporated herein by reference in their entireties.

**TECHNICAL FIELD**

The present invention relates to a method for treating abdominal discomfort with a chloride channel opener, especially, a prostaglandin compound.

Further, the present invention relates to a method for treating functional gastrointestinal disorders with a chloride channel opener, especially, a prostaglandin compound.

**BACKGROUND ART**

Abdominal indefinite complaint or abdominal discomfort is most often experienced in our daily lives, and it includes heartburn, nausea, emesis, anorexia, epigastric pain, abdominal bloating, chronic abdominal pain, abdominal discomfort, abnormal bowel movement such as constipation and diarrhea and the like. Various disorders may cause abdominal discomfort. It is also known that abdominal discomfort may also occur as a side effect of drug, medication or surgical procedure. However, it is not yet known as to the drug that may be used for safely and effectively treating abdominal discomfort.

Patients having functional gastrointestinal disorders often report abdominal discomfort. Functional gastrointestinal disorders are characterized by chronic or recurrent gastrointestinal symptoms which are not explained by any organic, i.e. structural or biochemical, abnormality. In general, functional disorders should be distinguished from morphological or organic disorders in which the organ structures have been abnormally changed. An organic disorder may accompany functional abnormality of organs but it is surely possible to diagnose if there is any underlying organic abnormality.

Stress may effect on various organs in various ways, and the typical example of such organs is gastrointestinal tract. The interaction among stress-brain-gastrointestinal organ is called brain-gut axis, and now a days, it draws great interest of the art. In the field of clinical medicine, a group of functional disorders in which the brain-gut axis plays a central role of the pathology is called functional gastrointestinal disorders.

Typical examples of functional gastrointestinal disorders include irritable bowel syndrome (IBS) and functional dyspepsia (FD). These terms are not used for exclusively determining the nature of separate disorders but most commonly used for expressing various overlapping symptoms manifested in the upper and lower gastrointestinal tracts.

IBS is an archetype disorder of functional gastrointestinal disorders with no underlying organic abnormality. IBS patient reports continued lower gastrointestinal symptoms such as abnormal bowel movement, abdominal pain, abdominal bloating and abdominal discomfort, as well as upper gastrointestinal symptoms such as epigastric pain, hypochondriac pain, nausea, anorexia, borborygmus, vomiting, belching and heartburn.

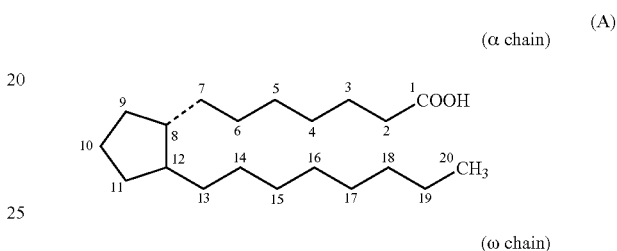
FD patient has no underlying organic disorder such as ulcer and reports continued upper gastrointestinal tract symptoms such as abdominal pain, nausea, anorexia and slow digestion. The term "dyspepsia" means chronic or repetitious pain or

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discomfort mainly occurring in epigastric region. Up to 60% of the dyspepsia patients have no underlying organic disorder and are diagnosed as FD.

As explained above, functional gastrointestinal disorders are a group of disorders in which the gastrointestinal symptoms continue for a long period or by repeating a period of recrudescence and palliation without clear organic abnormalities. No systematic method has been established for treating such disorder.

Prostaglandins (hereinafter, referred to as PG(s)) are members of class of organic carboxylic acids, which are contained in tissues or organs of human or other mammals, and exhibit a wide range of physiological activity. PGs found in nature (primary PGs) generally have a prostanoid acid skeleton as shown in the formula (A):



On the other hand, some of synthetic analogues of primary PGs have modified skeletons. The primary PGs are classified to PGAs, PGBs, PGCs, PGDs, PGEs, PGFs, PGGs, PGHs, PGIs and PGJs according to the structure of the five-membered ring moiety, and further classified into the following three types by the number and position of the unsaturated bond at the carbon chain moiety:

Subscript 1: 13,14-unsaturated-15-OH

Subscript 2: 5,6- and 13,14-diunsaturated-15-OH

Subscript 3: 5,6-, 13,14-, and 17,18-triunsaturated-15-OH.

Further, the PGFs are classified, according to the configuration of the hydroxyl group at the 9-position, into  $\alpha$  type (the hydroxyl group is an  $\alpha$ -configuration) and  $\beta$  type (the hydroxyl group is a  $\beta$ -configuration).

PGE<sub>1</sub> and PGE<sub>2</sub> and PGE<sub>3</sub> are known to have vasodilation, hypotension, gastric secretion decreasing, intestinal tract movement enhancement, uterine contraction, diuretic, bronchodilation and anti ulcer activities. PGF<sub>1 $\alpha$</sub> , PGF<sub>2 $\alpha$</sub>  and PGF<sub>3 $\alpha$</sub>  have been known to have hypertension, vasoconstriction, intestinal tract movement enhancement, uterine contraction, lutein body atrophy and bronchoconstriction activities.

The present inventor already found that prostaglandin compounds open chloride channels, especially CIC channels, more especially CIC-2 channel (WO 03/030912, this reference is herein incorporated by reference).

However, it is not known how chloride channel openers and/or prostaglandin compounds act on abdominal discomfort, or the functional gastrointestinal disorders.

**DISCLOSURE OF THE INVENTION**

The present inventor has conducted intensive studies and found that a chloride channel opener, especially prostaglandin compound have a significant effect on abdominal discomfort, especially, on functional gastrointestinal disorders such as IBS and FD, which resulted in the completion of the present invention.

Namely, the present invention relates to a method for treating abdominal discomfort in a mammalian subject, which

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comprises administration of an effective amount of a chloride channel opener, especially CIC channel opener, more especially CIC-2 opener such as prostaglandin compound to the subject.

The present invention further relates to a pharmaceutical composition for treating abdominal discomfort in a mammalian subject, which comprises an effective amount of a chloride channel opener, especially CIC channel opener, more especially CIC-2 channel opener such as prostaglandin compound.

Further more, the present invention relates to a use of a chloride channel opener, especially CIC channel opener, more especially CIC-2 channel opener such as prostaglandin compound for manufacturing a pharmaceutical composition for treating abdominal discomfort in a mammalian subject.

Another embodiment of the present invention relates to a method for treating functional gastrointestinal disorders in a mammalian subject, which comprises administration of an effective amount of a chloride channel opener, especially CIC channel opener, more especially CIC-2 channel opener such as prostaglandin compound to the subject.

The present invention further relates to a pharmaceutical composition for treating functional gastrointestinal disorders in a mammalian subject, which comprises an effective amount of a chloride channel opener, especially CIC channel opener, more especially CIC-2 channel opener such as prostaglandin compound.

Further more, the present invention relates to a use of a chloride channel opener, especially CIC channel operator, more especially CIC-2 channel such as prostaglandin compound for manufacturing a pharmaceutical composition for treating functional gastrointestinal disorders in a mammalian subject.

#### DETAILED DESCRIPTION OF THE INVENTION

The chloride channel opener used in the present invention is not particularly limited and may be any compound as far as it has a chloride channel opening activity. The chloride channel opening activity may be confirmed by measuring the increase of chloride-ion flows through a chloride channel in a cell membrane from inside to outside of the cell or in the opposite direction. For instance, it is possible to carry out a screening for a compound having chloride channel opening activity by using a known assay strategy such as the patch clamp. Preferred chloride channel opener is a CIC channel opener, especially a CIC-2 channel opener.

Examples of compounds having the opening activity of a CIC-2 channel include cyclooxygenase inhibitor, nonsteroidal anti-inflammatory agent (e.g. ibuprofen and ebselen), protein kinase A, oleic acid, elaidic acid, arachidonic acid, cell growth factor (e.g., TGF $\alpha$  (transforming growth factor- $\alpha$ ) and KGF (keratinocyte growth factor)), benzimidazole derivative and prostaglandin compound. Preferred compound of the present invention is a prostaglandin compound.

The nomenclature of the prostaglandin compounds used herein is based on the numbering system of the prostanic acid represented in the above formula (A).

The formula (A) shows a basic skeleton of the C-20 carbon atoms, but the present invention is not limited to those having the same number of carbon atoms. In the formula (A), the numbering of the carbon atoms which constitute the basic skeleton of the PG compounds starts at the carboxylic acid (numbered 1), and carbon atoms in the  $\alpha$ -chain are numbered 2 to 7 towards the five-membered ring, those in the ring are 8 to 12, and those in the  $\omega$ -chain are 13 to 20. When the number of carbon atoms is decreased in the  $\alpha$ -chain, the number is

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deleted in the order starting from position 2; and when the number of carbon atoms is increased in the  $\alpha$ -chain, compounds are named as substitution compounds having respective substituents at position 2 in place of the carboxy group (C-1). Similarly, when the number of carbon atoms is decreased in the  $\omega$ -chain, the number is deleted in the order starting from position 20; and when the number of carbon atoms is increased in the  $\omega$ -chain, the carbon atoms beyond position 20 are named as substituents. Stereochemistry of the compounds is the same as that of the above formula (A) unless otherwise specified.

In general, each of the terms PGD, PGE and PGF represents a PG compound having hydroxy groups at positions 9 and/or 11, but in the present specification, these terms also include those having substituents other than the hydroxy group at positions 9 and/or 11. Such compounds are referred to as 9-dehydroxy-9-substituted-PG compounds or 11-dehydroxy-11-substituted-PG compounds. A PG compound having hydrogen in place of the hydroxy group is simply named as 9- or 11-dehydroxy-PG compound.

As stated above, the nomenclature of the PG compounds is based on the prostanic acid skeleton. However, in case the compound has a similar partial structure as a prostaglandin, the abbreviation of "PG" may be used. Thus, a PG compound of which  $\alpha$ -chain is extended by two carbon atoms, that is, having 9 carbon atoms in the  $\alpha$ -chain is named as 2-decarboxy-2-(2-carboxyethyl)-PG compound. Similarly, a PG compound having 11 carbon atoms in the  $\alpha$ -chain is named as 2-decarboxy-2-(4-carboxybutyl)-PG compound. Further, a PG compound of which  $\omega$ -chain is extended by two carbon atoms, that is, having 10 carbon atoms in the  $\omega$ -chain is named as 20-ethyl-PG compound. These compounds, however, may also be named according to the IUPAC nomenclatures.

Examples of the analogs (including substituted derivative) or derivatives include a PG compound of which carboxy group at the end of  $\alpha$ -chain is esterified; a compound of which  $\alpha$ -chain is extended; physiologically acceptable salt thereof; a compound having a double bond at 2-3 position or a triple bond at position 5-6, a compound having substituent(s) at position 3, 5, 6, 16, 17, 18, 19 and/or 20; and a compound having lower alkyl or a hydroxy (lower) alkyl group at position 9 and/or 11 in place of the hydroxy group.

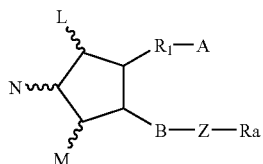
According to the present invention, preferred substituents at position 3, 17, 18 and/or 19 include alkyl having 1-4 carbon atoms, especially methyl and ethyl. Preferred substituents at position 16 include lower alkyl such as methyl and ethyl, hydroxy, halogen atoms such as chlorine and fluorine, and aryloxy such as trifluoromethylphenoxy. Preferred substituents at position 17 include lower alkyl such as methyl and ethyl, hydroxy, halogen atoms such as chlorine and fluorine, aryloxy such as trifluoromethylphenoxy. Preferred substituents at position 20 include saturated or unsaturated lower alkyl such as C1-4 alkyl, lower alkoxy such as C1-4 alkoxy, and lower alkoxy alkyl such as C1-4 alkoxy-C1-4 alkyl. Preferred substituents at position 5 include halogen atoms such as chlorine and fluorine. Preferred substituents at position 6 include an oxo group forming a carbonyl group. Stereochemistry of PGs having hydroxy, lower alkyl or hydroxy(lower) alkyl substituent at position 9 and/or 11 may be  $\alpha$ ,  $\beta$  or a mixture thereof.

Further, the above analogs or derivatives may be compounds having an alkoxy, cycloalkyl, cycloalkyloxy, phenoxy or phenyl group at the end of the  $\omega$ -chain where the chain is shorter than the primary PGs.

A preferred compounds used in the present invention is represented by the formula (I):

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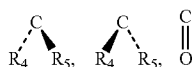


wherein L, M and N are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is —CH<sub>3</sub>, or —CH<sub>2</sub>OH, —COCH<sub>2</sub>OH, —COOH or a functional derivative thereof;

B is single bond, —CH<sub>2</sub>—CH<sub>2</sub>—, —CH=CH—, —C≡C—, —CH<sub>2</sub>—CH<sub>2</sub>—CH<sub>2</sub>—, —CH=CH—CH<sub>2</sub>—, —CH<sub>2</sub>—CH=CH—, —C≡C—CH<sub>2</sub>— or —CH<sub>2</sub>—C≡C—;

Z is



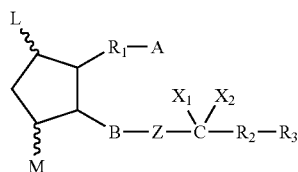
or single bond

wherein R<sub>4</sub> and R<sub>5</sub> are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein R<sub>4</sub> and R<sub>5</sub> are not hydroxy and lower alkoxy at the same time;

R<sub>1</sub> is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur; and

R<sub>a</sub> is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocyclic-oxy group; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic group; heterocyclic-oxy group.

A preferred compound used in the present invention is represented by the formula (II):



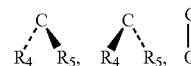
wherein L and M are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have one or more double bonds;

A is —CH<sub>3</sub>, or —CH<sub>2</sub>OH, —COCH<sub>2</sub>OH, —COOH or a functional derivative thereof;

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(I) B is a single bond, —CH<sub>2</sub>—CH<sub>2</sub>—, —CH=CH—, —C≡C—, —CH<sub>2</sub>—CH<sub>2</sub>—CH<sub>2</sub>—, —CH=CH—CH<sub>2</sub>—, —CH<sub>2</sub>—CH=CH—, —C≡C—CH<sub>2</sub>— or —CH<sub>2</sub>—C≡C—;

Z is



or single bond

wherein R<sub>4</sub> and R<sub>5</sub> are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein R<sub>4</sub> and R<sub>5</sub> are not hydroxy and lower alkoxy at the same time;

X<sub>1</sub> and X<sub>2</sub> are hydrogen, lower alkyl, or halogen;

R<sub>1</sub> is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur;

R<sub>2</sub> is a single bond or lower alkylene; and

R<sub>3</sub> is lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocyclic-oxy group.

In the above formula, the term “unsaturated” in the definitions for R<sub>1</sub> and R<sub>a</sub> is intended to include at least one or more double bonds and/or triple bonds that are isolatedly, separately or serially present between carbon atoms of the main and/or side chains. According to the usual nomenclature, an unsaturated bond between two serial positions is represented by denoting the lower number of the two positions, and an unsaturated bond between two distal positions is represented by denoting both of the positions.

The term “lower or medium aliphatic hydrocarbon” refers to a straight or branched chain hydrocarbon group having 1 to 14 carbon atoms (for a side chain, 1 to 3 carbon atoms are preferable) and preferably 1 to 10, especially 1 to 8 carbon atoms.

The term “halogen atom” covers fluorine, chlorine, bromine and iodine.

The term “lower” throughout the specification is intended to include a group having 1 to 6 carbon atoms unless otherwise specified.

The term “lower alkyl” refers to a straight or branched chain saturated hydrocarbon group containing 1 to 6 carbon atoms and includes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl and hexyl.

The term “lower alkylene” refers to a straight or branched chain bivalent saturated hydrocarbon group containing 1 to 6 carbon atoms and includes, for example, methylene, ethylene, propylene, isopropylene, butylene, isobutylene, t-butylene, pentylene and hexylene. The term “lower alkoxy” refers to a group of lower alkyl-O—, wherein lower alkyl is as defined above.

The term “hydroxy(lower)alkyl” refers to a lower alkyl as defined above which is substituted with at least one hydroxy group such as hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 1-methyl-1-hydroxyethyl.

The term “lower alkanoyloxy” refers to a group represented by the formula RCO-O—, wherein RCO- is an acyl group formed by oxidation of a lower alkyl group as defined above, such as acetyl.

The term “cyclo(lower)alkyl” refers to a cyclic group formed by cyclization of a lower alkyl group as defined above



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but contains three or more carbon atoms, and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "cyclo(lower)alkyloxy" refers to the group of cyclo(lower)alkyl-O—, wherein cyclo(lower)alkyl is as defined above.

The term "aryl" may include unsubstituted or substituted aromatic hydrocarbon rings (preferably monocyclic groups), for example, phenyl, tolyl, xylyl. Examples of the substituents are halogen atom and halo(lower)alkyl, wherein halogen atom and lower alkyl are as defined above.

The term "aryloxy" refers to a group represented by the formula ArO—, wherein Ar is aryl as defined above. The term "heterocyclic group" may include mono- to tri-cyclic, preferably monocyclic heterocyclic group which is 5 to 14, preferably 5 to 10 membered ring having optionally substituted carbon atom and 1 to 4, preferably 1 to 3 of 1 or 2 type of hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom. Examples of the heterocyclic group include furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, 2-pyrrolinyl, pyrrolidinyl, 2-imidazoliny, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, piperidino, piperazinyl, morpholino, indolyl, benzothienyl, quinolyl, isoquinolyl, purinyl, quinazoliny, carbazolyl, acridinyl, phenanthridinyl, benzimidazolyl, benzimidazoliny, benzothiazolyl, phenothiazinyl. Examples of the substituent in this case include halogen, and halogen substituted lower alkyl group, wherein halogen atom and lower alkyl group are as described above.

The term "heterocyclic-oxy group" means a group represented by the formula HcO—, wherein Hc is a heterocyclic group as described above.

The term "functional derivative" of A includes salts (preferably pharmaceutically acceptable salts), ethers, esters and amides.

Suitable "pharmaceutically acceptable salts" include conventionally used non-toxic salts, for example a salt with an inorganic base such as an alkali metal salt (such as sodium salt and potassium salt), an alkaline earth metal salt (such as calcium salt and magnesium salt), an ammonium salt; or a salt with an organic base, for example, an amine salt (such as methylamine salt, dimethylamine salt, cyclohexylamine salt, benzylamine salt, piperidine salt, ethylenediamine salt, ethanolamine salt, diethanolamine salt, triethanolamine salt, tris (hydroxymethylamino)ethane salt, monomethyl- monoethanolamine salt, procaine salt and caffeine salt), a basic amino acid salt (such as arginine salt and lysine salt), tetraalkyl ammonium salt and the like. These salts may be prepared by a conventional process, for example from the corresponding acid and base or by salt interchange.

Examples of the ethers include alkyl ethers, for example, lower alkyl ethers such as methyl ether, ethyl ether, propyl ether, isopropyl ether, butyl ether, isobutyl ether, t-butyl ether, pentyl ether and 1-cyclopropyl ethyl ether; and medium or higher alkyl ethers such as octyl ether, diethylhexyl ether, lauryl ether and cetyl ether; unsaturated ethers such as oleyl ether and linolenyl ether; lower alkenyl ethers such as vinyl ether, allyl ether; lower alkynyl ethers such as ethynyl ether and propynyl ether; hydroxy(lower)alkyl ethers such as hydroxyethyl ether and hydroxyisopropyl ether; lower alkoxy (lower)alkyl ethers such as methoxymethyl ether and 1-methoxyethyl ether; optionally substituted aryl ethers such as phenyl ether, tosyl ether, t-butylphenyl ether, salicyl ether, 3,4-di-methoxyphenyl ether and benzamidophenyl ether; and aryl(lower)alkyl ethers such as benzyl ether, trityl ether and benzhydryl ether.

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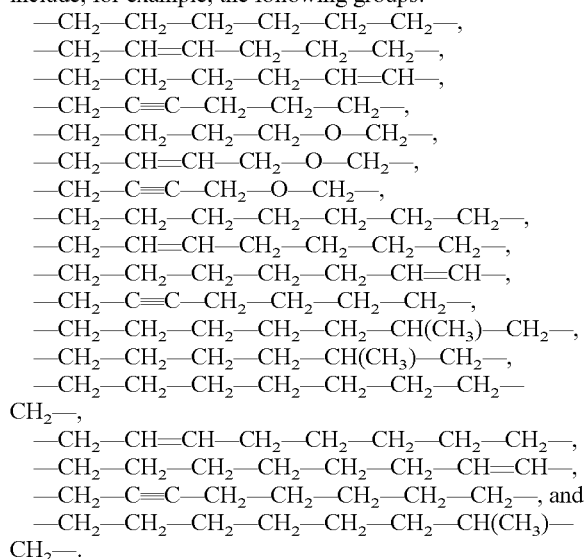
Examples of the esters include aliphatic esters, for example, lower alkyl esters such as methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester and 1-cyclopropylethyl ester; lower alkenyl esters such as vinyl ester and allyl ester; lower alkynyl esters such as ethynyl ester and propynyl ester; hydroxy(lower)alkyl ester such as hydroxyethyl ester; lower alkoxy (lower)alkyl esters such as methoxymethyl ester and 1-methoxyethyl ester; and optionally substituted aryl esters such as, for example, phenyl ester, tolyl ester, t-butylphenyl ester, salicyl ester, 3,4-di-methoxyphenyl ester and benzamidophenyl ester; and aryl(lower)alkyl ester such as benzyl ester, trityl ester and benzhydryl ester.

The amide of A mean a group represented by the formula —CONR'R", wherein each of R' and R" is hydrogen, lower alkyl, aryl, alkyl- or aryl-sulfonyl, lower alkenyl and lower alkynyl, and include for example lower alkyl amides such as methylamide, ethylamide, dimethylamide and diethylamide; arylamides such as anilide and toluidide; and alkyl- or aryl-sulfonylamides such as methylsulfonylamide, ethylsulfonylamide and tolylsulfonylamide.

Preferred examples of L and M include hydroxy and oxo, and especially, M is hydroxy and L is oxo which as a 5-membered ring structure of, so called, PGE type. Preferred example of A is —COOH, its pharmaceutically acceptable salt, ester or amide thereof.

Preferred example of X<sub>1</sub> and X<sub>2</sub> is fluorine, so called 16,16-difluoro type.

Preferred R<sub>1</sub> is a hydrocarbon residue containing 1-10 carbon atoms, preferably 6-10 carbon atoms. Further, at least one carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur. Examples of R<sub>1</sub> include, for example, the following groups:



Preferred Ra is a hydrocarbon containing 1-10 carbon atoms, more preferably, 1-8 carbon atoms. Ra may have one or two side chains having one carbon atom.

The configuration of the ring and the  $\alpha$ - and/or  $\omega$  chains in the above formula (I) and (II) may be the same as or different from that of the primary PGs. However, the present invention also includes a mixture of a compound having a primary type configuration and a compound of a non-primary type configuration.

In the present invention, the PG compound which is dihydro between 13 and 14, and keto (=O) at 15 position may be in the keto-hemiacetal equilibrium by formation of a hemiacetal between hydroxy at position 11 and keto at position 15.



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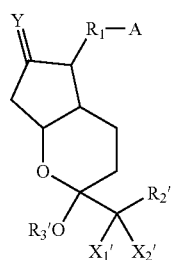
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For example, it has been revealed that when both of  $X_1$  and  $X_2$  are halogen atoms, especially, fluorine atoms, the compound contains a tautomeric isomer, bicyclic compound.

If such tautomeric isomers as above are present, the proportion of both tautomeric isomers varies with the structure of the rest of the molecule or the kind of the substituent present. Sometimes one isomer may predominantly be present in comparison with the other. However, it is to be appreciated that the present invention includes both isomers.

Further, the 15-keto-PG compounds used in the invention include the bicyclic compound and analogs or derivative thereof.

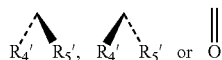
The bicyclic compound is represented by the formula (III)



wherein, A is  $-\text{CH}_3$ , or  $-\text{CH}_2\text{OH}$ ,  $-\text{COCH}_2\text{OH}$ ,  $-\text{COOH}$  or a functional derivative thereof;

$X_1'$  and  $X_2'$  are hydrogen, lower alkyl, or halogen;

Y is



wherein  $R_4'$  and  $R_5'$  are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein  $R_4'$  and  $R_5'$  are not hydroxy and lower alkoxy at the same time.

$R_1$  is a saturated or unsaturated divalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur; and

$R_2'$  is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocyclic-oxo group; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic group; heterocyclic-oxo group.

$R_3'$  is hydrogen, lower alkyl, cyclo(lower)alkyl, aryl or heterocyclic group.

Furthermore, while the compounds used in the invention may be represented by a formula or name based on keto-type regardless of the presence or absence of the isomers, it is to be noted that such structure or name does not intend to exclude the hemiacetal type compound.

In the present invention, any of isomers such as the individual tautomeric isomers, the mixture thereof, or optical isomers, the mixture thereof, a racemic mixture, and other steric isomers may be used in the same purpose.

Some of the compounds used in the present invention may be prepared by the method disclosed in U.S. Pat. Nos. 5,073,

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569, 5,166,174, 5,221,763, 5,212,324, 5,739,161 and 6,242,485 (these cited references are herein incorporated by reference).

The term "chloride or CIC or CIC-2 channel opener" used herein includes the compound which activates, promotes or modulates the  $\text{Cl}^-$  current,  $\text{Cl}^-$  secretion or  $\text{Cl}^-$  transport by opening chloride or CIC or CIC-2 channel.

According to the present invention a mammalian subject may be treated by the instant invention by administering the compound used in the present invention. The subject may be any mammalian subject including a human. The compound may be applied systemically or topically. Usually, the compound may be administered by oral administration, intravenous injection (including infusion), subcutaneous injection, intra rectal administration, intra vaginal administration, transdermal administration and the like. The dose may vary depending on the strain of the animal, age, body weight, symptom to be treated, desired therapeutic effect, administration route, term of treatment and the like. A satisfactory effect can be obtained by systemic administration 1-4 times per day or continuous administration at the amount of 0.001-1000  $\mu\text{g}/\text{kg}$  per day, more preferably 0.01-100  $\mu\text{g}/\text{kg}$ , most preferably 0.1-10  $\mu\text{g}/\text{kg}$ .

A typical treatment regimen entails administering to a human patient a composition containing from about 18 to about 30  $\mu\text{g}$  of active ingredient according to the invention from one to three times daily, with about 24  $\mu\text{g}$  two times per day being preferred. The composition for the oral administration may be administered with or without food and/or water.

The compound may preferably be formulated in a pharmaceutical composition suitable for administration in a conventional manner. The composition may be those suitable for oral administration, injection or perfusion as well as it may be an external agent, suppository or pessary.

The composition of the present invention may further contain physiologically acceptable additives. Said additives may include the ingredients used with the present compounds such as excipient, diluent, filler, solvent, lubricant, adjuvant, binder, disintegrator, coating agent, cupulating agent, ointment base, suppository base, aerosoling agent, emulsifier, dispersing agent, suspending agent, thickener, tonicity agent, buffering agent, soothing agent, preservative, antioxidant, corrigent, flavor, colorant a functional material such as cyclodextrin and biodegradable polymer, stabilizer. The additives are well known to the art and may be selected from those described in general reference books of pharmaceuticals.

The amount of the above-defined compound in the composition of the invention may vary depending on the formulation of the composition, and may generally be 0.00001-10.0 wt %, more preferably 0.0001-1.0 wt %, most preferably 0.001-0.1%.

Examples of solid compositions for oral administration include tablets, troches, sublingual tablets, capsules, pills, powders, granules and the like. The solid composition may be prepared by mixing one or more active ingredients with at least one inactive diluent. The composition may further contain additives other than the inactive diluents, for example, a lubricant, a disintegrator and a stabilizer. Tablets and pills may be coated with an enteric or gastroenteric film, if necessary. They may be covered with two or more layers. They may also be absorbed to a sustained release material, or microcapsulated. Additionally, the compositions may be encapsulated by means of an easily degradable material such gelatin. They may be further dissolved in an appropriate solvent such as fatty acid or its mono, di or triglyceride to be a soft capsule. Sublingual tablet may be used in need of fast-acting property.

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Examples of liquid compositions for oral administration include emulsions, solutions, suspensions, syrups and elixirs and the like. Said composition may further contain a conventionally used inactive diluents e.g. purified water or ethyl alcohol. The composition may contain additives other than the inactive diluents such as adjuvant e.g. wetting agents and suspending agents, sweeteners, flavors, fragrance and preservatives.

The composition of the present invention may be in the form of spraying composition, which contains one or more active ingredients and may be prepared according to a known method.

Examples of the injectable compositions of the present invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions and emulsions. Diluents for the aqueous solution or suspension may include, for example, distilled water for injection, physiological saline and Ringer's solution.

Non-aqueous diluents for solution and suspension may include, for example, propylene glycol, polyethylene glycol, vegetable oils such as olive oil, alcohols such as ethanol and polysorbate. The composition may further comprise additives such as preservatives, wetting agents, emulsifying agents, dispersing agents and the like. They may be sterilized by filtration through, e.g. a bacteria-retaining filter, compounding with a sterilizer, or by means of gas or radioisotope irradiation sterilization. The injectable composition may also be provided as a sterilized powder composition to be dissolved in a sterilized solvent for injection before use.

The present external agent includes all the external preparations used in the fields of dermatology and otolaryngology, which includes ointment, cream, lotion and spray.

Another form of the present invention is suppository or pessary, which may be prepared by mixing active ingredients into a conventional base such as cacao butter that softens at body temperature, and nonionic surfactants having suitable softening temperatures may be used to improve absorbability.

The term "treatment" used herein includes any means of control such as prevention, care, relief of the condition, attenuation of the condition and arrest of progression.

The term "abdominal discomfort" used herein includes any abdominal discomfort involved or being associated with any type of condition and/or diseases, or caused by drugs, medications or surgical procedures.

In the present specification and claims, "treatment of abdominal discomfort" or "treating abdominal discomfort" includes to relieve or to eliminate the abdominal discomfort. In addition, "treatment of functional gastrointestinal disorder" or "treating functional gastrointestinal disorder" covers to relieve or to eliminate abdominal discomfort which is associated with functional gastrointestinal disorders.

One of the typical disorders being accompanied by abdominal discomfort includes functional gastrointestinal disorders. Examples of the functional gastrointestinal disorders include irritable bowel syndrome and functional dyspepsia.

The pharmaceutical composition of the present invention may further contain other pharmacological ingredients as far as they do not contradict the purpose of the present invention.

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The further details of the present invention will follow with reference to test examples, which, however, are not intended to limit the present invention.

## EXAMPLE 1

## Methods

Patients with irritable bowel syndrome (IBS) were randomly allocated to the following two treatment groups.

Group 1: Test substance (13,14-dihydro-15-keto-16,16-difluoro-PGE<sub>1</sub>) 48 µg total (24 µg/breakfast+24 µg/dinner)

Group 2: Matching placebo (placebo/breakfast+placebo/dinner)

Each group underwent two weeks washout period and then began to administer oral test substance (capsules) or placebo (capsules) daily for 4 weeks. Test substance or placebo was taken two times a day (b.i.d) at breakfast with food and at least 8 ounces of water and at dinner with food and at least 8 ounces of water. Patients were asked to evaluate abdominal discomfort upon waking in the morning, using a 5-point scale (Score: 0=absent, 1=mild, 2=moderate, 3=severe, 4=very severe) at 4 weeks after the initiation of the treatments.

## Results

As shown in Table 1, test substance of this invention significantly improved the abdominal discomfort in the patients with IBS.

TABLE 1

Effect of test substance on abdominal discomfort in patients with IBS		
Abdominal discomfort score, Mean ± SD (N)		
Week	Placebo	Test Substance
Baseline	2.31 ± 0.788 (26)	2.25 ± 0.803 (32)
Week 4	2.19 ± 0.895 (26)	1.48 ± 1.029** (31)

Test substance: 13,14-dihydro-15-keto-16,16-difluoro-PGE<sub>1</sub>

\*\*p < 0.01 (van Elteren test stratified by center)

## EXAMPLE 2

## Method

Patients with occasional constipation were randomly allocated to the following two treatment groups.

Group 1: Test substance (13,14-dihydro-15-keto-16,16-difluoro-PGE<sub>1</sub>) 48 µg total (24 µg/breakfast+24 µg/dinner)

Group 2: Matching placebo (placebo/breakfast+placebo/dinner)

Each group underwent two weeks washout period and then began to administer oral test substance (capsules) or placebo (capsules) daily for 4 weeks. During the washout period, the patient's bowel habit was documented to confirm the existence of constipation. Constipation is defined as, on average, less than three spontaneous bowel movements per week. All existing laxative medication was withdrawn at the start of the washout period and the patients were instructed not to change their diet or lifestyle during the study.

Test substance or placebo was taken orally for a total treatment period of 4 weeks; it was taken two times a day (b.i.d) at

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breakfast with food and at least 8 ounces of water and at dinner with food and at least 8 ounces of water.

The patients were asked to evaluate abdominal discomfort upon waking in the morning, using a 5-point scale (Score: 0=absent, 1=mild, 2=moderate, 3=severe, 4=very severe) at 2 and 4 weeks after the initiation of the treatments.

## Results

As shown in Table 2, test substance of this invention significantly improved the abdominal discomfort in patients with constipation.

TABLE 2

Effect of test substance on abdominal discomfort in patients with constipation		
Abdominal discomfort score, Mean $\pm$ SD (N)		
	Placebo	Test Substance
Week 2	1.41 $\pm$ 1.035 (122)	1.09 $\pm$ 1.047* (116)
Week 3	1.64 $\pm$ 1.114 (122)	1.27 $\pm$ 1.057* (117)
Week 4	1.52 $\pm$ 1.038 (122)	1.22 $\pm$ 1.060* (117)

Test substance: 13,14-dihydro-15-keto-16,16-difluoro-PGE<sub>1</sub>

\*p < 0.05 (van Elteren test stratified by center)

## EXAMPLE 3

## Methods

Patients with irritable bowel syndrome (IBS) were randomly allocated to the following two treatment groups.

Group 1: Test substance (13,14-dihydro-15-keto-16,16-difluoro-PGE<sub>1</sub>) 48  $\mu$ g total (24  $\mu$ g/breakfast+24  $\mu$ g/dinner)

Group 2: Matching placebo (placebo/breakfast+placebo/dinner)

Each group underwent two weeks washout period and then began to administer oral test substance (capsules) or placebo (capsules) daily for 4 weeks. Test substance or placebo was taken two times a day (b.i.d) at breakfast with food and at least 8 ounces of water and at dinner with food and at least 8 ounces of water. The patients were asked to evaluate abdominal bloating upon waking in the morning, using a 5-point scale (Score: 0=absent, 1=mild, 2=moderate, 3=severe, 4=very severe) at 4 weeks after the initiation of the treatments.

## Results

As shown in Table 3, test substance of this invention significantly improved the abdominal bloating in patients with IBS.

TABLE 3

Effect of test substance on abdominal bloating in patients with IBS		
Abdominal bloating score, Mean $\pm$ SD (N)		
Week	Placebo	Test Substance
Baseline	2.46 $\pm$ 0.859 (26)	2.50 $\pm$ 0.916 (32)
Week 4	2.42 $\pm$ 0.945 (26)	1.74 $\pm$ 0.999** (31)

Test substance: 13,14-dihydro-15-keto-16,16-difluoro-PGE<sub>1</sub>

\*\*p < 0.01 (van Elteren test stratified by center)

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## EXAMPLE 4

## Methods

Patients with irritable bowel syndrome (IBS) exhibiting dyschezia were randomly allocated to the following two treatment groups.

Group 1: Test substance (13,14-dihydro-15-keto-16,16-difluoro-PGE<sub>1</sub>) 48  $\mu$ g total (24  $\mu$ g/breakfast+24  $\mu$ g/dinner)

Group 2: Matching placebo (placebo/breakfast+placebo/dinner)

Each group underwent two weeks washout period and then began to administer oral test substance (capsules) or placebo (capsules) daily for 4 weeks. Test substance or placebo was taken two times a day (b.i.d) at breakfast with food and at least 8 ounces of water and at dinner with food and at least 8 ounces of water. After 3 consecutive days of not having spontaneous bowel movement, the investigator could prescribe to the patient 10 mg bisacodyl suppository as a rescue medication. If this was not effective, Fleet® enema could be used. During the study period, each patient documented bowel activity. A spontaneous bowel movement was defined as any bowel movement except for that occurred within 24 hours after the rescue medication. Frequency of spontaneous bowel movements at Baseline, Weeks 1, 2, 3 and 4 were analyzed.

## Results

As shown in Table 4, test substance of this invention significantly improved the spontaneous bowel movement frequency in patients with IBS exhibiting dyschezia.

TABLE 4

Effect of test substance on spontaneous bowel movement frequency rates in patients with IBS exhibiting dyschezia		
Spontaneous Bowel Movement Frequency Rates, Mean $\pm$ SD (N)		
Week	Placebo	Test Substance
Baseline	1.85 $\pm$ 2.310 (26)	1.43 $\pm$ 0.773 (32)
Week 1	3.58 $\pm$ 2.887 (26)	6.50 $\pm$ 4.108** (32)
Week 2	2.84 $\pm$ 2.481 (26)	5.58 $\pm$ 4.003** (32)
Week 3	2.30 $\pm$ 2.170 (26)	5.93 $\pm$ 4.775** (32)
Week 4	2.21 $\pm$ 2.399 (26)	5.17 $\pm$ 4.333* (32)

Test substance: 13,14-dihydro-15-keto-16,16-difluoro-PGE<sub>1</sub>

\*p < 0.05, \*\* p < 0.01 (van Elteren test stratified by center)

What is claimed is:

1. A method for treating irritable bowel syndrome in a mammalian subject, which comprises administering an effective amount of 13,14-dihydro-15-keto-16,16-difluoro-18-methyl-prostaglandin E<sub>1</sub>, or a salt, ether, ester or amide thereof, to the subject.

2. The method as described in claim 1, which comprises administering an effective amount of 13,14-dihydro-15-keto-16,16-difluoro-18-methyl-prostaglandin E<sub>1</sub>, or a pharmaceutically acceptable salt, ester or amide thereof.

3. The method as described in claim 1, which comprises systemic administration 1-4 times per day or continuous administration in the amount of 0.01-100  $\mu$ g/kg per day or a 13,14-dihydro-15-keto-16,16-difluoro-18-methyl-prostaglandin E<sub>1</sub> compound.

4. A method for treating as described in claim 2, wherein the administration is in the amount of 0.1-10  $\mu$ g/kg per day.

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5. The method as described in claim 1, which comprises systemic administration 1-4 times per day or continuous administration at the amount of 0.01-100  $\mu$ g/kg per day.

6. The method as described in claim 5, wherein the administration is at the amount of 0.1-10  $\mu$ g/kg per day.

7. A method for treating irritable bowel syndrome in a mammalian subject, which comprises administering an effective amount of 13,14-dihydro-15-keto-16,16-difluoro prostaglandin E<sub>1</sub> or a salt, ether, ester or amide thereof, to the subject.

8. The method as described in claim 7, which comprises administering an effective amount of 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E<sub>1</sub>, or a pharmaceutically acceptable salt, ester or amide thereof.

9. The method for treating irritable bowel syndrome in a as described in claim 8, which comprises systemic administration 1-4 times per day or continuous administration in the amount of 0.01-100  $\mu$ g/kg per day.

10. The method as described in claim 8, wherein the administration is in the amount of 0.1-10  $\mu$ g/kg per day.

11. The method as described in claim 7, which comprises systemic administration 1-4 times per day or continuous administration at the amount of 0.01-100  $\mu$ g/kg per day.

12. The method as described in claim 7, wherein the administration is at the amount of 0.1-10  $\mu$ g/kg per day.

13. A method for treating abdominal discomfort associated with irritable bowel syndrome in a mammalian subject, which comprises administering an effective amount of 13,14-dihydro-15-keto-16,16-difluoro-18-methyl-prostaglandin E<sub>1</sub>, or a salt, ether, ester or amide thereof, to the subject.

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14. The method as described in claim 13, which comprises administering an effective amount of 13,14-dihydro-15-keto-16,16-difluoro-18-methyl-prostaglandin E<sub>1</sub>, or a pharmaceutically acceptable salt, ester or amide thereof.

5 15. The method as described in claim 14, which comprises systemic administration 1-4 times per day or continuous administration in the amount of 0.01-100  $\mu$ g/kg per day.

16. The method as described in claim 13, which comprises systemic administration 1-4 times per day or continuous administration in the amount of 0.01-100  $\mu$ g/kg per day.

10 17. The method as described in claim 13, wherein the administration is in the amount of 0.1-10  $\mu$ g/kg per day.

15 18. A method for treating abdominal discomfort associated with irritable bowel syndrome in a mammalian subject, which comprises administering an effective amount of 13,14-dihydro-15-keto-16,16-difluoro prostaglandin E<sub>1</sub>, or a salt, ether, ester or amide thereof, to the subject.

19. The method as described in claim 18, which comprises administering an effective amount of 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E<sub>1</sub>, or a pharmaceutically acceptable salt, ester or amide thereof.

20 20. The method as described in claim 19, which comprises systemic administration 1-4 times per day or continuous administration in the amount of 0.01-100  $\mu$ g/kg per day.

25 21. The method as described in claim 18, which comprises systemic administration 1-4 times per day or continuous administration in the amount of 0.01-100  $\mu$ g/kg per day.

22. The method as described in claim 18, wherein the administration is in the amount of 0.1-10  $\mu$ g/kg per day.

\* \* \* \* \*

# **EXHIBIT B**

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

(10) **Patent No.:** **US 8,097,653 B2**  
 (45) **Date of Patent:** **\*Jan. 17, 2012**

(54) **DOSAGE UNIT COMPRISING A PROSTAGLANDIN ANALOG FOR TREATING CONSTIPATION**

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(73) Assignee: **Sucampo AG**, Zug (CH)

(\* ) 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.: **10/293,516**

(22) Filed: **Nov. 14, 2002**

(65) **Prior Publication Data**

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(51) **Int. Cl.**

**A61K 31/557** (2006.01)  
**A61K 31/35** (2006.01)

(52) **U.S. Cl.** ..... **514/573; 514/456**

(58) **Field of Classification Search** ..... **514/456, 514/460, 892, 211, 573**

See application file for complete search history.

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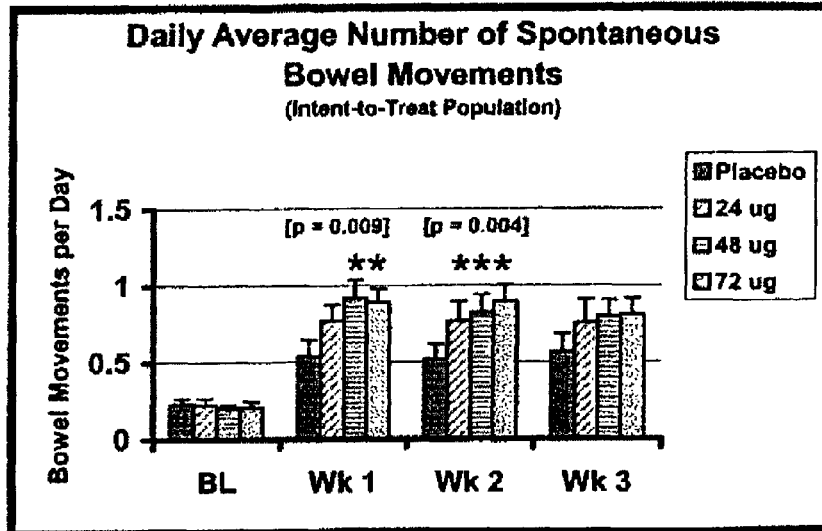
*Assistant Examiner* — Gigi Huang

(74) *Attorney, Agent, or Firm* — Sughrue Mion, PLLC

(57) **ABSTRACT**

A dosage unit for treating constipation in a human patient is described. The dosage unit of the invention comprises a halogenated prostaglandin analog and a pharmaceutically suitable excipient. The dosage unit relieves constipation without substantial side effects.

**7 Claims, 3 Drawing Sheets**





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Fig. 1

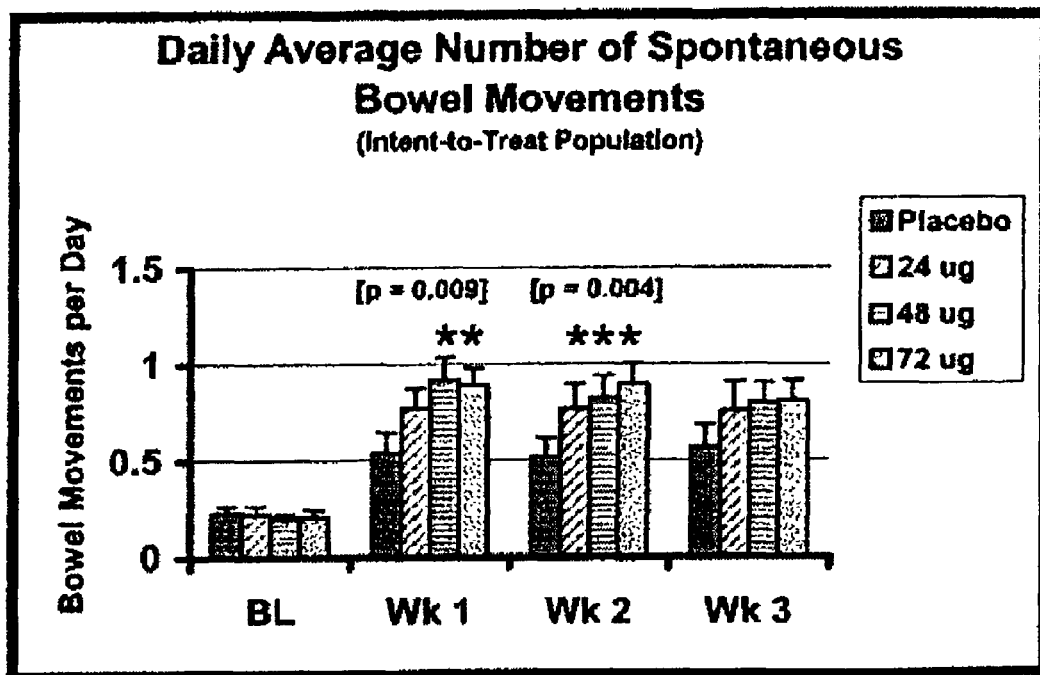




Fig. 2

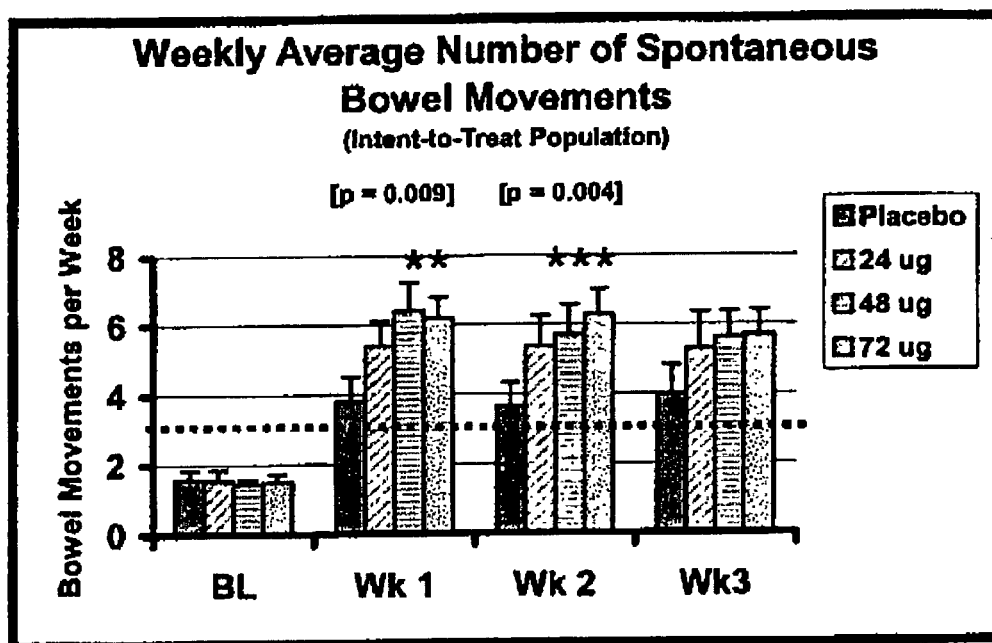
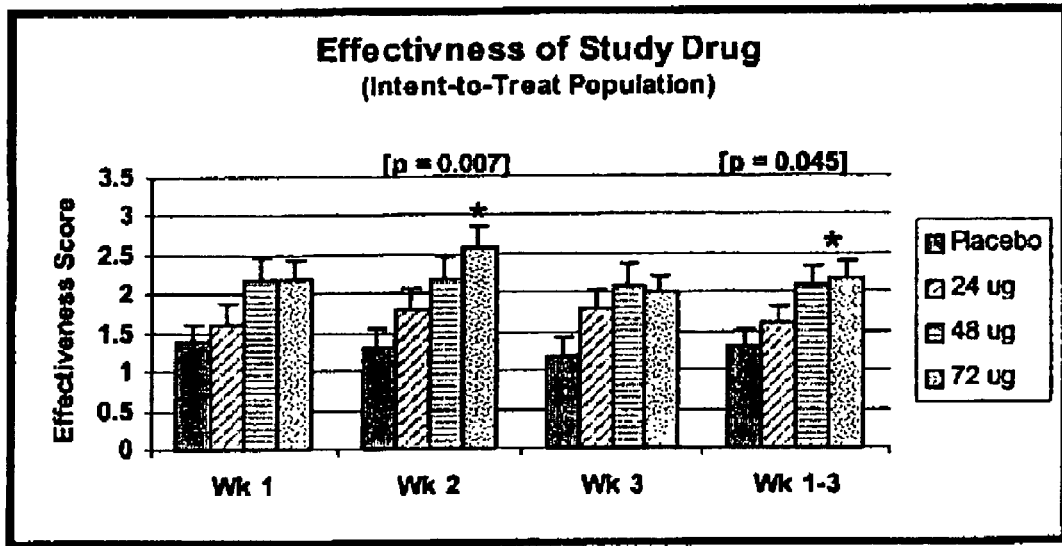


Fig. 3



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**1**

**DOSAGE UNIT COMPRISING A  
PROSTAGLANDIN ANALOG FOR TREATING  
CONSTIPATION**

This application claims benefit to Provisional Application No. 60/331,316 filed Nov. 14, 2001, the disclosure of which is incorporated herein by reference.

TECHNICAL FIELD

The present invention relates to a novel dosage unit of a halogenated prostaglandin analog for the treatment and prevention of constipation in human patients.

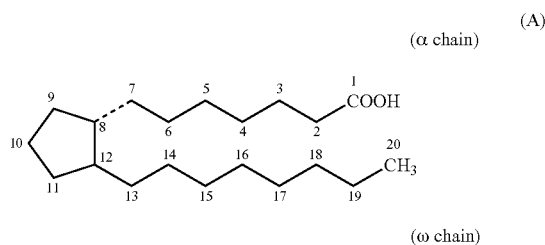
BACKGROUND ART

Constipation is generally defined as infrequent and difficult passage of stool. Medical reporting estimates that one of every 50 people in the United States suffers from constipation, making it one of the most common disorders among Americans. Constipation is more likely to affect females than males and more likely to occur in older adults, showing an exponential increase after the age of 65. The actual occurrence of constipation is likely higher than reported, as many individuals suffer at home without seeking professional care.

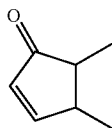
Although in some instances constipation may be caused by obstruction, most constipation can be associated with factors such as a diet low in soluble and insoluble fibers, inadequate exercise, medication use (in particular, opiate analgesics, anticholinergic antidepressants, antihistamines, and vinca alkaloids), bowel disorders, neuromuscular disorders, metabolic disorders, poor abdominal pressure or muscular atony.

A precise quantitative definition of constipation has been difficult to establish due to the wide range of perceived "normal" bowel habits, as well as the diverse array of symptoms and signs associated with constipation. The FDA has recognized a need for prescriptive treatment of occasional constipation.

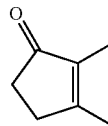
Prostaglandins (hereinafter, referred to as PGs) are members of class of organic carboxylic acids, which are contained in tissues or organs of human or other mammals, and exhibit a wide range of physiological activity. PGs found in nature (primary PGs) generally have a prostanoid acid skeleton as shown in the formula (A):



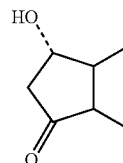
PGs are classified into several types according to the structure and substituents on the five-membered ring, for example, Prostaglandins of the A series (PGAs);

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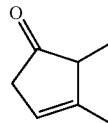
Prostaglandins of the B series (PGBs);



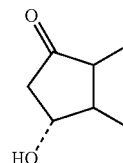
10 Prostaglandins of the C series (PGCs);



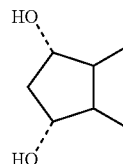
20 Prostaglandins of the D series (PGDs);



30 Prostaglandins of the E series (PGEs);



40 Prostaglandins of the F series (PGFs);



50 and the like. Further, they are classified into PG<sub>1</sub>s containing a 13,14-double bond; PG<sub>2</sub>s containing, 5,6- and 13,14-double bonds; and PG<sub>3</sub>s containing 5,6-, 13,14- and 17,18-double bonds. PGs are known to have various pharmacological and physiological activities, for example, vasodilatation, inducing of inflammation, platelet aggregation, stimulating uterine muscle, stimulating intestinal muscle, anti-ulcer effect and the like. The major prostaglandins produced in the human gastrointestinal (GI) system are those of the E, I and F series (Sellin, *Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, and Management*. (WB Saunders Company, 1998); Robert, *Physiology of the Gastrointestinal Tract* 1407-1434 (Raven, 1981); Rampton, *Prostaglandins: Biology and Chemistry of Prostaglandins and Related Eicosanoids* 323-344 (Churchill Livingstone, 1988); Hawkey, et al., *Gastroenterology*, 89: 1162-1188 (1985); Eberhart, et al., *Gastroenterology*, 109: 285-301 (1995)).

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Under normal physiological conditions, endogenously produced prostaglandins play a major role in maintaining GI function, including regulation of intestinal motility and transit, and regulation of fecal consistency. (Sellin, *Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, and Management*. (W B Saunders Company, 1998); Robert, *Physiology of the Gastrointestinal Tract* 1407-1434 (Raven, 1981); Rampton, *Prostaglandins: Biology and Chemistry of Prostaglandins and Related Eicosanoids* 323-344 (Churchill Livingstone, 1988); Hawkey, et al., *Gastroenterology*, 89: 1162-1188 (1985); Eberhart, et al., *Gastroenterology*, 109: 285-301 (1995); Robert, *Adv Prostaglandin Thromboxane Res.* 2:507-520 (1976); Main, et al., *Postgrad Med J*, 64 Suppl 1: 3-6 (1988); Sanders, *Am J Physiol*, 247: G117 (1984); Pairet, et al., *Am J Physiol*, 250 (3 pt 1): G302-G308 (1986); Gaginella, *Textbook of Secretory Diarrhea* 15-30 (Raven Press, 1990)). When administered in pharmacological doses, both PGE<sub>2</sub> and PGF<sub>2α</sub> have been shown to stimulate intestinal transit and to cause diarrhea (Robert, *Physiology of the Gastrointestinal Tract* 1407-1434 (Raven, 1981); Rampton, *Prostaglandins: Biology and Chemistry of Prostaglandins and Related Eicosanoids* 323-344 (Churchill Livingstone, 1988); Robert, *Adv Prostaglandin Thromboxane Res.* 2:507-520 (1976)). Furthermore, the most commonly reported side effect of misoprostol, a PGE<sub>1</sub> analogue developed for the treatment of peptic ulcer disease, is diarrhea (Monk, et al., *Drugs* 33 (1): 1-30 (1997)).

PGE or PGF can stimulate the intestines and cause intestinal contraction, but the enteropooling effect is poor. Accordingly, it is impossible to use PGEs or PGFs as cathartics because of side effects such as stomachache caused by the intestinal contraction.

Multiple mechanisms, including modifying enteric nerve responses, altering smooth muscle contraction, stimulating mucous secretion, stimulating cellular ionic (in particular electrogenic Cl<sup>-</sup> transport) and increasing intestinal fluid volume have been reported to contribute to the GI effects of prostaglandins (Robert, *Physiology of the Gastrointestinal Tract* 1407-1434 (Raven, 1981); Rampton, *Prostaglandins: Biology and Chemistry of Prostaglandins and Related Eicosanoids* 323-344 (Churchill Livingstone, 1988); Hawkey, et al., *Gastroenterology*, 89: 1162-1188 (1985); Eberhart, et al., *Gastroenterology*, 109: 285-301 (1995); Robert, *Adv Prostaglandin Thromboxane Res.* 2:507-520 (1976); Main, et al., *Postgrad Med J*, 64 Suppl 1: 3-6 (1988); Sanders, *Am J Physiol*, 247: G117 (1984); Pairet, et al., *Am J Physiol*, 250 (3 pt 1): G302-G308 (1986); Gaginella, *Textbook of Secretory Diarrhea* 15-30 (Raven Press, 1990); Federal Register Vol. 50, No. 10 (GPO, 1985); Pierce, et al., *Gastroenterology* 60 (1): 22-32 (1971); Beubler, et al., *Gastroenterology*, 90: 1972 (1986); Clarke, et al., *Am J Physiol* 259: G62 (1990); Hunt, et al., *J Vet Pharmacol Ther*, 8 (2): 165-173 (1985); Dajani, et al., *Eur J Pharmacol*, 34(1): 105-113 (1975); Sellin, *Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, and Management* 1451-1471 (W B Saunders Company, 1998)). Prostaglandins have additionally been shown to have cytoprotective effects (Sellin, *Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, and Management*. (W B Saunders Company, 1998); Robert, *Physiology of the Gastrointestinal Tract* 1407-1434 (Raven, 1981); Robert, *Adv Prostaglandin Thromboxane Res* 2:507-520 (1976); Wallace, et al., *Aiiment Pharmacol Ther* 9: 227-235 (1995)).

U.S. Pat. No. 5,317,032 to Ueno et al. describes prostaglandin analog cathartics, including the existence of bicyclic tautomers and U.S. Pat. No. 6,414,016 to Ueno describes the bicyclic tautomers as having pronounced activity as anti-constipation agents. The bicyclic tautomers, substituted by

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one or more halogen atoms can be employed in small doses for relieving constipation. At the C-16 position, especially, fluorine atoms, can be employed in small doses for relieving constipation. The doses, however, by which these prostaglandin analogs are optimally effective is not known. Moreover, the range at which the PG analogs are safe, while yet exerting therapeutic effects, needs to be determined. Clinical dose-ranging studies will be necessary to evaluate the safety and tolerance of PG analogs.

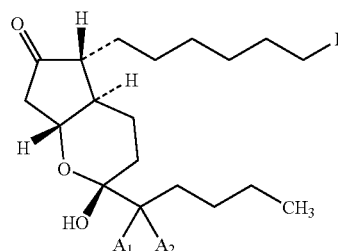
## DISCLOSURE OF INVENTION

It is therefore an object of this invention to provide a dosage formulation and a workable, therapeutic approach for relieving and preventing constipation in human patients.

That is, the present invention provides a dosage unit for use in relieving or preventing constipation in a human patient comprising

- (i) a prostaglandin (PG) analog represented by Formula (I) and/or its tautomer in the range of about 6-96 μg:

Formula (I)



where A<sub>1</sub> and A<sub>2</sub> are the same or different halogen atoms and

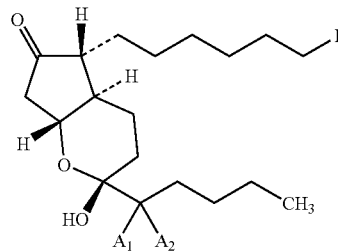
B is —COOH, including its pharmaceutically acceptable salts, esters or amides; and

- (ii) a pharmaceutically suitable excipient.

Another object of the present invention is to provide a method for treating constipation in a human patient. Accordingly, the instant invention also provides a method for relieving or preventing constipation in a human patient that comprises administering to the patient a dosage unit comprising

- (i) a PG analog, represented by Formula (I) and/or its tautomer in the range of about 6-96 μg:

Formula (I)



where A<sub>1</sub> and A<sub>2</sub> are the same or different halogen atoms and

B is —COOH, including its pharmaceutically acceptable salts, esters or amides; and

- (ii) a pharmaceutically suitable excipient.

According to the invention, the halogenated PG analog of formula (I) is preferably halogenated with fluorine atoms, to

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have a cathartic effect. The dosage unit of the invention comprises the PG analog of formula (I) and/or its tautomer in the range of about 6-96  $\mu\text{g}$  per unit. A total daily dose of about 24-72  $\mu\text{g}$  is also preferred. For example, the preferable total daily dose of the PG analog is about 48  $\mu\text{g}$ .

According to the invention, the pharmaceutical excipient may preferably be a medium chain fatty acid to provide a dosage unit is administered orally.

#### BRIEF DESCRIPTION OF DRAWINGS

FIG. 1. Graph of daily average number of spontaneous bowel movements in the intent-to-treat population. Daily bowel movements were assessed for the 0  $\mu\text{g}$ , 24  $\mu\text{g}$ , 48  $\mu\text{g}$  and 72  $\mu\text{g}$  doses of Compound A during 0, 1, 2 and 3 weeks of medicating.

In the graph, [ ]=statistically significant overall p-value based on a Cochran-Mantel Haenszel (CMH) test using modified ridit scores, controlling for site, and using Shaffer's modified sequentially rejective multiple test procedure. \*=statistically significant pairwise comparison based on a Cochran-Mantel Haenszel (CMH) test comparing placebo to active drug using modified ridit scores, controlling for site and using Shaffer's modified sequentially rejective multiple test procedure.

FIG. 2. Graph of weekly average number of spontaneous bowel movements in the intent-to-treat population. Average number of bowel movements were compared across the different treatment groups during 0 weeks, week 1, week 2 and week 3.

In the graph, [ ]=statistically significant overall p-value based on a Cochran-Mantel Haenszel (CMH) test using modified ridit scores, controlling for site, and using Shaffer's modified sequentially rejective multiple test procedure. \*=statistically significant pairwise comparison based on a Cochran-Mantel Haenszel (CMH) test comparing placebo to active drug using modified ridit scores, controlling for site and using Shaffer's modified sequentially rejective multiple test procedure. Dotted line represents the cut-line for constipation defined as <3 spontaneous bowel movements per week.

FIG. 3. Graph of study drug effectiveness in the intent-to-treat population. Effectiveness of study drug for the different treatment groups was rated on a scale of 0-4, 4 being the most effective.

In the graph, [ ]=statistically significant overall p-value based on a Cochran-Mantel Haenszel (CMH) test using modified ridit scores, controlling for site, and using Shaffer's modified sequentially rejective multiple test procedure. \*=statistically significant pairwise comparison based on a Cochran-Mantel Haenszel (CMH) test comparing placebo to active drug using modified ridit scores, controlling for site and using Shaffer's modified sequentially rejective multiple test procedure. Rating scale: 0=not at all effective, 1=a little bit effective, 2=moderately effective, 3=quite a bit effective and 4=extremely effective.

#### DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a dosage unit for an anti-constipation composition comprising a halogenated prostaglandin analog as an active ingredient.

Cathartics are thought to work by the combination of one or more mechanisms to increase the water content of feces and promote transfer of the content in the intestines. Halogenated prostaglandin analogs of formula (I) appear to alleviate constipation by mainly acting on the intestinal mucosa to affect

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the transfer of electrolytes and water from intestinal walls into blood vessels and/or from blood vessels into intestines. These results in reduced water absorption and/or increased water secretion through intestines, increased intraintestinal water pool and transfer of the intraintestinal content.

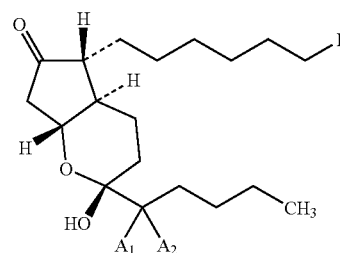
The present inventors have discovered a dosage regimen and suitable formulations of halogenated prostaglandin analogs for the treatment and prevention of constipation. A dosage unit comprising a PG analog and a pharmaceutically suitable excipient is described herein.

#### Preparing a Dosage Unit

The dosage unit comprises a prostaglandin analog of formula (I) and a pharmaceutically suitable excipient. The amount of the PG analog present in the dosage unit typically is in the range of about 6-96  $\mu\text{g}$ . As used herein, the term "about" when used in conjunction with a unit of measure can be defined as  $\pm 30\%$  and  $\pm 20\%$ , preferably  $\pm 10\%$ . For example, the range of about 6-96  $\mu\text{g}$  preferably means the range of 5.4-105.6  $\mu\text{g}$ . The preferred dose is in the range of about 24-72  $\mu\text{g}$ . In a more preferred embodiment, the dose is in the range of about 24-60  $\mu\text{g}$ . For example, the dose of said halogenated composition can be about 48  $\mu\text{g}$ . The dosage unit of the invention can be used for constipation treatment and prevention remedies for humans.

#### (i) PG Analogs

The PG analog, in the present invention is represented by formula (I):



Formula (I)

where  $A_1$  and  $A_2$  are halogen atoms and B is  $-\text{COOH}$ , its pharmaceutically acceptable salt, ester or amide.

The term "halogen" is used conventionally to include fluorine, chlorine, bromine, and iodine atoms. Particularly preferable halogen atoms for  $A_1$  and  $A_2$  are fluorine atoms.

The halogenated PG analog of formula (I) used in the present invention may be an amide, a salt or an ester. Such salts include pharmaceutically acceptable salts, for example, those of alkali metals such as sodium and potassium; those of alkaline earth metals such as calcium and magnesium; those of physiologically acceptable ammonium salts such as ammonia, methylamine, dimethylamine, cyclopropylamine, cyclohexylamine, benzylamine, piperidine, ethylenediamine, monoethanolamine, diethanolamine, triethanolamine, monomethylmonoethanolamine, tromethamine, lysine, procaine, caffeine, arginine and tetralkylammonium salt, and the like. These salts may be prepared by a conventional process, for example, from the corresponding acid and base or by salt interchange.

Such esters include, for example, straight or branched alkyl esters, which may contain one or more unsaturated bonds such as methyl, ethyl, propyl, butyl, isopropyl, isobutyl, t-butyl, pentyl and 2-ethylhexyl.

Preferred amides are methyl, ethyl, propyl, isopropyl and butyl amides.

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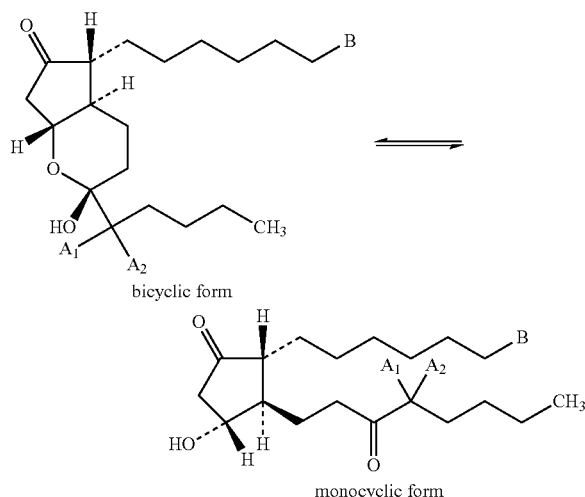
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In a preferred embodiment, the dosage unit comprises a PG analog of formula (I) in which A<sub>1</sub> and A<sub>2</sub> are fluorine atoms. Still more preferred is the one in which B is —COOH.

A dosage unit, as defined herein, is a unit of halogenated PG analog to be administered. Single or multiple dosage units may be administered, making up the dose, a quantity of halogenated PG analog that produces the desired cathartic effect.

The active agent of this invention exists as a bicyclic compound in a solid state, but partially forms a tautomer of the above compound when dissolved in a solvent. In the absence of water, compounds represented by formula (I) exist predominantly in the form of the bicyclic compound. In aqueous media, it is believed that hydrogen bonding occurs between, for example, the ketone position at the C-15 position, thereby hindering bicyclic ring formation. In addition, it is believed that the halogen atoms at the C-16 position promote bicyclic ring formation. The tautomerism between the hydroxy at the C-11 position and the keto moiety at the C-15 position, shown below, is especially significant in the case of compounds having a 13,14 single bond and two fluorine atoms the C-16 position.

Accordingly, the dosage unit of the present invention may comprise isomers of the halogenated PG analog compounds. For example, mono-cyclic tautomers having a keto group at the C-15 position and halogen atoms at the C-16 position.



A preferred compound according to the invention in its monocyclic form can be named as 13,14-dihydro-15-keto-16,16-difluoro-PGE<sub>1</sub>, according to conventional prostaglandin nomenclature.

(ii) The Pharmaceutically Suitable Excipient

According to the invention, the dosage unit of the invention may be formulated in any form. The pharmaceutically suitable excipient may be, therefore, selected depending on the desired form of the dosage unit. According to the invention, “pharmaceutically suitable excipient” means an inert substance, which is suitable for the form, combined with the active ingredient of the invention.

For example, solid composition for oral administration of the present invention may include tablets, preparations, granules and the like. In such a solid composition, one or more active ingredients may be mixed with at least one inactive diluent, for example, lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinyl pyrrolidone, magnesium aluminate metasilicate and the like.

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According to the usual work-up, the composition may contain additives other than inactive diluent, for example, lubricant such as magnesium stearate; disintegrant such as fibrous calcium gluconate; stabilizer such as cyclodextrin, for example, α-, β- or γ-cyclodextrin; etherified cyclodextrin such as dimethyl-α-, dimethyl-β-, trimethyl-β-, or hydroxypropyl-β-cyclodextrin; branched cyclodextrin such as glucosyl-, maltosyl-cyclodextrin; formylated cyclodextrin, cyclodextrin containing sulfur; phospholipid and the like. When the above cyclodextrins are used, inclusion compound with cyclodextrins may be sometimes formed to enhance stability. Alternatively, phospholipid may be sometimes used to form liposome, resulting in enhanced stability.

Tablets or pills may be coated with film soluble in the stomach or intestine such as sugar, gelatin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose phthalate as needed. Further, they may be formed as capsules with absorbable substances such as gelatins. Preferably, the dosage unit is formulated in a soft gelatin capsule with liquid contents of the halogenated PG analog and a medium chain fatty acid triglyceride. Examples of the medium chain fatty acid triglyceride used in the present invention include a triglyceride of a saturated or unsaturated fatty acid having 6-14 carbon atoms which may have a branched chain. A preferred fatty acid is a straight chain saturated fatty acid, for example caproic acid (C6), caprylic acid (C8), capric acid (C10), lauric acid (C12) and myristic acid (C14). In addition, two or more medium chain fatty acid triglycerides may be used in combination. Further suitable excipients are disclosed in the published PCT application WO 01/27099.

A liquid composition for oral administration may be pharmaceutically acceptable emulsion, solution, suspension, syrup, elixir, as well as generally used inactive diluent. Such composition may contain, in addition to the inactive diluent, adjuvants such as lubricants and suspensions, sweetening agents, flavoring agents, preservatives, solubilizers, anti-oxidants and the like. The details of the additives may be selected from those described in any general textbooks in the pharmaceutical field. Such liquid compositions may be directly enclosed in soft capsules. Solutions for parenteral administration, for example, suppository, enema and the like according to the present invention include sterile, aqueous or non-aqueous solution, suspension, emulsion, detergent and the like. The aqueous solution and suspension includes, for example, distilled water, physiological saline and Ringer's solution.

The non-aqueous solution and suspension include, for example, propylene glycol, polyethylene glycol, fatty acid triglyceride, vegetable oil such as olive oil, alcohols such as ethanol, polysorbate and the like. Such composition may contain adjuvants such as preservatives, wetting agent, emulsifier, dispersant, anti-oxidants and the like.

The dosage unit of the present invention is parenterally acceptable, however orally is preferred. The test substance is preferably dissolved in Panacet 800 (medium chain fatty acid triglyceride manufactured by Nippon Oil & Fat Co., Ltd., Amagasaki, Japan) and filled in a capsule (each capsule contains 200 μL of the mixture).

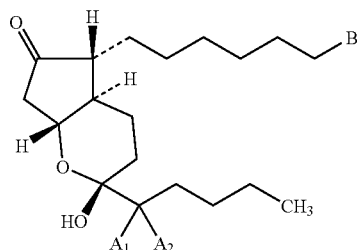
A Method for Treating Constipation

The invention further provides a method for relieving or preventing constipation in a human patient that comprises administering to the patient a dosage unit comprising (i) a PG analog represented by Formula (I) or its tautomers in the range of about 6-96 μg:



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Formula I

and (ii) a pharmaceutically suitable excipient.  $A_1$  and  $A_2$  of the PG analog represented by Formula (I) are halogen atoms and B is  $-\text{COOH}$ , its pharmaceutically acceptable salt, ester or amide. Preferably, the halogen atoms are fluorine atoms.

According to the method of the invention, the dosage unit of the present invention can be administered systemically or locally by means of oral or parental administration, including a suppository, enema and the like. Single or multiple dosage units may be administered to achieve the desired dose.

Preferably, the total daily dose of the PG analog is in the range of about 24-72  $\mu\text{g}$ . Also preferable, the total daily dose of the PG analog is in the range of about 24-60  $\mu\text{g}$ . Still more preferably, the total daily dose of the PG analog is about 48  $\mu\text{g}$ . The dose may vary somewhat, at the discretion of the physician, depending the age and weight of the patient, conditions, therapeutic effect, administration route, treatment time and the like.

### EXAMPLES

The following examples illustrate the present invention but are not in any way intended to limit the scope of this invention. The following abbreviations are used in the examples below:

AE	Adverse Event
ITT	Intent To Treat
PO	Per Os (Orally)
PP	Per Protocol
SE	Safety Evaluable

All randomized patients who took at least one dose of double-blind study medication constituted the safety evaluable (SE) population. These patients were included in the demographic data, baseline characteristic data and safety analysis. For efficacy, the same data set was used and is referred to as the intent-to-treat (ITT) population. Patients who did not comply with the treatment regimen or who took disallowed concomitant medication were considered protocol violators. Key efficacy analyses were also performed on the per-protocol (PP) population, which excluded all data for the affected weeks for protocol violators. Patients whose treatments were adjusted were analyzed in their original treatment group (i.e., as randomized).

#### Example 1

##### Phase I Dosage Studies

The safety and tolerance of oral Compound A (13,14-dihydro-15-keto-16,16-difluoro-PGE<sub>1</sub>) was evaluated in 16 volunteers in a single-dose Phase I study (Phase Ia) at rising per-person doses of 6  $\mu\text{g}$ , 12  $\mu\text{g}$ , 24  $\mu\text{g}$ , 48  $\mu\text{g}$ , 72  $\mu\text{g}$ , and 96

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$\mu\text{g}$  compared and in 24 volunteers in a multiple-dose Phase I study (Phase Ib) at rising per-person doses of 24  $\mu\text{g}$ , 30  $\mu\text{g}$ , and 36  $\mu\text{g}$  of Compound A administered three times a day (TID) (i.e., total daily per person doses of 72  $\mu\text{g}$ , 90  $\mu\text{g}$  and 108  $\mu\text{g}$ ) for 6 days.

The dose-limiting toxicity in the Phase I studies was nausea. The maximum tolerated single per-person dose of Compound A was 96  $\mu\text{g}$  and the maximum tolerated multiple per-person dose of Compound A was 36  $\mu\text{g}$  taken TID (i.e., a 108  $\mu\text{g}$  total daily dose).

##### Single Rising Dose Study

96  $\mu\text{g}$  was the maximum tolerated single oral Compound A dose. In the Phase Ia study, serious adverse events (SAE) did not occur at any dose level, but there were a total of 49 AEs. These occurred in 13 of the 17 volunteers and all resolved. Volunteers receiving placebo experienced five AEs. Most AEs could be categorized as either responses or events commonly reported in Phase I clinical trials (such as headache and lightheadedness) or expected pharmacodynamic responses of Compound A (such as loose bowel movements, diarrhea and abdominal cramping).

The number of adverse events increased with dose. The increase in frequency and severity of AEs found between the first four dose increments and the final two dose increments, coupled with the further increase in AEs between the final two dose increments, suggested that 96  $\mu\text{g}$  was the maximum tolerated single oral Compound A dose.

Bowel movement frequency was assessed during the 24 hour period after dosing for each dose-level group. Bowel movements were experienced in the placebo and in all active dose groups. There was a trend for increased bowel movements in subjects treated with Compound A as compared to those treated with placebo. The most striking effects were seen in subjects treated at the 96  $\mu\text{g}$  dose level. Compared to only three of twelve subjects experiencing bowel movements in the placebo group, all six subjects in the 96  $\mu\text{g}$  Compound A group experienced bowel movements. Furthermore, the average number of bowel movements per subject in this Compound A group (1.5) was three times greater than the average number of bowel movements per subject in the placebo group (0.5).

##### Multiple Rising Dose Study

Compound A was determined to be optimal when administered at the 24  $\mu\text{g}$  dose TID and determined to be safe and tolerable up to 36  $\mu\text{g}$  when administered TID for at least 6 days. The AEs that were experienced were those that were associated with the expected pharmacologic action of Compound A. However, given that the maximal total number of bowel movements was achieved at the 24  $\mu\text{g}$  dose level, and that increasing doses were not associated with increased pharmacodynamic effects, but were associated with an increased AE profile, the 24  $\mu\text{g}$  dose level was determined to be the best tolerated effective dose in healthy volunteers.

The volunteers experienced no SAEs. The main dose limiting side effect observed during the study was nausea. At the 24  $\mu\text{g}$  dose level, one volunteer had three bouts of nausea and at the 30  $\mu\text{g}$  dose level, two volunteers experienced a total of three bouts of nausea. At the 36  $\mu\text{g}$  dose level, there was a notable increase in the incidence of nausea, with thirteen bouts of nausea being experienced by five out of six volunteers dosed at this level. Further to this, one volunteer at the 36  $\mu\text{g}$  level experienced twelve episodes of diarrhea or loose stools, two episodes of nausea and three episodes of abdominal cramps during the dosing period. All vital signs and ECG measurements were normal throughout the study period and no central nervous system or physical abnormalities

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observed. The 36  $\mu\text{g}$  dose level was determined to be the maximum tolerated multiple oral dose for the T1D treatment regimen.

Bowel movement frequency was assessed in this study as well. As in the Phase I single rising dose study, the Compound A treatment groups exhibited more bowel movements than the placebo group. A total of 193 bowel movements were experienced in this study. Of these, 31 occurred in the placebo group, 70 in the 24  $\mu\text{g}$  group, 51 in the 30  $\mu\text{g}$  group and 41 in the 36  $\mu\text{g}$  group.

### Example 2

#### Phase II Dosage Studies

Eligible patients were treated with either placebo or total daily doses of 24  $\mu\text{g}$ , 48  $\mu\text{g}$  or 72  $\mu\text{g}$  of Compound A for 21 days. One placebo or Compound A capsule was taken 3 times each day (AM, Noon, and PM). Compound A was administered as 24  $\mu\text{g}$  oral capsules. Patients assigned to receive the total daily 24  $\mu\text{g}$  Compound A dose took one Compound A capsule in the AM and one matching placebo capsule both at Noon and in the PM; patients assigned to receive the total daily 48  $\mu\text{g}$  Compound A dose took one Compound A capsule in both the AM and PM and one matching placebo capsule at Noon; patients assigned to receive the total daily 72  $\mu\text{g}$  Compound A dose took one Compound A capsule in the AM, at Noon, and in the PM.

Based on the overall efficacy results, doses of Compound A as low as 24  $\mu\text{g}$  tended to relieve constipation, however, based on statistical analyses, the minimum effective dose of Compound A was 48  $\mu\text{g}$  per day. Compared to placebo treatment, patients taking 48  $\mu\text{g}$  or 72  $\mu\text{g}$  of Compound A experienced statistically significant increases in the daily average number of spontaneous bowel movements at Week 1 and Week 2. Administration of 48  $\mu\text{g}$  or 72  $\mu\text{g}$  of Compound A produced a statistically significant increase in the proportion of patients who had a spontaneous bowel movement on Day 1. Statistically significant improvements in stool consistency were observed at all post-baseline time points in patients taking 48  $\mu\text{g}$  and 72  $\mu\text{g}$  of Compound A. Statistically significant improvements in constipation severity were observed at

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Week 3 in patients taking 48  $\mu\text{g}$  of Compound A and at Weeks 2 and 3 in patients taking 72  $\mu\text{g}$  of Compound A.

What is claimed is:

1. A method for relieving constipation in a human patient in need of relief of constipation that comprises administering to the patient a dosage unit comprising (i) 24  $\mu\text{g}$   $\pm$  10% of a PG analog represented by Formula (I) and/or its tautomer and (ii) a pharmaceutically suitable excipient:

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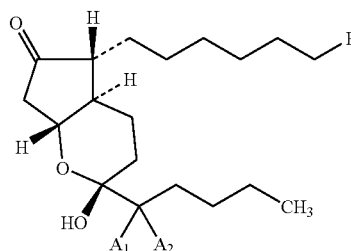
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Formula (I)



where  $A_1$  and  $A_2$  are fluorine atoms and B is  $-\text{COOH}$ , including its pharmaceutically acceptable salts, esters or amides, to thereby relieve constipation in the patient,

wherein said dosage unit is administered enough times per day so that the total daily dose of the PG analog is in the range of about 48-72  $\mu\text{g}$ .

2. The method of claim 1, wherein said PG analog is a monocyclic tautomer of formula (I).

3. The method of claim 1, wherein said pharmaceutically suitable excipient is orally acceptable.

4. The method of claim 1, wherein said pharmaceutically suitable excipient is a medium chain fatty acid.

5. The method of claim 1, wherein said dosage unit is administered enough times per day so that the total daily dose of the PG analog is about 48  $\mu\text{g}$ .

6. The method of claim 1, wherein the amount of the PG analog in the dosage unit is 24  $\mu\text{g}$ .

7. The method of claim 1, wherein B is  $-\text{COOH}$ .

\* \* \* \* \*



# **EXHIBIT C**

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

(10) **Patent No.:** **US 8,389,542 B2**  
 (45) **Date of Patent:** **\*Mar. 5, 2013**

(54) **DOSAGE UNIT COMPRISING A PROSTAGLANDIN ANALOG FOR TREATING CONSTIPATION**

(75) Inventors: **Ryuji Ueno**, Potomac, MD (US); **Myra L. Patchen**, Fairfax, VA (US)

(73) Assignee: **Sucampo AG**, Zug (CH)

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

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/330,942**

(22) Filed: **Dec. 20, 2011**

(65) **Prior Publication Data**  
 US 2012/0088824 A1 Apr. 12, 2012

**Related U.S. Application Data**  
 (62) Division of application No. 10/293,516, filed on Nov. 14, 2002, now Pat. No. 8,097,653.  
 (60) Provisional application No. 60/331,316, filed on Nov. 14, 2001.

(51) **Int. Cl.**  
**A61K 31/44** (2006.01)  
**A61K 31/34** (2006.01)  
**A61K 31/19** (2006.01)

(52) **U.S. Cl.** ..... **514/302**; 514/469; 514/573  
 (58) **Field of Classification Search** ..... 514/302, 514/469  
 See application file for complete search history.

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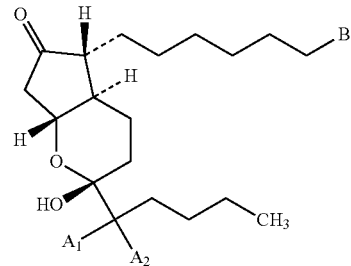
A. Robert, J.E. Nezamis, C. Lancaster, A.J. Hanchar, and M.S. Klepper, Enteropooling Assay: A Test for Diarrhea Produced by Prostaglandins; Prostaglandins, May 1976, vol. 11, No. 5, 809-828.

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 (74) *Attorney, Agent, or Firm* — Sughrue Mion, PLLC

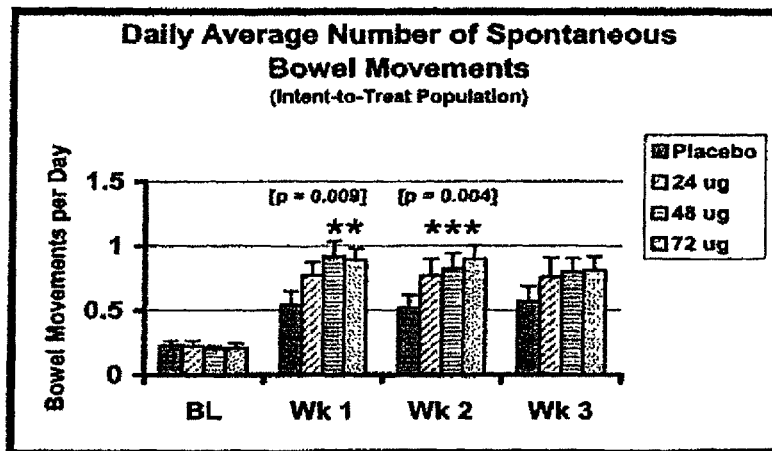
(57) **ABSTRACT**

A dosage unit for treating constipation in a human patient is described. The dosage unit of the invention includes a halogenated prostaglandin analog and a pharmaceutically suitable excipient. The dosage unit relieves constipation without substantial side effects. In particular, the dosage unit includes a prostaglandin (PG) analog represented by Formula (I) and/or its tautomers, and a pharmaceutically suitable excipient, wherein the dosage unit contains the PG analog in an amount of 24 µg±10%:



Formula (I)

13 Claims, 3 Drawing Sheets



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Fig. 1

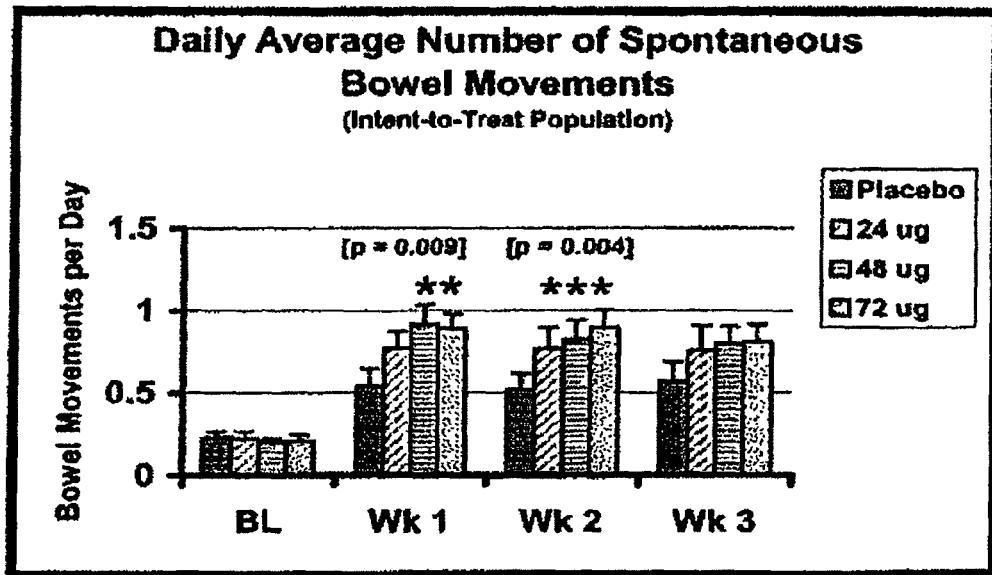


Fig. 2

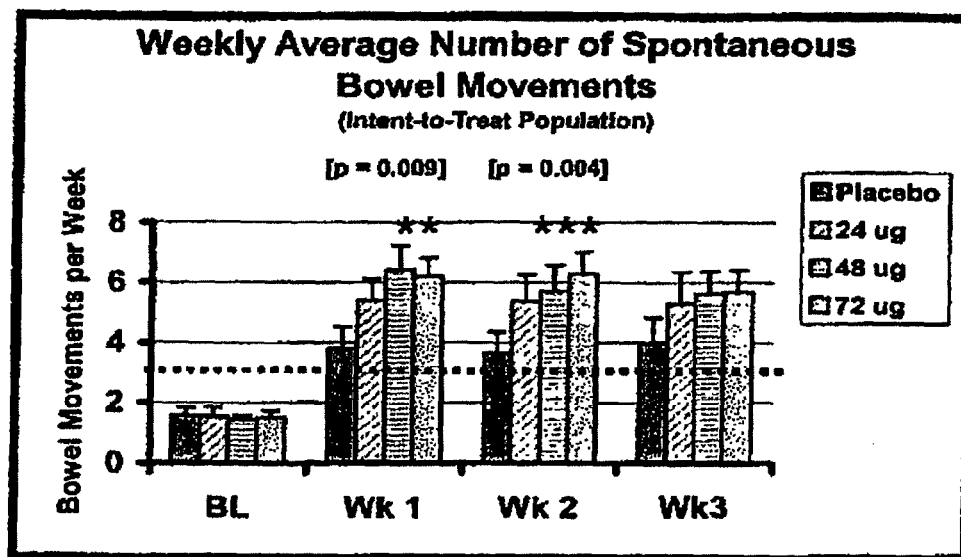
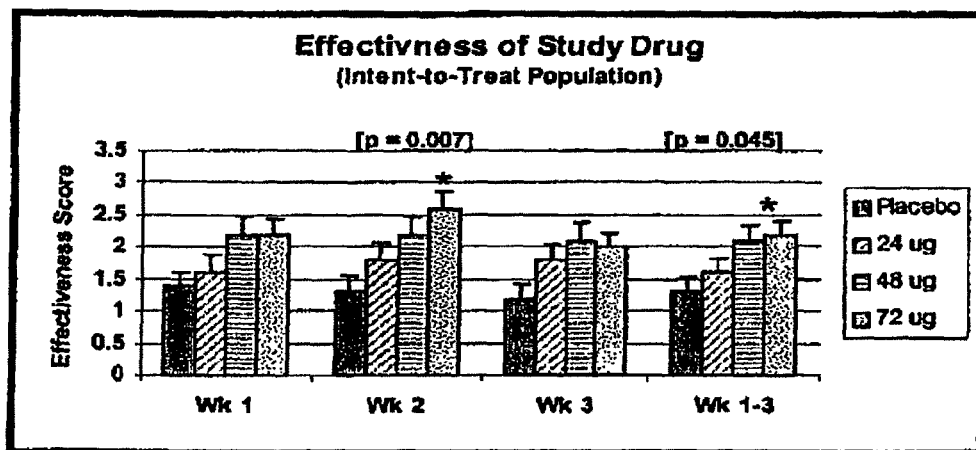


Fig. 3



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**DOSAGE UNIT COMPRISING A  
PROSTAGLANDIN ANALOG FOR TREATING  
CONSTIPATION**

CROSS REFERENCE TO RELATED  
APPLICATIONS

This application is a divisional application of application Ser. No. 10/293,516 filed Nov. 14, 2002, which claims benefit to Provisional Application No. 60/331,316 filed Nov. 14, 2001, the disclosures of all of which are incorporated herein by reference.

TECHNICAL FIELD

The present invention relates to a novel dosage unit of a halogenated prostaglandin analog for the treatment and prevention of constipation in human patients.

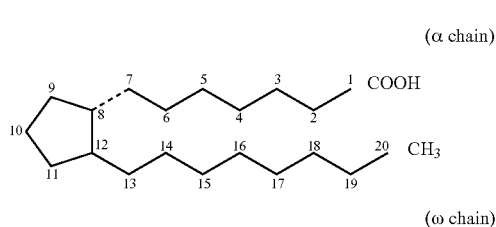
BACKGROUND ART

Constipation is generally defined as infrequent and difficult passage of stool. Medical reporting estimates that one of every 50 people in the United States suffers from constipation, making it one of the most common disorders among Americans. Constipation is more likely to affect females than males and more likely to occur in older adults, showing an exponential increase after the age of 65. The actual occurrence of constipation is likely higher than reported, as many individuals suffer at home without seeking professional care.

Although in some instances constipation may be caused by obstruction, most constipation can be associated with factors such as a diet low in soluble and insoluble fibers, inadequate exercise, medication use (in particular, opiate analgesics, anticholinergic antidepressants, antihistamines, and vinca alkaloids), bowel disorders, neuromuscular disorders, metabolic disorders, poor abdominal pressure or muscular atony.

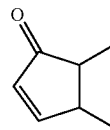
A precise quantitative definition of constipation has been difficult to establish due to the wide range of perceived "normal" bowel habits, as well as the diverse array of symptoms and signs associated with constipation. The FDA has recognized a need for prescriptive treatment of occasional constipation.

Prostaglandins (hereinafter, referred to as PGs) are members of class of organic carboxylic acids, which are contained in tissues or organs of human or other mammals, and exhibit a wide range of physiological activity. PGs found in nature (primary PGs) generally have a prostanoid acid skeleton as shown in the formula (A):

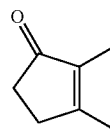


PGs are classified into several types according to the structure and substituents on the five-membered ring, for example, Prostaglandins of the A series (PGAs);

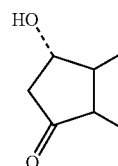
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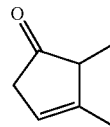
Prostaglandins of the B series (PGBs);



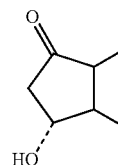
Prostaglandins of the C series (PGCs);



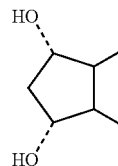
Prostaglandins of the D series (PGDs);



Prostaglandins of the E series (PGEs);



Prostaglandins of the F series (PGFs);



and the like. Further, they are classified into PG<sub>1</sub>s containing a 13,14-double bond; PG<sub>2</sub>s containing 5,6- and 13,14-double bonds; and PG<sub>3</sub>s containing 5,6-, 13,14- and 17,18-double bonds. PGs are known to have various pharmacological and physiological activities, for example, vasodilatation, inducing of inflammation, platelet aggregation, stimulating uterine

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muscle, stimulating intestinal muscle, anti-ulcer effect and the like. The major prostaglandins produced in the human gastrointestinal (GI) system are those of the E, I and F series (Sellin, *Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, and Management*. (WB Saunders Company, 1998); Robert, *Physiology of the Gastrointestinal Tract* 1407-1434 (Raven, 1981); Rampton, *Prostaglandins: Biology and Chemistry of Prostaglandins and Related Eicosanoids* 323-344 (Churchill Livingstone, 1988); Hawkey, et al., *Gastroenterology*, 89: 1162-1188 (1985); Eberhart, et al., *Gastroenterology*, 109: 285-301 (1995)).

Under normal physiological conditions, endogenously produced prostaglandins play a major role in maintaining GI function, including regulation of intestinal motility and transit, and regulation of fecal consistency. (Sellin, *Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, and Management*. (WB Saunders Company, 1998); Robert, *Physiology of the Gastrointestinal Tract* 1407-1434 (Raven, 1981); Rampton, *Prostaglandins: Biology and Chemistry of Prostaglandins and Related Eicosanoids* 323-344 (Churchill Livingstone, 1988); Hawkey, et al., *Gastroenterology*, 89: 1162-1188 (1985); Eberhart, et al., *Gastroenterology*, 109: 285-301 (1995); Robert, *Adv Prostaglandin Thromboxane Res*, 2:507-520 (1976); Main, et al., *Postgrad Med J*, 64 Suppl 1: 3-6 (1988); Sanders, *Am J Physiol*, 247: G117 (1984); Pairet, et al., *Am J Physiol*, 250 (3 pt 1): G302-G308 (1986); Gaginella, *Textbook of Secretory Diarrhea* 15-30 (Raven Press, 1990)). When administered in pharmacological doses, both PGE<sub>2</sub> and PGF<sub>2α</sub> have been shown to stimulate intestinal transit and to cause diarrhea (Robert, *Physiology of the Gastrointestinal Tract* 1407-1434 (Raven, 1981); Rampton, *Prostaglandins: Biology and Chemistry of Prostaglandins and Related Eicosanoids* 323-344 (Churchill Livingstone, 1988); Robert, *Adv Prostaglandin Thromboxane Res*, 2:507-520 (1976)). Furthermore, the most commonly reported side effect of misoprostol, a PGE<sub>1</sub> analogue developed for the treatment of peptic ulcer disease, is diarrhea (Monk, et al., *Drugs* 33 (1): 1-30 (1997)).

PGE or PGF can stimulate the intestines and cause intestinal contraction, but the enteropooling effect is poor. Accordingly, it is impossible to use PGEs or PGFs as cathartics because of side effects such as stomachache caused by the intestinal contraction.

Multiple mechanisms, including modifying enteric nerve responses, altering smooth muscle contraction, stimulating mucous secretion, stimulating cellular ionic (in particular electrogenic Cl<sup>-</sup> transport) and increasing intestinal fluid volume have been reported to contribute to the GI effects of prostaglandins (Robert, *Physiology of the Gastrointestinal Tract* 1407-1434 (Raven, 1981); Rampton, *Prostaglandins: Biology and Chemistry of Prostaglandins and Related Eicosanoids* 323-344 (Churchill Livingstone, 1988); Hawkey, et al., *Gastroenterology*, 89: 1162-1188 (1985); Eberhart, et al., *Gastroenterology*, 109: 285-301 (1995); Robert, *Adv Prostaglandin Thromboxane Res*, 2:507-520 (1976); Main, et al., *Postgrad Med J*, 64 Suppl 1: 3-6 (1988); Sanders, *Am J Physiol*, 247: G117 (1984); Pairet, et al., *Am J Physiol*, 250 (3 pt 1): G302-G308 (1986); Gaginella, *Textbook of Secretory Diarrhea* 15-30 (Raven Press, 1990); Federal Register Vol. 50, No. 10 (GPO, 1985); Pierce, et al., *Gastroenterology* 60 (1): 22-32 (1971); Beubler, et al., *Gastroenterology*, 90: 1972 (1986); Clarke, et al., *Am J Physiol* 259: G62 (1990); Hunt, et al., *J Vet Pharmacol Ther*, 8 (2): 165-173 (1985);

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Dajani, et al., *Eur J Pharmacol*, 34(1): 105-113 (1975); Sellin, *Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, and Management* 1451-1471 (WB Saunders Company, 1998)). Prostaglandins have additionally been shown to have cytoprotective effects (Sellin, *Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, and Management*. (WB Saunders Company, 1998); Robert, *Physiology of the Gastrointestinal Tract* 1407-1434 (Raven, 1981); Robert, *Adv Prostaglandin Thromboxane Res* 2:507-520 (1976); Wallace, et al., *Aiment Pharmacol Ther* 9: 227-235 (1995)).

U.S. Pat. No. 5,317,032 to Ueno et al. describes prostaglandin analog cathartics, including the existence of bicyclic tautomers and U.S. Pat. No. 6,414,016 to Ueno describes the bicyclic tautomers as having pronounced activity as anti-constipation agents. The bicyclic tautomers, substituted by one or more halogen atoms can be employed in small doses for relieving constipation. At the C-16 position, especially, fluorine atoms, can be employed in small doses for relieving constipation. The doses, however, by which these prostaglandin analogs are optimally effective is not known. Moreover, the range at which the PG analogs are safe, while yet exerting therapeutic effects, needs to be determined. Clinical dose-ranging studies will be necessary to evaluate the safety and tolerance of PG analogs.

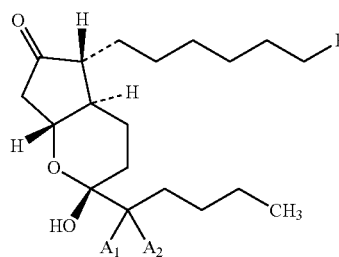
## DISCLOSURE OF INVENTION

It is therefore an object of this invention to provide a dosage formulation and a workable, therapeutic approach for relieving and preventing constipation in human patients.

That is, the present invention provides a dosage unit for use in relieving or preventing constipation in a human patient comprising

(i) a prostaglandin (PG) analog represented by Formula (I) and/or its tautomer in the range of about 6-96 μg:

Formula (I)



where A<sub>1</sub> and A<sub>2</sub> are the same or different halogen atoms and

B is —COOH, including its pharmaceutically acceptable salts, esters or amides; and

(ii) a pharmaceutically suitable excipient.

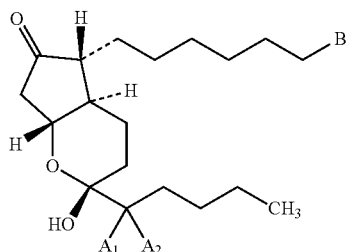
Another object of the present invention is to provide a method for treating constipation in a human patient. Accordingly, the instant invention also provides a method for relieving or preventing constipation in a human patient that comprises administering to the patient a dosage unit comprising

(i) a PG analog, represented by Formula (I) and/or its tautomer in the range of about 6-96 μg:



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Formula (I)

where  $A_1$  and  $A_2$  are the same or different halogen atoms and

B is  $-\text{COOH}$ , including its pharmaceutically acceptable salts, esters or amides; and

(ii) a pharmaceutically suitable excipient.

According to the invention, the halogenated PG analog of formula (I) is preferably halogenated with fluorine atoms, to have a cathartic effect. The dosage unit of the invention comprises the PG analog of formula (I) and/or its tautomer in the range of about 6-96  $\mu\text{g}$  per unit. A total daily dose of about 24-72  $\mu\text{g}$  is also preferred. For example, the preferable total daily dose of the PG analog is about 48  $\mu\text{g}$ .

According to the invention, the pharmaceutical excipient may preferably be a medium chain fatty acid to provide a dosage unit is administered orally.

#### BRIEF DESCRIPTION OF DRAWINGS

FIG. 1. Graph of daily average number of spontaneous bowel movements in the intent-to-treat population. Daily bowel movements were assessed for the 0  $\mu\text{g}$ , 24  $\mu\text{g}$ , 48  $\mu\text{g}$  and 72  $\mu\text{g}$  doses of Compound A during 0, 1, 2 and 3 weeks of medicating.

In the graph, [ ] = statistically significant overall p-value based on a Cochran-Mantel Haenszel (CMH) test using modified ridit scores, controlling for site, and using Shaffer's modified sequentially rejective multiple test procedure. \* = statistically significant pairwise comparison based on a Cochran-Mantel Haenszel (CMH) test comparing placebo to active drug using modified ridit scores, controlling for site and using Shaffer's modified sequentially rejective multiple test procedure.

FIG. 2. Graph of weekly average number of spontaneous bowel movements in the intent-to-treat population. Average number of bowel movements were compared across the different treatment groups during 0 weeks, week 1, week 2 and week 3.

In the graph, [ ] = statistically significant overall p-value based on a Cochran-Mantel Haenszel (CMH) test using modified ridit scores, controlling for site, and using Shaffer's modified sequentially rejective multiple test procedure. \* = statistically significant pairwise comparison based on a Cochran-Mantel Haenszel (CMH) test comparing placebo to active drug using modified ridit scores, controlling for site and using Shaffer's modified sequentially rejective multiple test procedure. Dotted line represents the cut-line for constipation defined as  $<3$  spontaneous bowel movements per week.

FIG. 3. Graph of study drug effectiveness in the intent-to-treat population. Effectiveness of study drug for the different treatment groups was rated on a scale of 0-4, 4 being the most effective.

In the graph, [ ] = statistically significant overall p-value based on a Cochran-Mantel Haenszel (CMH) test using

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modified ridit scores, controlling for site, and using Shaffer's modified sequentially rejective multiple test procedure. \* = statistically significant pairwise comparison based on a Cochran-Mantel Haenszel (CMH) test comparing placebo to active drug using modified ridit scores, controlling for site and using Shaffer's modified sequentially rejective multiple test procedure. Rating scale: 0 = not at all effective, 1 = a little bit effective, 2 = moderately effective, 3 = quite a bit effective and 4 = extremely effective.

#### DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a dosage unit for an anti-constipation composition comprising a halogenated prostaglandin analog as an active ingredient.

Cathartics are thought to work by the combination of one or more mechanisms to increase the water content of feces and promote transfer of the content in the intestines. Halogenated prostaglandin analogs of formula (I) appear to alleviate constipation by mainly acting on the intestinal mucosa to affect the transfer of electrolytes and water from intestinal walls into blood vessels and/or from blood vessels into intestines. These results in reduced water absorption and/or increased water secretion through intestines, increased intraintestinal water pool and transfer of the intraintestinal content.

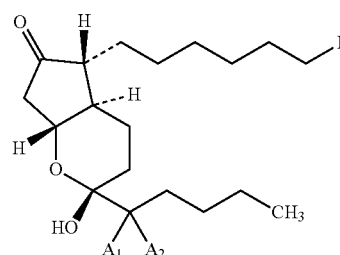
The present inventors have discovered a dosage regimen and suitable formulations of halogenated prostaglandin analogs for the treatment and prevention of constipation. A dosage unit comprising a PG analog and a pharmaceutically suitable excipient is described herein.

#### Preparing a Dosage Unit

The dosage unit comprises a prostaglandin analog of formula (I) and a pharmaceutically suitable excipient. The amount of the PG analog present in the dosage unit typically is in the range of about 6-96  $\mu\text{g}$ . As used herein, the term "about" when used in conjunction with a unit of measure can be defined as  $\pm 30\%$  and  $\pm 20\%$ , preferably  $\pm 10\%$ . For example, the range of about 6-96  $\mu\text{g}$  preferably means the range of 5.4-105.6  $\mu\text{g}$ . The preferred dose is in the range of about 24-72  $\mu\text{g}$ . In a more preferred embodiment, the dose is in the range of about 24-60  $\mu\text{g}$ . For example, the dose of said halogenated composition can be about 48  $\mu\text{g}$ . The dosage unit of the invention can be used for constipation treatment and prevention remedies for humans.

#### (i) PG Analogs

The PG analog, in the present invention is represented by formula (I):



Formula (I)

where  $A_1$  and  $A_2$  are halogen atoms and B is  $-\text{COOH}$ , its pharmaceutically acceptable salt, ester or amide.

The term "halogen" is used conventionally to include fluorine, chlorine, bromine, and iodine atoms. Particularly preferable halogen atoms for  $A_1$  and  $A_2$  are fluorine atoms.

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The halogenated PG analog of formula (I) used in the present invention may be an amide, a salt or an ester. Such salts include pharmaceutically acceptable salts, for example, those of alkali metals such as sodium and potassium; those of alkaline earth metals such as calcium and magnesium; those of physiologically acceptable ammonium salts such as ammonia, methylamine, dimethylamine, cyclopropylamine, cyclohexylamine, benzylamine, piperidine, ethylenediamine, monoethanolamine, diethanolamine, triethanolamine, monomethylmonoethanolamine, tromethamine, lysine, procaine, caffeine, arginine and tetraalkylammonium salt, and the like. These salts may be prepared by a conventional process, for example, from the corresponding acid and base or by salt interchange.

Such esters include, for example, straight or branched alkyl esters, which may contain one or more unsaturated bonds such as methyl, ethyl, propyl, butyl, isopropyl, isobutyl, t-butyl, pentyl and 2-ethylhexyl.

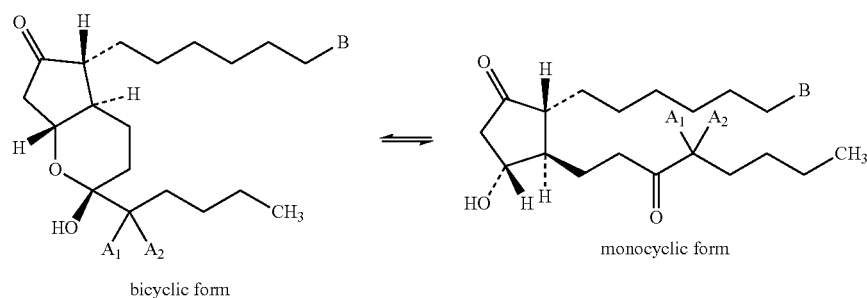
Preferred amides are methyl, ethyl, propyl, isopropyl and butyl amides.

In a preferred embodiment, the dosage unit comprises a PG analog of formula (I) in which A<sub>1</sub> and A<sub>2</sub> are fluorine atoms. Still more preferred is the one in which B is —COOH.

A dosage unit, as defined herein, is a unit of halogenated PG analog to be administered. Single or multiple dosage units may be administered, making up the dose, a quantity of halogenated PG analog that produces the desired cathartic effect.

The active agent of this invention exists as a bicyclic compound in a solid state, but partially forms a tautomer of the above compound when dissolved in a solvent. In the absence of water, compounds represented by formula (I) exist predominantly in the form of the bicyclic compound. In aqueous media, it is believed that hydrogen bonding occurs between, for example, the ketone position at the C-15 position, thereby hindering bicyclic ring formation. In addition, it is believed that the halogen atoms at the C-16 position promote bicyclic ring formation. The tautomerism between the hydroxy at the C-11 position and the keto moiety at the C-15 position, shown below, is especially significant in the case of compounds having a 13,14 single bond and two fluorine atoms the C-16 position.

Accordingly, the dosage unit of the present invention may comprise isomers of the halogenated PG analog compounds. For example, mono-cyclic tautomers having a keto group at the C-15 position and halogen atoms at the C-16 position.



A preferred compound according to the invention in its monocyclic form can be named as 13,14-dihydro-15-keto-16,16-difluoro-PGE<sub>1</sub>, according to conventional prostaglandin nomenclature.

(ii) The Pharmaceutically Suitable Excipient

According to the invention, the dosage unit of the invention may be formulated in any form. The pharmaceutically suit-

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able excipient may be, therefore, selected depending on the desired form of the dosage unit. According to the invention, "pharmaceutically suitable excipient" means an inert substance, which is suitable for the form, combined with the active ingredient of the invention.

For example, solid composition for oral administration of the present invention may include tablets, preparations, granules and the like. In such a solid composition, one or more active ingredients may be mixed with at least one inactive diluent, for example, lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinyl pyrrolidone, magnesium aluminate metasilicate and the like. According to the usual work-up, the composition may contain additives other than inactive diluent, for example, lubricant such as magnesium stearate; disintegrant such as fibrous calcium gluconate; stabilizer such as cyclodextrin, for example,  $\alpha$ -,  $\beta$ - or  $\gamma$ -cyclodextrin; etherified cyclodextrin such as dimethyl- $\alpha$ -, dimethyl- $\beta$ -, trimethyl- $\beta$ -, or hydroxypropyl- $\beta$ -cyclodextrin; branched cyclodextrin such as glucosyl-, maltosyl-cyclodextrin; formylated cyclodextrin, cyclodextrin containing sulfur; phospholipid and the like. When the above cyclodextrins are used, inclusion compound with cyclodextrins may be sometimes formed to enhance stability. Alternatively, phospholipid may be sometimes used to form liposome, resulting in enhanced stability.

Tablets or pills may be coated with film soluble in the stomach or intestine such as sugar, gelatin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose phthalate as needed. Further, they may be formed as capsules with absorbable substances such as gelatins. Preferably, the dosage unit is formulated in a soft gelatin capsule with liquid contents of the halogenated PG analog and a medium chain fatty acid triglyceride. Examples of the medium chain fatty acid triglyceride used in the present invention include a triglyceride of a saturated or unsaturated fatty acid having 6-14 carbon atoms which may have a branched chain. A preferred fatty acid is a straight chain saturated fatty acid, for example caproic acid (C6), caprylic acid (C8), capric acid (C10), lauric acid (C12) and myristic acid (C14). In addition, two or more medium chain fatty acid triglycerides may be used in combination. Further suitable excipients are disclosed in the published PCT application WO 01/27099.

A liquid composition for oral administration may be pharmaceutically acceptable emulsion, solution, suspension, syrup, elixir, as well as generally used inactive diluent. Such

composition may contain, in addition to the inactive diluent, adjuvants such as lubricants and suspensions, sweetening agents, flavoring agents, preservatives, solubilizers, anti-oxidants and the like. The details of the additives may be selected from those described in any general textbooks in the pharmaceutical field. Such liquid compositions may be directly enclosed in soft capsules. Solutions for parenteral adminis-

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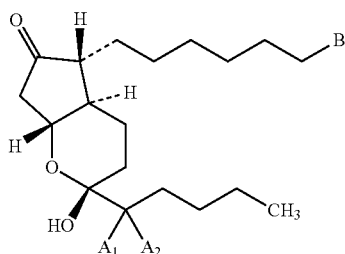
tration, for example, suppository, enema and the like according to the present invention include sterile, aqueous or non-aqueous solution, suspension, emulsion, detergent and the like. The aqueous solution and suspension includes, for example, distilled water, physiological saline and Ringer's solution.

The non-aqueous solution and suspension include, for example, propylene glycol, polyethylene glycol, fatty acid triglyceride, vegetable oil such as olive oil, alcohols such as ethanol, polysorbate and the like. Such composition may contain adjuvants such as preservatives, wetting agent, emulsifier, dispersant, anti-oxidants and the like.

The dosage unit of the present invention is parenterally acceptable, however orally is preferred. The test substance is preferably dissolved in Panacet 800 (medium chain fatty acid triglyceride manufactured by Nippon Oil & Fat Co., Ltd., Amagasaki, Japan) and filled in a capsule (each capsule contains 200  $\mu$ L of the mixture).

#### A Method for Treating Constipation

The invention further provides a method for relieving or preventing constipation in a human patient that comprises administering to the patient a dosage unit comprising (i) a PG analog represented by Formula (I) or its tautomers in the range of about 6-96  $\mu$ g:



Formula I

and (ii) a pharmaceutically suitable excipient.  $A_1$  and  $A_2$  of the PG analog represented by Formula (I) are halogen atoms and B is  $-\text{COOH}$ , its pharmaceutically acceptable salt, ester or amide. Preferably, the halogen atoms are fluorine atoms.

According to the method of the invention, the dosage unit of the present invention can be administered systemically or locally by means of oral or parental administration, including a suppository, enema and the like. Single or multiple dosage units may be administered to achieve the desired dose.

Preferably, the total daily dose of the PG analog is in the range of about 24-72  $\mu$ g. Also preferable, the total daily dose of the PG analog is in the range of about 24-60  $\mu$ g. Still more preferably, the total daily dose of the PG analog is about 48  $\mu$ g. The dose may vary somewhat, at the discretion of the physician, depending on the age and weight of the patient, conditions, therapeutic effect, administration route, treatment time and the like.

#### EXAMPLES

The following examples illustrate the present invention but are not in any way intended to limit the scope of this invention. The following abbreviations are used in the examples below:

AE Adverse Event  
 ITT Intent To Treat  
 PO Per Os (Orally)  
 PP Per Protocol  
 SE Safety Evaluable

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All randomized patients who took at least one dose of double-blind study medication constituted the safety evaluable (SE) population. These patients were included in the demographic data, baseline characteristic data and safety analysis. For efficacy, the same data set was used and is referred to as the intent-to-treat (ITT) population. Patients who did not comply with the treatment regimen or who took disallowed concomitant medication were considered protocol violators. Key efficacy analyses were also performed on the per-protocol (PP) population, which excluded all data for the affected weeks for protocol violators. Patients whose treatments were adjusted were analyzed in their original treatment group (i.e., as randomized).

#### Example 1

##### Phase I Dosage Studies

The safety and tolerance of oral Compound A (13,14-dihydro-15-keto-16,16-difluoro-PGE<sub>1</sub>) was evaluated in 16 volunteers in a single-dose Phase I study (Phase Ia) at rising per-person doses of 6  $\mu$ g, 12  $\mu$ g, 24  $\mu$ g, 48  $\mu$ g, 72  $\mu$ g, and 96  $\mu$ g compared and in 24 volunteers in a multiple-dose Phase I study (Phase Ib) at rising per-person doses of 24  $\mu$ g, 30  $\mu$ g, and 36  $\mu$ g of Compound A administered three times a day (TID) (i.e., total daily per person doses of 72  $\mu$ g, 90  $\mu$ g and 108  $\mu$ g) for 6 days.

The dose-limiting toxicity in the Phase I studies was nausea. The maximum tolerated single per-person dose of Compound A was 96  $\mu$ g and the maximum tolerated multiple per-person dose of Compound A was 36  $\mu$ g taken TID (i.e., a 108  $\mu$ g total daily dose).

##### Single Rising Dose Study

96  $\mu$ g was the maximum tolerated single oral Compound A dose. In the Phase Ia study, serious adverse events (SAE) did not occur at any dose level, but there were a total of 49 AEs. These occurred in 13 of the 17 volunteers and all resolved. Volunteers receiving placebo experienced five AEs. Most AEs could be categorized as either responses or events commonly reported in Phase I clinical trials (such as headache and lightheadedness) or expected pharmacodynamic responses of Compound A (such as loose bowel movements, diarrhea and abdominal cramping).

The number of adverse events increased with dose. The increase in frequency and severity of AEs found between the first four dose increments and the final two dose increments, coupled with the further increase in AEs between the final two dose increments, suggested that 96  $\mu$ g was the maximum tolerated single oral Compound A dose.

Bowel movement frequency was assessed during the 24 hour period after dosing for each dose-level group. Bowel movements were experienced in the placebo and in all active dose groups. There was a trend for increased bowel movements in subjects treated with Compound A as compared to those treated with placebo. The most striking effects were seen in subjects treated at the 96  $\mu$ g dose level. Compared to only three of twelve subjects experiencing bowel movements in the placebo group, all six subjects in the 96  $\mu$ g Compound A group experienced bowel movements. Furthermore, the average number of bowel movements per subject in this Compound A group (1.5) was three times greater than the average number of bowel movements per subject in the placebo group (0.5).

##### Multiple Rising Dose Study

Compound A was determined to be optimal when administered at the 24  $\mu$ g dose TID and determined to be safe and tolerable up to 36  $\mu$ g when administered TID for at least 6

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days. The AEs that were experienced were those that were associated with the expected pharmacologic action of Compound A. However, given that the maximal total number of bowel movements was achieved at the 24  $\mu\text{g}$  dose level, and that increasing doses were not associated with increased pharmacodynamic effects, but were associated with an increased AE profile, the 24  $\mu\text{g}$  dose level was determined to be the best tolerated effective dose in healthy volunteers.

The volunteers experienced no SAEs. The main dose limiting side effect observed during the study was nausea. At the 24  $\mu\text{g}$  dose level, one volunteer had three bouts of nausea and at the 30  $\mu\text{g}$  dose level, two volunteers experienced a total of three bouts of nausea. At the 36  $\mu\text{g}$  dose level, there was a notable increase in the incidence of nausea, with thirteen bouts of nausea being experienced by five out of six volunteers dosed at this level. Further to this, one volunteer at the 36  $\mu\text{g}$  level experienced twelve episodes of diarrhea or loose stools, two episodes of nausea and three episodes of abdominal cramps during the dosing period. All vital signs and ECG measurements were normal throughout the study period and no central nervous system or physical abnormalities observed. The 36  $\mu\text{g}$  dose level was determined to be the maximum tolerated multiple oral dose for the TID treatment regimen.

Bowel movement frequency was assessed in this study as well. As in the Phase I single rising dose study, the Compound A treatment groups exhibited more bowel movements than the placebo group. A total of 193 bowel movements were experienced in this study. Of these, 31 occurred in the placebo group, 70 in the 24  $\mu\text{g}$  group, 51 in the 30  $\mu\text{g}$  group and 41 in the 36  $\mu\text{g}$  group.

### Example 2

#### Phase II Dosage Studies

Eligible patients were treated with either placebo or total daily doses of 24  $\mu\text{g}$ , 48  $\mu\text{g}$  or 72  $\mu\text{g}$  of Compound A for 21 days. One placebo or Compound A capsule was taken 3 times each day (AM, Noon, and PM). Compound A was administered as 24  $\mu\text{g}$  oral capsules. Patients assigned to receive the total daily 24  $\mu\text{g}$  Compound A dose took one Compound A capsule in the AM and one matching placebo capsule both at Noon and in the PM; patients assigned to receive the total daily 48  $\mu\text{g}$  Compound A dose took one Compound A capsule in both the AM and PM and one matching placebo capsule at Noon; patients assigned to receive the total daily 72  $\mu\text{g}$  Compound A dose took one Compound A capsule in the AM, at Noon, and in the PM.

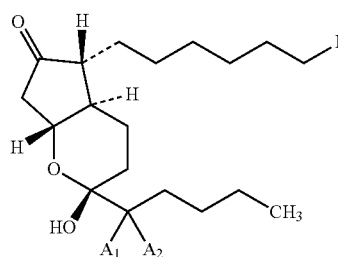
Based on the overall efficacy results, doses of Compound A as low as 24  $\mu\text{g}$  tended to relieve constipation, however, based on statistical analyses, the minimum effective dose of Compound A was 48  $\mu\text{g}$  per day. Compared to placebo treatment, patients taking 48  $\mu\text{g}$  or 72  $\mu\text{g}$  of Compound A experienced statistically significant increases in the daily average number

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of spontaneous bowel movements at Week 1 and Week 2. Administration of 48  $\mu\text{g}$  or 72  $\mu\text{g}$  of Compound A produced a statistically significant increase in the proportion of patients who had a spontaneous bowel movement on Day 1. Statistically significant improvements in stool consistency were observed at all post-baseline time points in patients taking 48  $\mu\text{g}$  and 72  $\mu\text{g}$  of Compound A. Statistically significant improvements in constipation severity were observed at Week 3 in patients taking 48  $\mu\text{g}$  of Compound A and at Weeks 2 and 3 in patients taking 72  $\mu\text{g}$  of Compound A.

What is claimed is:

1. A dosage unit comprising a prostaglandin (PG) analog represented by Formula (I) and/or its tautomers, and a pharmaceutically suitable excipient, wherein the dosage unit contains said PG analog in an amount of 24  $\mu\text{g}$   $\pm$  10%:



Formula (I)

where  $A_1$  and  $A_2$  are fluorine atoms and B is  $-\text{COOH}$ , including its pharmaceutically acceptable salts, esters or amides.

2. The dosage unit of claim 1, wherein said PG analog is the monocyclic tautomer of formula (I).

3. The dosage unit of claim 1, wherein said PG analog is the bi-cyclic tautomer of formula (I).

4. The dosage unit of claim 1, wherein said pharmaceutically suitable excipient is orally acceptable.

5. The dosage unit of claim 1, wherein said pharmaceutically suitable excipient is a medium chain fatty acid.

6. The dosage unit of claim 1, wherein B is  $-\text{COOH}$ .

7. The dosage unit of claim 1, which is suitable for use in a human patient.

8. The dosage unit of claim 7, which is suitable for use in relieving or preventing constipation.

9. The dosage unit of claim 5, wherein B is  $-\text{COOH}$ .

10. The dosage unit of claim 1, wherein the PG analog is present in an amount of 24  $\mu\text{g}$ .

11. The dosage unit of claim 10, wherein B is  $-\text{COOH}$ .

12. The dosage unit of claim 10, wherein said pharmaceutically suitable excipient is a medium chain fatty acid.

13. The dosage unit of claim 11, wherein said pharmaceutically suitable excipient is a medium chain fatty acid.

\* \* \* \* \*

# **EXHIBIT D**

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

(10) **Patent No.:** **US 8,026,393 B2**  
 (45) **Date of Patent:** **Sep. 27, 2011**

(54) **SOFT-GELATIN CAPSULE FORMULATION**

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(73) Assignees: **Sucampo AG**, Zug (CH); **R-Tech Ueno, Ltd.**, Tokyo (JP)

(\* ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 275 days.

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(21) Appl. No.: **11/656,476**

(22) Filed: **Jan. 23, 2007**

(65) **Prior Publication Data**  
 US 2007/0172523 A1 Jul. 26, 2007

**Related U.S. Application Data**

(60) Provisional application No. 60/761,360, filed on Jan. 24, 2006.

(51) **Int. Cl.**  
**C07C 61/06** (2006.01)  
**C07C 61/20** (2006.01)

(52) **U.S. Cl.** ..... **562/504**; 514/513

(58) **Field of Classification Search** ..... None  
 See application file for complete search history.

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*Primary Examiner* — Daniel Sullivan  
*Assistant Examiner* — Yevegeny Valenrod  
 (74) *Attorney, Agent, or Firm* — Sughrue Mion, PLLC

(57) **ABSTRACT**

The present invention discloses a soft gelatin capsule formulation of a 15-keto-prostaglandin compound, which comprises: a soft gelatin capsule shell comprising gelatin and sugar alcohol as a plasticizer, and a mixture comprising a 15-keto-prostaglandin compound and a pharmaceutically acceptable vehicle which is filled in the shell. By encapsulating the 15-keto-prostaglandin compound in the specified soft gelatin capsule shell, stability of the compound is significantly improved.

**22 Claims, No Drawings**



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**SOFT-GELATIN CAPSULE FORMULATION****CROSS REFERENCE TO RELATED APPLICATION**

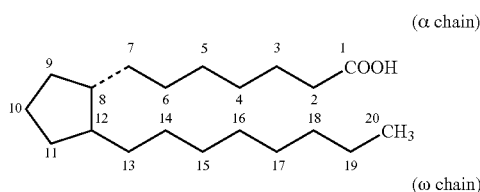
This application claims the benefit of U.S. Provisional Application No. US60/761,360 filed Jan. 24, 2006.

**FIELD OF THE INVENTION**

The present invention relates to a soft-gelatin capsule formulation of a therapeutically effective 15-keto-prostaglandin compound.

**BACKGROUND ART**

Prostaglandins (hereinafter, referred to as PGs) are members of class of organic carboxylic acids, which are contained in tissues or organs of human and other mammals, and exhibit a wide range of physiological activities. PGs found in nature (primary PGs) have, as a general structural property thereof, a prostanic acid skeleton as shown in the formula (A):



On the other hand, some synthetic analogues have modified skeletons. The primary PGs are classified into PGAs, PGBs, PGCs, PGDs, PGEs, PGFs, PGGs, PGHs, PGIs and PGJs on the basis of the structural property of the five membered ring moiety, and further classified into the following three types by the number and position of the unsaturated bond in the carbon chain moiety.

Type 1 (subscript 1): 13,14-unsaturated-15-OH

Type 2 (subscript 2): 5,6- and 13,14-diunsaturated-15-OH

Type 3 (subscript 3): 5,6-, 13,14-, and 17,18-triunsaturated-15-OH.

Further, PGFs are classified on the basis of the configuration of the hydroxyl group at the 9-position into a type (wherein the hydroxyl group is of the  $\alpha$ -configuration) and  $\beta$  type (wherein the hydroxyl group is of the  $\beta$ -configuration).

In addition, some 15-keto-PGs (PGs having an oxo group at position 15 in place of the hydroxy group) and 13,14-dihydro-15-keto-PGs have been known as substances naturally produced by enzymatic actions during metabolism of the primary PGs and have some therapeutic effect. 15-keto-PGs have been disclosed in U.S. Pat. Nos. 5,073,569, 5,534,547, 5,225,439, 5,166,174, 5,428,062, 5,380,709, 5,886,034, 6,265,440, 5,106,869, 5,221,763, 5,591,887, 5,770,759 and 5,739,161. The contents of these publications are herein incorporated by reference.

For example, 15-keto-16-halogen prostaglandin compounds are useful as cathartics (U.S. Pat. No. 5,317,032, the contents of the reference is herein incorporated by reference). For treating gastrointestinal diseases, the agent is preferably formulated as an orally administrable dosage form. In general, PG compounds are less soluble in water and become significantly unstable under the presence of water. A capsulated formulation comprises a 15-keto-16-halogen PG compound and a solvent which can maintain the stability of the compound such as glyceride had been proposed (WO01/

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027099 (U.S. Pat. No. 6,583,174), the contents of the cited reference is herein incorporated by reference.

Elastic shell of a soft gelatin capsule, in general, incorporates a plasticizer in addition to gelatin. Examples of plasticizer include glycerin, propylene glycol, sorbitol, maltitol, sugar alcohol solution derived from corn starch (Anidrisorb™, Polysorb™), i.e. a mixture of sorbitol, sorbitane, mannitol and hydrogenated starch hydrolysate, hydrogenated maltose starch syrup, i.e. a mixture of maltitol, sorbitol and oligosaccharide alcohol.

**SUMMARY OF THE INVENTION**

An object of the present invention is to provide an orally administrable dosage form of a 15-keto-prostaglandin compound which has an excellent shelf stability.

Accordingly, the instant application provides a soft gelatin capsule formulation of a 15-keto-prostaglandin compound, which comprises:

a soft gelatin capsule shell comprising gelatin and a sugar alcohol as a plasticizer, and

a mixture comprising a 15-keto-prostaglandin compound and a pharmaceutically acceptable vehicle, which is filled in the shell.

The invention is also provides a method for improving stability of a 15-keto-prostaglandin compound which comprises, dissolving the 15-keto-prostaglandin in a pharmaceutically acceptable solvent and incorporating the solution in a soft-gelatin capsule whose shell comprises gelatin and a sugar alcohol as a plasticizer.

**DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS**

The nomenclature of the PG compounds used herein is based on the numbering system of prostanoic acid represented in the above formula (A).

The formula (A) shows a basic skeleton of the C-20 PG compound, but the present invention is not limited to those having the same number of carbon atoms. In the formula (A), the numbering of the carbon atoms which constitute the basic skeleton of the PG compounds starts at the carboxylic acid (numbered 1), and carbon atoms in the  $\alpha$ -chain are numbered 2 to 7 towards the five-membered ring, those in the ring are 8 to 12, and those in the  $\omega$ -chain are 13 to 20. When the number of carbon atoms is decreased in the  $\alpha$ -chain, the number is deleted in the order starting from position 2; and when the number of carbon atoms is increased in the  $\alpha$ -chain, compounds are named as substitution compounds having respective substituents at position 2 in place of carboxy group (C-1). Similarly, when the number of carbon atoms is decreased in the  $\omega$ -chain, the number is deleted in the order starting from position 20; and when the number of carbon atoms is increased in the  $\omega$ -chain, compounds are named as substitution compounds having respective substituents at position 20. Stereochemistry of the compounds is the same as that of the above formula (A) unless otherwise specified.

In general, each of PGD, PGE and PGF represents a PG compound having hydroxy groups at positions 9 and/or 11, but in the present specification and claims they also include those having substituents other than the hydroxyl groups at positions 9 and/or 11. Such compounds are referred to as 9-dehydroxy-9-substituted-PG compounds or 11-dehydroxy-11-substituted-PG compounds. A PG compound having hydrogen in place of the hydroxy group is simply named as 9- or 11-dehydroxy compound.

As stated above, the nomenclature of PG compounds is based on the prostanoic acid skeleton. However, in case the compound has a similar partial construction as a prostaglandin, the abbreviation of "PG" may be used. Thus, a PG com-



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compound of which  $\alpha$ -chain is extended by two carbon atoms, that is, having 9 carbon atoms in the  $\alpha$ -chain is named as 2-decarboxy-2-(2-carboxyethyl)-PG compound. Similarly, a PG compound having 11 carbon atoms in the  $\alpha$ -chain is named as 2-decarboxy-2-(4-carboxybutyl)-PG compound. Further, a PG compound of which  $\omega$ -chain is extended by two carbon atoms, that is, having 10 carbon atoms in the  $\omega$ -chain is named as 20-ethyl-PG compound. These compounds, however, may also be named according to the IUPAC nomenclatures.

The 15-keto-PG compound used in the present invention may be any derivative of a PG insofar as having an oxo group at position 15 in place of the hydroxy group, and may further include a compound having one double bond between positions 13 and 14 (15-keto-PG type 1 compound), two double bonds between positions 13 and 14, and positions 5 and 6 (15-keto-PG type 2 compound), and three double bonds between positions 5 and 6, positions 13 and 14, and positions 17 and 18 (15-keto-PG type 3 compound), and a derivative thereof wherein the bond between the positions 13 and 14 is single bond, in place of the double bond (13,14-dihydro-15-keto-PG compound).

Examples of the analogue including substitution compounds or derivatives include a PG compound of which the carboxy group at the end of the alpha chain is esterified; physiologically acceptable salt thereof; an unsaturated derivative having a double bond between positions 2 and 3 or a triple bond between positions 5 and 6; PG compounds having substituent(s) on carbon atom(s) at position(s) 3, 5, 6, 16, 17, 18, 19 and/or 20; and PG compounds having lower alkyl or a hydroxy (lower) alkyl group at position 9 and/or 11 in place of the hydroxy group.

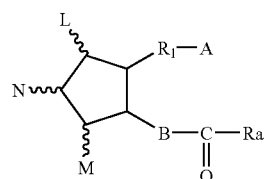
According to the present invention, preferred substituents on the carbon atom at position(s) 3, 17, 18 and/or 19 include alkyl having 1 to 6 carbon atoms, especially methyl and ethyl. Preferred substituents on the carbon atom at position 16 include lower alkyl such as methyl and ethyl, hydroxy, halogen atom such as chlorine and fluorine, and aryloxy such as trifluoromethylphenoxy. Preferred substituents on the carbon atom at position 17 include halogen atom such as chlorine and fluorine. Preferred substituents on the carbon atom at position 20 include saturated or unsaturated lower alkyl such as  $C_{1-4}$  alkyl, lower alkoxy such as  $C_{1-4}$  alkoxy, and lower alkoxy alkyl such as  $C_{1-4}$  alkoxy- $C_{1-4}$  alkyl. Preferred substituents on the carbon atom at position 5 include halogen atoms such as chlorine and fluorine. Preferred substituents on the carbon atom at position 6 include an oxo group forming a carbonyl group. Stereochemistry of PGs having hydroxy, lower alkyl or hydroxy(lower)alkyl substituent on the carbon atom at positions 9 and 11 may be  $\alpha$ ,  $\beta$  or a mixture thereof.

Further, the above described derivatives may have a  $\omega$  chain shorter than that of the primary PGs and a substituent such as alkoxy, cyclohexyl, cyclohexyloxy, phenoxy and phenyl at the end of the truncated  $\omega$ -chain.

Especially preferred compounds include a 13,14-dihydro-15-keto-PG compound that has a single bond between positions 13 and 14; a 15-keto-16-mono or 16,16-di-halogen PG compound that has at least one halogen atom, especially fluorine, at carbon atom of position 16; a 15-keto-PGE compound that has hydroxy group at position 9 and oxo group at position 11 of the five membered ring.

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A preferred prostaglandin compound used in the present invention is represented by the formula (I):



wherein L, M and N are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

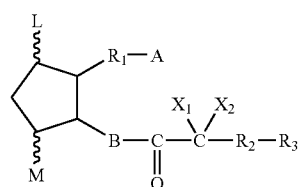
A is  $-\text{CH}_3$ , or  $-\text{CH}_2\text{OH}$ ,  $-\text{COCH}_2\text{OH}$ ,  $-\text{COOH}$  or a functional derivative thereof;

B is  $-\text{CH}_2-\text{CH}_2-$ ,  $-\text{CH}=\text{CH}-$  or  $-\text{C}\equiv\text{C}-$ ;

R<sub>1</sub> is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, lower alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur; and

Ra is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocycloxy group; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic group; heterocycloxy group.

A more preferred prostaglandin compound used in the present invention is represented by the formula (II):



wherein L and M are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have one or more double bonds;

A is  $-\text{CH}_3$ , or  $-\text{CH}_2\text{OH}$ ,  $-\text{COCH}_2\text{OH}$ ,  $-\text{COOH}$  or a functional derivative thereof;

B is  $-\text{CH}_2-\text{CH}_2-$ ,  $-\text{CH}=\text{CH}-$  or  $-\text{C}\equiv\text{C}-$ ;

X<sub>1</sub> and X<sub>2</sub> are hydrogen, lower alkyl, or halogen;

R<sub>1</sub> is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, lower alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur;

R<sub>2</sub> is a single bond or lower alkylene; and

R<sub>3</sub> is lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocycloxy group.

In the above formula, the term "unsaturated" in the definitions for R<sub>1</sub> and Ra is intended to include at least one or more double bonds and/or triple bonds that are isolatedly, separately or serially present between carbon atoms of the main and/or side chains. According to the usual nomenclature, an

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unsaturated bond between two serial positions is represented by denoting the lower number of the two positions, and an unsaturated bond between two distal positions is represented by denoting both of the positions.

The term "lower or medium aliphatic hydrocarbon" refers to a straight or branched chain hydrocarbon group having 1 to 14 carbon atoms (for a side chain, 1 to 3 carbon atoms are preferable) and preferably 1 to 10, especially 6 to 10 carbon atoms for R<sub>1</sub> and 1 to 10, especially, 1 to 8 carbon atoms for Ra.

The term "halogen" covers fluorine, chlorine, bromine and iodine.

The term "lower" is intended to include a group having 1 to 6 carbon atoms unless otherwise specified.

The term "lower alkyl" refers to a straight or branched chain saturated hydrocarbon group containing 1 to 6 carbon atoms and includes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl and hexyl.

The term "lower alkoxy" refers to a group of lower alkyl-O—, wherein lower alkyl is as defined above.

The term "hydroxy(lower)alkyl" refers to a lower alkyl as defined above which is substituted with at least one hydroxy group such as hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 1-methyl-1-hydroxyethyl.

The term "lower alkanoyloxy" refers to a group represented by the formula RCO—O—, wherein RCO— is an acyl group formed by oxidation of a lower alkyl group as defined above, such as acetyl.

The term "cyclo(lower)alkyl" refers to a cyclic group formed by cyclization of a lower alkyl group as defined above but contains three or more carbon atoms, and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "cyclo(lower)alkyloxy" refers to the group of cyclo(lower)alkyl-O—, wherein cyclo(lower)alkyl is as defined above.

The term "aryl" may include unsubstituted or substituted aromatic hydrocarbon rings (preferably monocyclic groups), for example, phenyl, tolyl, xylyl. Examples of the substituents are halogen atom and halo(lower)alkyl, wherein halogen atom and lower alkyl are as defined above.

The term "aryloxy" refers to a group represented by the formula ArO—, wherein Ar is aryl as defined above.

The term "heterocyclic group" may include mono- to tricyclic, preferably monocyclic heterocyclic group which is 5 to 14, preferably 5 to 10 membered ring having optionally substituted carbon atom and 1 to 4, preferably 1 to 3 of 1 or 2 type of hetero atoms selected from nitrogen, oxygen and sulfur. Examples of the heterocyclic group include furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, 2-pyrrolinyl, pyrrolidinyl, 2-imidazolyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, piperidino, piperazinyl, morpholino, indolyl, benzothienyl, quinolyl, isoquinolyl, purinyl, quinazolyl, carbazolyl, acridinyl, phenanthridinyl, benzimidazolyl, benzimidazolyl, benzothiazolyl, phenothiazinyl. Examples of the substituent in this case include halogen, and halogen substituted lower alkyl group, wherein halogen atom and lower alkyl group are as described above.

The term "heterocycloxy group" means a group represented by the formula HcO—, wherein Hc is a heterocyclic group as described above.

The term "functional derivative" of A includes salts, preferably pharmaceutically acceptable salts, ethers, esters and amides.

Suitable "pharmaceutically acceptable salts" include salts formed with non-toxic bases conventionally used in pharmaceutical field, for example a salt with an inorganic base such as an alkali metal salt (such as sodium salt and potassium salt), an alkaline earth metal salt (such as calcium salt and magnesium salt), an ammonium salt; or a salt with an organic base, for example, an amine salt including such as methy-

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lamine salt, dimethylamine salt, cyclohexylamine salt, benzylamine salt, piperidine salt, ethylenediamine salt, ethanolamine salt, diethanolamine salt, triethanolamine salt, tris (hydroxymethylamino)ethane salt, monomethylmonoethanolamine salt, procaine salt and caffeine salt), a basic amino acid salt (such as arginine salt and lysine salt), tetraalkyl ammonium salt and the like. These salts may be prepared by a conventional process, for example from the corresponding acid and base or by salt interchange.

Examples of the ethers include alkyl ethers, for example, lower alkyl ethers such as methyl ether, ethyl ether, propyl ether, isopropyl ether, butyl ether, isobutyl ether, t-butyl ether, pentyl ether and 1-cyclopropyl ethyl ether; and medium or higher alkyl ethers such as octyl ether, diethylhexyl ether, lauryl ether and cetyl ether; unsaturated ethers such as oleyl ether and linolenyl ether; lower alkenyl ethers such as vinyl ether, allyl ether; lower alkynyl ethers such as ethynyl ether and propynyl ether; hydroxy(lower)alkyl ethers such as hydroxyethyl ether and hydroxyisopropyl ether; lower alkoxy (lower)alkyl ethers such as methoxymethyl ether and 1-methoxyethyl ether; optionally substituted aryl ethers such as phenyl ether, tosyl ether, t-butylphenyl ether, salicyl ether, 3,4-di-methoxyphenyl ether and benzamidophenyl ether; and aryl(lower)alkyl ethers such as benzyl ether, trityl ether and benzhydryl ether.

Examples of the esters include aliphatic esters, for example, lower alkyl esters such as methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester and 1-cyclopropylethyl ester; lower alkenyl esters such as vinyl ester and allyl ester; lower alkynyl esters such as ethynyl ester and propynyl ester; hydroxy(lower)alkyl ester such as hydroxyethyl ester; lower alkoxy (lower)alkyl esters such as methoxymethyl ester and 1-methoxyethyl ester; and optionally substituted aryl esters such as, for example, phenyl ester, tolyl ester, t-butylphenyl ester, salicyl ester, 3,4-di-methoxyphenyl ester and benzamidophenyl ester; and aryl(lower)alkyl ester such as benzyl ester, trityl ester and benzhydryl ester.

The amide of A means a group represented by the formula —CONR'R'', wherein each of R' and R'' is hydrogen, lower alkyl, aryl, alkyl- or aryl-sulfonyl, lower alkenyl and lower alkynyl, and include for example lower alkyl amides such as methylamide, ethylamide, dimethylamide and diethylamide; arylamides such as anilide and toluidide; and alkyl- or aryl-sulfonylamides such as methylsulfonylamide, ethylsulfonylamide and tolylsulfonylamide.

Preferred examples of L and M include hydroxy and oxo, and especially, M is hydroxy and L is oxo which has a 5-membered ring structure of, so called, PGE type.

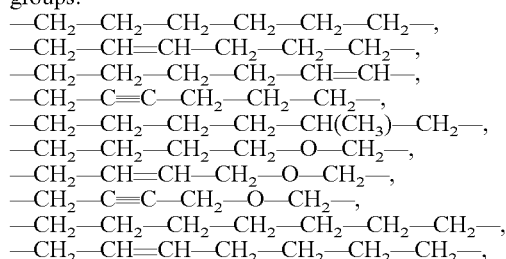
Preferred example of A is —COOH, its pharmaceutically acceptable salt, ester or amide thereof.

Preferred example of B is —CH<sub>2</sub>—CH<sub>2</sub>—, which provide the structure of so-called, 13,14-dihydro type.

Preferred example of X<sub>1</sub> and X<sub>2</sub> is that at least one of them is halogen, more preferably, both of them are halogen, especially, fluorine that provides a structure of, so called 16,16-difluoro type.

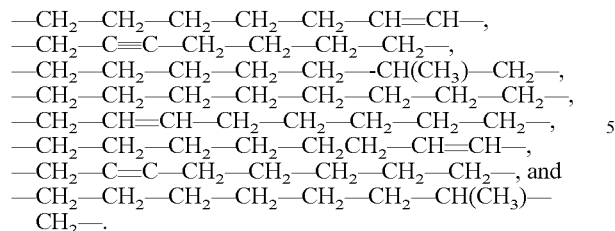
Preferred R<sub>1</sub> is a hydrocarbon residue containing 1-10 carbon atoms, preferably 6 to 10 carbon atoms. Further, at least one carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur.

Examples of R<sub>1</sub> include, for example, the following groups:



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Preferred Ra is a hydrocarbon containing 1 to 10 carbon atoms, more preferably, 1 to 8 carbon atoms. Ra may have one or two side chains having one carbon atom.

The configuration of the ring and the  $\alpha$ - and/or  $\omega$  chains in the above formula (I) and (II) may be the same as or different from that of the primary PGs. However, the present invention also includes a mixture of a compound having a primary type configuration and a compound of a non-primary type configuration.

The typical example of the present compounds are 13,14-dihydro-15-keto-16-mono- or 16,16-di-fluoro PGE compound and its derivative or analogue.

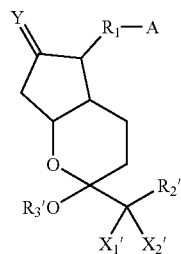
In the present invention, the 15-keto-PG compound may be in the keto-acetal equilibrium by formation of a hemiacetal between hydroxy at position 11 and keto at position 15.

For example, it has been revealed that when both of X<sub>1</sub> and X<sub>2</sub> are halogen atoms, especially, fluorine atoms, the compound contains a tautomeric isomer, bi-cyclic compound.

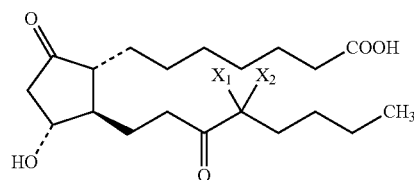
If such tautomeric isomers as above are present, the proportion of both tautomeric isomers varies with the structure of the rest of the molecule or the kind of the substituent present. Sometimes one isomer may predominantly be present in comparison with the other. However, it is to be appreciated that the present invention includes both isomers.

Further, the 15-keto-PG compounds used in the invention include the bi-cyclic compound and analogs or derivatives thereof.

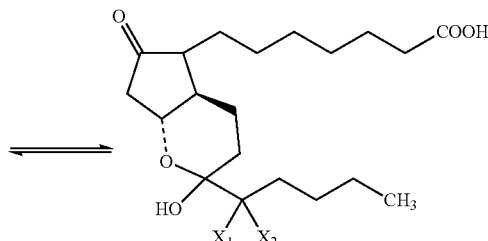
The bi-cyclic compound is represented by the formula (III):



(III)



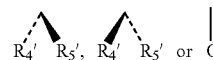
Tautomer I



Tautomer II

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wherein, A is  $-\text{CH}_3$ , or  $-\text{CH}_2\text{OH}$ ,  $-\text{COCH}_2\text{OH}$ ,  $-\text{COOH}$  or a functional derivative thereof;  
X<sub>1</sub>' and X<sub>2</sub>' are hydrogen, lower alkyl, or halogen;  
Y is



wherein R<sub>4</sub>' and R<sub>5</sub>' are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl, wherein R<sub>4</sub>' and R<sub>5</sub>' are not hydroxy and lower alkoxy at the same time;

R<sub>1</sub>' is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, lower alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur;

R<sub>2</sub>' is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocycloxy group; lower alkyl; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic group; heterocycloxy group; and

R<sub>3</sub>' is hydrogen, lower alkyl, cyclo(lower)alkyl, aryl or heterocyclic group.

Furthermore, while the compounds used in the invention may be represented by a formula or name based on keto-type regardless of the presence or absence of the isomers, it is to be noted that such structure or name does not intend to exclude the acetal type compound.

In the present invention, any of isomers such as the individual tautomeric isomers, the mixture thereof, or optical isomers, the mixture thereof, a racemic mixture, and other steric isomers may be used in the same purpose.

Some of the compounds used in the present invention may be prepared by the method disclosed in U.S. Pat. Nos. 5,073,569, 5,166,174, 5,221,763, 5,212,324, 5,739,161 and 6,242,485, the contents of these references are herein incorporated by reference.

It has been known that 13,14-dihydro-15-keto-prostaglandin compound having the formula as shown below (Tautomer I) may be in equilibrium with its tautomeric isomer (tautomer II) (See U.S. Pat. No. 5,166,174, U.S. Pat. No. 5,225,439, U.S. Pat. No. 5,284,858, U.S. Pat. No. 5,380,709, U.S. Pat. No. 5,428,062 and U.S. Pat. No. 5,886,034, the contents of these references are herein incorporated by reference.)

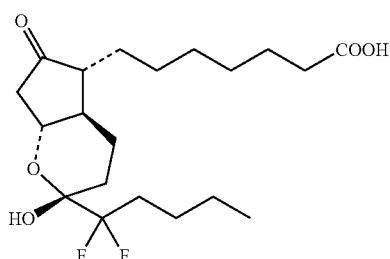
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It is considered that the halogen atom(s) at X<sub>1</sub> and/or X<sub>2</sub> promote bi-cyclic ring formation, such as the compound 1 or 2 below. In addition, in the absence of water, the tautomeric compounds as above exist predominantly in the form of the bi-cyclic compound. In aqueous media, it is supposed that hydrogen bonding occurs between the water molecule and, for example, the keto group on the hydrocarbon chain, thereby hindering bi-cyclic ring formation. The bi-cyclic/mono-cyclic structures, for example, may be present in a ratio of 6:1 in D<sub>2</sub>O; 10:1 in CD<sub>3</sub>OD-D<sub>2</sub>O and 96:4 in CDCl<sub>3</sub>. In the instant specification and claims, tautomeric mixture containing the bi-cyclic compound in a ratio even greater to substantially 100% bi-cyclic compound is within this invention.

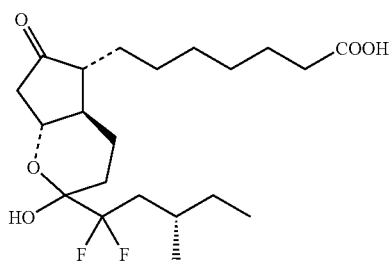
Embodiment of the bi-cyclic compound of the present invention include the Compounds 1 and 2 shown below.

Compound 1:



7-[(2R,4aR,5R,7aR)-2-(1,1-difluoropentyl)-2-hydroxy-6-oxooctahydrocyclopenta[b]pyran-5-yl]heptanoic acid

Compound 2:



7-[(4aR,5R,7aR)-2-[(3S)-1,1-difluoro-3-methylpentyl]-2-hydroxy-6-oxooctahydrocyclopenta[b]pyran-5-yl]heptanoic acid

According to the present invention, the pharmaceutically acceptable vehicle is not specifically limited as long as the vehicle can disperse the 15-keto-PG therein and does not significantly deteriorate the stability of the compound. In view of manufacturing soft gelatin capsule formulation, a solvent which is liquid at the room temperature. A solution, dispersion or mixture of the 15-keto-PG in the solvent may be filled in the capsule.

Examples of the pharmaceutically acceptable vehicles preferably used in the instant invention may be fatty acid esters, i.e. an ester of fatty acid and an alcohol, and polyols.

Preferred fatty acid which consists the fatty acid ester is a medium or higher chain fatty acid having at least C<sub>6</sub>, preferably C<sub>6</sub>-24 carbon atoms, for example caproic acid (C<sub>6</sub>), caprylic acid (C<sub>8</sub>), capric acid (C<sub>10</sub>), lauric acid (C<sub>12</sub>) and

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myristic acid (C<sub>14</sub>), palmitic acid (C<sub>16</sub>), palmitoleic acid (C<sub>16</sub>), stearic acid (C<sub>18</sub>), oleic acid (C<sub>18</sub>), linoleic acid (C<sub>18</sub>), linolenic acid (C<sub>18</sub>), ricinolic acid (C<sub>18</sub>) and arachic acid (C<sub>20</sub>). Preferred alcohols which consists the fatty acid ester may comprise C<sub>1</sub>-6 monovalent alcohol and polyols such as glycerin, polyethylene glycol and propylene glycol.

Preferred fatty acid esters may include a glyceride of a saturated or unsaturated fatty acid which may have a branched chain and a propylene glycol fatty acid ester. Two or more glycerides may be used as a mixture.

Examples of the mixture of glycerides are mixture of caprylic acid triglyceride and capric acid triglyceride, vegetable oils such as castor oil, corn oil, olive oil, sesame oil, rape oil, salad oil, cottonseed oil, camellia oil, peanut oil, palm oil and sunflower oil.

A fatty acid ester derived from a fatty acid and a monovalent alcohol is also preferably used as a pharmaceutically acceptable vehicle. The fatty acid ester may preferably be an ester of C<sub>8</sub>-20 fatty acid and a C<sub>2</sub>-3 monovalent alcohol, such as isopropyl myristate, isopropyl palmitate, ethyl linoleate and ethyl oleate.

Examples of polyols may preferably include alcohols having two or three hydroxy groups such as glycerin, polyethylene glycol and propylene glycol.

According to the present invention, the mixture which is filled in the soft-gelatin capsule shell may be obtained by dissolving or dispersing the above-described 15-keto-prostaglandin compound in the above described pharmaceutically acceptable vehicle which is liquid at the room temperature. When it is difficult to dissolve the 15-keto-PG compound directly in the vehicle, each of them may be dissolved in a solvent in which both of them are soluble respectively, and then the solutions may be combined.

The amount of the solvent in the mixture relative to the amount of the 15-keto-PG compound is not limited as long as the 15-keto-PG is stable in the final formulation. In general, the amount of the vehicle per one part of the 15-keto-PG compound may be 1-5,000,000, preferably, 5-1,000,000 and most preferably, 10-500,000 parts by weight.

The mixture used in the invention may further comprise an oil solvent such as mineral oil, liquid paraffin, and tocopherol. The mixture of the present invention may further comprise another pharmaceutically active ingredient.

In a preferred embodiment, the composition of the present invention is substantially free of water. The term "substantially free of water" means that the composition does not contain water that is intentionally added. It is understood that many materials contain water that is taken up from the atmosphere or is present as a coordination complex in its normal state. Water taken up by hygroscopic materials or present as a hydrate is permissibly present in the compositions of this embodiment. According to the embodiment, any water that is present in the composition should not be present in amounts such that the water will have a deleterious effect to the composition of the present invention.

According to the present invention, the shell of the soft gelatin capsule is manufactured from gelatin and a sugar alcohol as a plasticizer.

Sugar alcohol used in the present invention is an alcohol obtained by hydrogen reduction of the aldehyde group of a saccharide. For example, sorbitol, mannitol, maltitol, lactitol, palatinol, xylitol, erythritol, sugar alcohol solution derived from corn starch, i.e. a mixture of sorbitol, sorbitan, mannitol



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and hydrogenated starch hydrolysate, hydrogenated maltose starch syrup, i.e. a mixture of maltitol, sorbitol and oligosaccharide alcohol. Preferred sugar alcohols may include sorbitol, maltitol, sugar alcohol solution derived from corn starch and hydrogenated maltose starch syrup. Especially, sugar alcohol solution derived from corn starch and available on market under the name "Anidrisorb™" or "Polysorb™" is preferably used.

According to the invention, the amount of the sugar alcohol used for preparing the shell of the soft gelatin capsule is not specifically limited as long as the physical properties of the resulting capsule is not deteriorated. In general, the amount of sugar alcohol plasticizer is 20 to 60 parts by weight, preferably, 30 to 50 parts by weight per 100 parts by weight of gelatin.

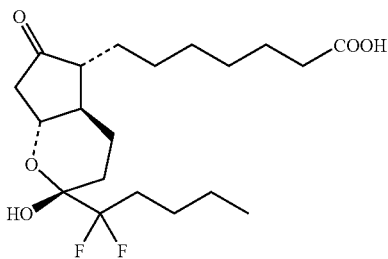
The soft gelatin capsule formulation of the 15-keto-PG compound may be manufactured according to a conventional manner using the above described liquid mixture and a mixture of gelatin and the plasticizer.

The present invention will be explained in more detail by means of the following examples, which are illustrated by way of example only and never intended to limit the scope of the present invention.

## Reference Example 1

Compound 1 was dissolved in a vehicle shown in table 1 below to give 240 µg/g solution (sample). The precise concentration of compound 1 in the sample was determined by means of HPLC (day 0). Then, the sample was put in a hard grass container and kept at 55° C. for 10 days, and then the precise concentration of the compound 1 in the sample was determined by means of HPLC (day 10).

Compound 1



The determination of the concentration of the compound in the sample was carried out as follows. About 0.2 g of the sample was mixed with exactly 2 ml of internal standard solution and then with a dissolving agent shown in Table 1 to give 5 mL of sample solution. About 12 mg of the reference standard compound 1 was weighted precisely and added with acetonitrile to give exactly 100 ml solution. Exactly 0.8 ml of the solution was obtained and added with exactly 4 ml of the internal standard solution, and then added with the dissolving agent to give 10 ml of standard solution.

The fluorescent labeling agent was added to the respective solution, stirred and stood at room temperature. Then, respective solution in an amount that theoretically gives 3-6 ng of compound 1 was loaded on the column and analyzed under the condition as follows:

HPLC Analysis Condition:

Column; 5 mm×25 cm stainless steel column packed with octadecylsilane treated silica gel for HPLC (5 µm)

Mobile phase: mixture of acetonitrile HPLC grade: methanol HPLC grade: ammonium acetate (0.05 mol/L)

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Temperature: 35° C.

Detector: spectrophotofluorometer

Results are shown in Table 1:

TABLE 1

Assay results of compound 1 after 55° C. storage				
	vehicle	dissolving agent	concentration of compound 1 <sup>1)</sup>	
			day 0	day 10
1	hydrogenated maltose starch syrup	acetonitrile/Water (1:1)	—	24.4%
2	Sugar alcohol solution derived from corn starch <sup>2)</sup>	methanol	—	26.2%
3	glycerin	methanol	92.0%	78.0%
4	propylene glycol	acetonitrile	97.8%	88.6%
5	polyethylene glycol 400	acetonitrile	98.2%	90.1%

<sup>1)</sup>Percentage based on a theoretical amount (240 µg/g)

<sup>2)</sup>Polysorb 85/70/00™, ROQUETTE AMERICA, Inc.

## Example 1

One hundred (100) parts by weight of gelatin (type A, high bloom, SKW Biosystems #195F) and 35 parts by weight of a plasticizer shown in Table 2 were mixed in water and dried to give gelatin piece. Compound 1 was dissolved in medium chain fatty acid triglyceride (USP/NF grade) to give a liquid mixture comprising 60 µg/g of the compound. 0.5 g of the liquid mixture and 0.5 g of each gelatin piece were put together in a sealed container and kept at 40° C. for 21 days. Then, the concentration of compound 1 contained in the liquid mixture was determined in the same manner as Reference Example 1. Results are shown in Table 2:

TABLE 2

Stability data of compound 1/medium chain fatty acid triglyceride (MCT) solution (60 µg/g)		
plasticizer	water content (after dried)	concentration of compound 1
		gelatin piece after storage <sup>1)</sup>
glycerin	23%	86.8%
sugar alcohol solution derived from corn starch <sup>2)</sup>	25%	92.0%

<sup>1)</sup>Percentage based on a theoretical amount (60 µg/g)

<sup>2)</sup>Polysorb 85/70/00™, ROQUETTE AMERICA, Inc.

According to the reference example 1, in case the 15-keto-prostaglandin compound of the invention and the sugar alcohol were contacted directly, stability of the compound was significantly lowered. In contrast, in case the 15-keto-PG compound was directly contacted with a polyol such as glycerin, the stability of the compound was maintained. It has surprisingly revealed by Example 1 that the stability of the 15-keto-prostaglandin contacted with gelatin piece prepared using sugar alcohol as a plasticizer was better than that contacted with gelatin piece with glycerin as a plasticizer.

## Example 2

Sugar alcohol solution derived from corn starch in an amount shown in Table 3 was added in an appropriate amount

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of water, stirred and heated. Then, gelatin 100 parts by weight was added thereto to give gelatin solution. Compound 1 was dissolved in medium chain fatty acid triglyceride (USP/NF grade) to give a fill solution containing 240  $\mu\text{g/g}$  of compound 1. The gelatin solution and the liquid mixture were loaded or capsule forming and filling machine to give capsule containing the fill solution therein, and the capsule was dried to give soft gelatin capsule.

The capsule was put in a sealed container and kept at 40° C. for 3 months. The concentration of compound 1 in the fill solution contained in the capsule was determined after 1, 2 and 3 months storage in the same manner as Reference Example 1.

TABLE 3

Stability of soft gelatin capsule of compound 1						
soft gelatin capsule (parts by weight)		conc. (% of Initial) 40° C.				
		1 mo	2 mo	3 mo		
gelatin	100	sugar	35	99.9%	100.3%	99.2%
		alcohol	45	—	100.5%	100.0%
		solution <sup>1)</sup>	55	—	99.3%	100.0%

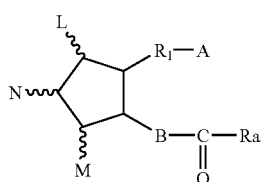
<sup>1)</sup>Polysorb 85/70/00™, ROQUETTE AMERICA, Inc., derived from corn starch

What is claimed is:

1. A soft gelatin capsule formulation of a 15-keto-prostaglandin compound, which comprises:

a soft gelatin capsule shell comprising gelatin and a sugar alcohol as a plasticizer, and  
a mixture comprising a 15-keto-prostaglandin compound and a pharmaceutically acceptable vehicle, which is filled in the shell.

2. The formulation of claim 1, wherein the 15-keto-prostaglandin compound is a compound of the formula (I):



wherein L, M and N are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is —CH<sub>3</sub>, or —CH<sub>2</sub>OH, —COCH<sub>2</sub>OH, —COOH or a functional derivative thereof;

B is —CH<sub>2</sub>—CH<sub>2</sub>—, —CH=CH— or —C≡C—;

R<sub>1</sub> is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, lower alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur; and

Ra is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkyl, lower

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alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocycloxy group; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic group; heterocycloxy group.

3. The formulation of claim 1, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-prostaglandin compound.

4. The formulation of claim 1, wherein the 15-keto-prostaglandin compound is a 15-keto-16-mono or 16,16-di-halogen-prostaglandin compound.

5. The formulation of claim 1, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16-mono- or 16,16-di-halogen-prostaglandin compound.

6. The formulation of claim 1, wherein the 15-keto-prostaglandin compound is a 15-keto-16-mono- or 16,16-difluoro-prostaglandin compound.

7. The formulation of claim 1, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16-mono- or 16,16-difluoro-prostaglandin compound.

8. The formulation of claim 1, wherein the 15-keto-prostaglandin compound is a 15-keto-prostaglandin E compound.

9. The formulation of claim 1, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E<sub>1</sub>.

10. The formulation of claim 1, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16,16-difluoro-18S-methyl-prostaglandin E<sub>1</sub>.

11. The formulation of claim 1, wherein the sugar alcohol is selected from the group consisting of sorbitol, maltitol, sugar alcohol solution derived from corn starch, hydrogenated maltose syrup and a mixture thereof.

12. The formulation of claim 1, wherein the sugar alcohol comprises sorbitol and sorbitan as its major component.

13. A method for stabilizing a 15-keto-prostaglandin compound, which comprises: dissolving, dispersing or mixing the 15-keto-prostaglandin in a pharmaceutically acceptable vehicle to give a liquid mixture, and incorporating the liquid mixture in a soft gelatin capsule which comprises gelatin and a sugar alcohol as a plasticizer such that a soft gelatin capsule formulation of claim 1 is prepared.

14. A method for stabilizing a 15-keto-prostaglandin compound, which comprises encapsulating the compound together with a glyceride in a soft gelatin capsule shell comprising gelatin and a sugar alcohol as a plasticizer such that a soft gelatin capsule formulation of claim 1 is prepared.

15. The formulation of claim 1, wherein the pharmaceutically acceptable vehicle is a medium chain fatty acid triglyceride.

16. The method of claim 14, wherein the glyceride is a medium chain fatty acid triglyceride.

17. The formulation of claim 1, wherein the pharmaceutically acceptable vehicle is a fatty acid ester or a polyol.

18. The formulation of claim 1, wherein the pharmaceutically acceptable vehicle is glycerin or propylene glycol.

19. The formulation of claim 1, wherein the pharmaceutically acceptable vehicle is a fatty acid ester or glycerin.

20. The formulation of claim 1, wherein the pharmaceutically acceptable vehicle is a glyceride.

21. The formulation of claim 1, wherein the pharmaceutically acceptable vehicle is a fatty acid ester.

22. The formulation of claim 1, wherein the pharmaceutically acceptable vehicle is glycerin.

\* \* \* \* \*

# **EXHIBIT E**



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

(10) **Patent No.:** **US 8,338,639 B2**  
 (45) **Date of Patent:** **\*Dec. 25, 2012**

(54) **SOFT-GELATIN CAPSULE FORMULATION**

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(73) Assignees: **Sucampo AG**, Zug (CH); **R-Tech Ueno, Ltd.**, Tokyo (JP)

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

(21) Appl. No.: **13/210,556**

(22) Filed: **Aug. 16, 2011**

(65) **Prior Publication Data**

US 2011/0300211 A1 Dec. 8, 2011

**Related U.S. Application Data**

(63) Continuation of application No. 11/656,476, filed on Jan. 23, 2007, now Pat. No. 8,026,393.

(60) Provisional application No. 60/761,360, filed on Jan. 24, 2006.

(51) **Int. Cl.**  
**C07C 61/06** (2006.01)  
**C07C 61/20** (2006.01)

(52) **U.S. Cl.** ..... **562/504**; 514/513

(58) **Field of Classification Search** ..... None  
 See application file for complete search history.

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(57) **ABSTRACT**

The present invention provides a soft gelatin capsule formulation of a 15-keto-prostaglandin compound, which includes: a soft gelatin capsule shell including gelatin and sugar alcohol as a plasticizer, and a mixture including a 15-keto-prostaglandin compound and a pharmaceutically acceptable vehicle which is filled in the shell. By encapsulating the 15-keto-prostaglandin compound in the specified soft gelatin capsule shell, stability of the compound is significantly improved.

**23 Claims, No Drawings**

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**SOFT-GELATIN CAPSULE FORMULATION****CROSS REFERENCE TO RELATED APPLICATIONS**

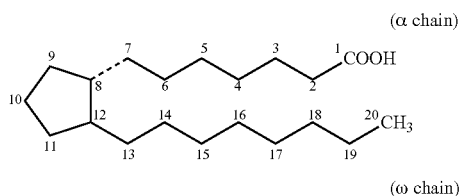
This is a continuation of application Ser. No. 11/656,476 filed Jan. 23, 2007, and claims the benefit of U.S. Provisional Application No. 60/761,360 filed Jan. 24, 2006. The disclosure of application Ser. No. 11/656,476 is hereby incorporated by reference.

**FIELD OF THE INVENTION**

The present invention relates to a soft-gelatin capsule formulation of a therapeutically effective 15-keto-prostaglandin compound.

**BACKGROUND ART**

Prostaglandins (hereinafter, referred to as PGs) are members of class of organic carboxylic acids, which are contained in tissues or organs of human and other mammals, and exhibit a wide range of physiological activities. PGs found in nature (primary PGs) have, as a general structural property thereof, a prostanoid acid skeleton as shown in the formula (A):



On the other hand, some synthetic analogues have modified skeletons. The primary PGs are classified into PGAs, PGBs, PGCs, PGDs, PGEs, PGFs, PGHs, PGLs and PGJs on the basis of the structural property of the five membered ring moiety, and further classified into the following three types by the number and position of the unsaturated bond in the carbon chain moiety.

Type 1 (subscript 1): 13,14-unsaturated-15-OH

Type 2 (subscript 2): 5,6- and 13,14-diunsaturated-15-OH

Type 3 (subscript 3): 5,6-, 13,14-, and 17,18-triunsaturated-15-OH.

Further, PGFs are classified on the basis of the configuration of the hydroxyl group at the 9-position into  $\alpha$  type (wherein the hydroxyl group is of the  $\alpha$ -configuration) and  $\beta$  type (wherein the hydroxyl group is of the  $\beta$ -configuration).

In addition, some 15-keto-PGs (PGs having an oxo group at position 15 in place of the hydroxy group) and 13,14-dihydro-15-keto-PGs have been known as substances naturally produced by enzymatic actions during metabolism of the primary PGs and have some therapeutic effect. 15-keto-PGs have been disclosed in U.S. Pat. Nos. 5,073,569, 5,534,547, 5,225,439, 5,166,174, 5,428,062, 5,380,709, 5,886,034, 6,265,440, 5,106,869, 5,221,763, 5,591,887, 5,770,759 and 5,739,161. The contents of these publications are herein incorporated by reference.

For example, 15-keto-16-halogen prostaglandin compounds are useful as cathartics (U.S. Pat. No. 5,317,032, the contents of the reference is herein incorporated by reference). For treating gastrointestinal diseases, the agent is preferably formulated as an orally administrable dosage form. In gen-

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eral, PG compounds are less soluble in water and become significantly unstable under the presence of water. A capsulated formulation comprises a 15-keto-16-halogen PG compound and a solvent which can maintain the stability of the compound such as glyceride had been proposed (WO01/027099 (U.S. Pat. No. 6,583,174), the contents of the cited reference is herein incorporated by reference.

Elastic shell of a soft gelatin capsule, in general, incorporates a plasticizer in addition to gelatin. Examples of plasticizer include glycerin, propylene glycol, sorbitol, maltitol, sugar alcohol solution derived from corn starch (Anidrisorb™, Polysorb™), i.e. a mixture of sorbitol, sorbitane, mannitol and hydrogenated starch hydrolysate, hydrogenated maltose starch syrup, i.e. a mixture of maltitol, sorbitol and oligosaccharide alcohol.

**SUMMARY OF THE INVENTION**

An object of the present invention is to provide an orally administrable dosage form of a 15-keto-prostaglandin compound which has an excellent shelf stability.

Accordingly, the instant application provides a soft gelatin capsule formulation of a 15-keto-prostaglandin compound, which comprises:

a soft gelatin capsule shell comprising gelatin and a sugar alcohol as a plasticizer, and

a mixture comprising a 15-keto-prostaglandin compound and a pharmaceutically acceptable vehicle, which is filled in the shell.

The invention is also provides a method for improving stability of a 15-keto-prostaglandin compound which comprises, dissolving the 15-keto-prostaglandin in a pharmaceutically acceptable solvent and incorporating the solution in a soft-gelatin capsule whose shell comprises gelatin and a sugar alcohol as a plasticizer.

**DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS**

The nomenclature of the PG compounds used herein is based on the numbering system of prostanoid acid represented in the above formula (A).

The formula (A) shows a basic skeleton of the C-20 PG compound, but the present invention is not limited to those having the same number of carbon atoms. In the formula (A), the numbering of the carbon atoms which constitute the basic skeleton of the PG compounds starts at the carboxylic acid (numbered 1), and carbon atoms in the  $\alpha$ -chain are numbered 2 to 7 towards the five-membered ring, those in the ring are 8 to 12, and those in the  $\omega$ -chain are 13 to 20. When the number of carbon atoms is decreased in the  $\alpha$ -chain, the number is deleted in the order starting from position 2; and when the number of carbon atoms is increased in the  $\alpha$ -chain, compounds are named as substitution compounds having respective substituents at position 2 in place of carboxy group (C-1). Similarly, when the number of carbon atoms is decreased in the  $\omega$ -chain, the number is deleted in the order starting from position 20; and when the number of carbon atoms is increased in the  $\omega$ -chain, compounds are named as substitution compounds having respective substituents at position 20. Stereochemistry of the compounds is the same as that of the above formula (A) unless otherwise specified.

In general, each of PGD, PGE and PGF represents a PG compound having hydroxy groups at positions 9 and/or 11, but in the present specification and claims they also include those having substituents other than the hydroxyl groups at positions 9 and/or 11. Such compounds are referred to as

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9-dehydroxy-9-substituted-PG compounds or 11-dehydroxy-11-substituted-PG compounds. A PG compound having hydrogen in place of the hydroxy group is simply named as 9- or 11-dehydroxy compound.

As stated above, the nomenclature of PG compounds is based on the prostanoic acid skeleton. However, in case the compound has a similar partial construction as a prostaglandin, the abbreviation of "PG" may be used. Thus, a PG compound of which a-chain is extended by two carbon atoms, that is, having 9 carbon atoms in the  $\alpha$ -chain is named as 2-decarboxy-2-(2-carboxyethyl)-PG compound. Similarly, a PG compound having 11 carbon atoms in the  $\alpha$ -chain is named as 2-decarboxy-2-(4-carboxybutyl)-PG compound. Further, a PG compound of which a-chain is extended by two carbon atoms, that is, having 10 carbon atoms in the  $\omega$ -chain is named as 20-ethyl-PG compound. These compounds, however, may also be named according to the IUPAC nomenclatures.

The 15-keto-PG compound used in the present invention may be any derivative of a PG insofar as having an oxo group at position 15 in place of the hydroxy group, and may further include a compound having one double bond between positions 13 and 14 (15-keto-PG type 1 compound), two double bonds between positions 13 and 14, and positions and 6 (15-keto-PG type 2 compound), and three double bonds between positions 5 and 6, positions 13 and 14, and positions 17 and 18 (15-keto-PG type 3 compound), and a derivative thereof wherein the bond between the positions and 14 is single bond, in place of the double bond (13,14-dihydro-15-keto-PG compound).

Examples of the analogue including substitution compounds or derivatives include a PG compound of which the carboxy group at the end of the alpha chain is esterified; physiologically acceptable salt thereof; an unsaturated derivative having a double bond between positions 2 and 3 or a triple bond between positions 5 and 6; PG compounds having substituent(s) on carbon atom(s) at position(s) 3, 5, 6, 16, 17, 18, 19 and/or 20; and PG compounds having lower alkyl or a hydroxy (lower) alkyl group at position 9 and/or 11 in place of the hydroxy group.

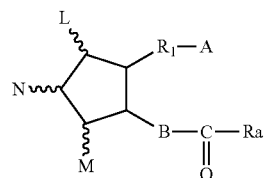
According to the present invention, preferred substituents on the carbon atom at position(s) 3, 17, 18 and/or 19 include alkyl having 1 to 6 carbon atoms, especially methyl and ethyl. Preferred substituents on the carbon atom at position 16 include lower alkyl such as methyl and ethyl, hydroxy, halogen atom such as chlorine and fluorine, and aryloxy such as trifluoromethylphenoxy. Preferred substituents on the carbon atom at position 17 include halogen atom such as chlorine and fluorine. Preferred substituents on the carbon atom at position 20 include saturated or unsaturated lower alkyl such as C<sub>1-4</sub> alkyl, lower alkoxy such as C<sub>1-4</sub> alkoxy, and lower alkoxy alkyl such as C<sub>1-4</sub> alkoxy-C<sub>1-4</sub> alkyl. Preferred substituents on the carbon atom at position 5 include halogen atoms such as chlorine and fluorine. Preferred substituents on the carbon atom at position 6 include an oxo group forming a carbonyl group. Stereochemistry of PGs having hydroxy, lower alkyl or hydroxy(lower)alkyl substituent on the carbon atom at positions 9 and 11 may be  $\alpha$ ,  $\beta$  or a mixture thereof.

Further, the above described derivatives may have a co chain shorter than that of the primary PGs and a substituent such as alkoxy, cyclohexyl, cyclohexyloxy, phenoxy and phenyl at the end of the truncated  $\omega$ -chain.

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Especially preferred compounds include a 13,14-dihydro-15-keto-PG compound that has a single bond between positions 13 and 14; a 15-keto-16-mono or 16,16-di-halogen PG compound that has at least one halogen atom, especially fluorine, at carbon atom of position 16; a 15-keto-PGE compound that has hydroxy group at position 9 and oxo group at position 11 of the five membered ring.

A preferred prostaglandin compound used in the present invention is represented by the formula (I):



(I)

wherein L, M and N are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

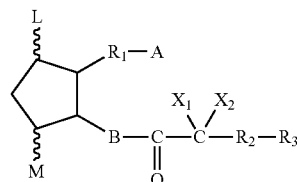
A is —CH<sub>3</sub>, or —CH<sub>2</sub>OH, —COCH<sub>2</sub>OH, —COOH or a functional derivative thereof;

B is —CH<sub>2</sub>—CH<sub>2</sub>—, —CH=CH— or —C≡C—;

R<sub>1</sub> is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, lower alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur; and

R<sub>a</sub> is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocycloxy group; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic group; heterocycloxy group.

A more preferred prostaglandin compound used in the present invention is represented by the formula (II):



(II)

wherein L and M are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have one or more double bonds;

A is —CH<sub>3</sub>, or —CH<sub>2</sub>OH, —COCH<sub>2</sub>OH, —COOH or a functional derivative thereof;

B is —CH<sub>2</sub>—CH<sub>2</sub>—, —CH=CH— or —C≡C—;

X<sub>1</sub> and X<sub>2</sub> are hydrogen, lower alkyl, or halogen;

R<sub>1</sub> is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, lower alkyl, hydroxy, oxo, aryl or het-

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erocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur;

R<sub>2</sub> is a single bond or lower alkylene; and

R<sub>3</sub> is lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocycloxy group.

In the above formula, the term "unsaturated" in the definitions for R<sub>1</sub> and Ra is intended to include at least one or more double bonds and/or triple bonds that are isolatedly, separately or serially present between carbon atoms of the main and/or side chains. According to the usual nomenclature, an unsaturated bond between two serial positions is represented by denoting the lower number of the two positions, and an unsaturated bond between two distal positions is represented by denoting both of the positions.

The term "lower or medium aliphatic hydrocarbon" refers to a straight or branched chain hydrocarbon group having 1 to 14 carbon atoms (for a side chain, 1 to 3 carbon atoms are preferable) and preferably 1 to 10, especially 6 to 10 carbon atoms for R<sub>1</sub> and 1 to 10, especially, 1 to 8 carbon atoms for Ra.

The term "halogen" covers fluorine, chlorine, bromine and iodine.

The term "lower" is intended to include a group having 1 to 6 carbon atoms unless otherwise specified.

The term "lower alkyl" refers to a straight or branched chain saturated hydrocarbon group containing 1 to 6 carbon atoms and includes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl and hexyl.

The term "lower alkoxy" refers to a group of lower alkyl-O—, wherein lower alkyl is as defined above.

The term "hydroxy(lower)alkyl" refers to a lower alkyl as defined above which is substituted with at least one hydroxy group such as hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 1-methyl-1-hydroxyethyl.

The term "lower alkanoyloxy" refers to a group represented by the formula RCO—O—, wherein RCO— is an acyl group formed by oxidation of a lower alkyl group as defined above, such as acetyl.

The term "cyclo(lower)alkyl" refers to a cyclic group formed by cyclization of a lower alkyl group as defined above but contains three or more carbon atoms, and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "cyclo(lower)alkyloxy" refers to the group of cyclo(lower)alkyl-O—, wherein cyclo(lower)alkyl is as defined above.

The term "aryl" may include unsubstituted or substituted aromatic hydrocarbon rings (preferably monocyclic groups), for example, phenyl, tolyl, xylyl. Examples of the substituents are halogen atom and halo(lower)alkyl, wherein halogen atom and lower alkyl are as defined above.

The term "aryloxy" refers to a group represented by the formula ArO—, wherein Ar is aryl as defined above.

The term "heterocyclic group" may include mono- to tricyclic, preferably monocyclic heterocyclic group which is 5 to 14, preferably 5 to 10 membered ring having optionally substituted carbon atom and 1 to 4, preferably 1 to 3 of 1 or 2 type of hetero atoms selected from nitrogen, oxygen and sulfur. Examples of the heterocyclic group include furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl,

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imidazolyl, pyrazolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, 2-pyrrolinyl, pyrrolidinyl, 2-imidazolyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, piperidino, piperazinyl, morpholino, indolyl, benzothienyl, quinolyl, isoquinolyl, purinyl, quinazolyl, carbazolyl, acridinyl, phenanthridinyl, benzimidazolyl, benzimidazolyl, benzothiazolyl, phenothiazinyl. Examples of the substituent in this case include halogen, and halogen substituted lower alkyl group, wherein halogen atom and lower alkyl group are as described above.

The term "heterocycloxy group" means a group represented by the formula HcO-, wherein Hc is a heterocyclic group as described above.

The term "functional derivative" of A includes salts, preferably pharmaceutically acceptable salts, ethers, esters and amides.

Suitable "pharmaceutically acceptable salts" include salts formed with non-toxic bases conventionally used in pharmaceutical field, for example a salt with an inorganic base such as an alkali metal salt (such as sodium salt and potassium salt), an alkaline earth metal salt (such as calcium salt and magnesium salt), an ammonium salt; or a salt with an organic base, for example, an amine salt including such as methylamine salt, dimethylamine salt, cyclohexylamine salt, benzylamine salt, piperidine salt, ethylenediamine salt, ethanolamine salt, diethanolamine salt, triethanolamine salt, tris(hydroxymethylamino)ethane salt, monomethylmonoethanolamine salt, procaine salt and caffeine salt), a basic amino acid salt (such as arginine salt and lysine salt), tetraalkyl ammonium salt and the like. These salts may be prepared by a conventional process, for example from the corresponding acid and base or by salt interchange.

Examples of the ethers include alkyl ethers, for example, lower alkyl ethers such as methyl ether, ethyl ether, propyl ether, isopropyl ether, butyl ether, isobutyl ether, t-butyl ether, pentyl ether and 1-cyclopropyl ethyl ether; and medium or higher alkyl ethers such as octyl ether, diethylhexyl ether, lauryl ether and cetyl ether; unsaturated ethers such as oleyl ether and linolenyl ether; lower alkenyl ethers such as vinyl ether, allyl ether; lower alkynyl ethers such as ethynyl ether and propynyl ether; hydroxy(lower)alkyl ethers such as hydroxyethyl ether and hydroxyisopropyl ether; lower alkoxy (lower)alkyl ethers such as methoxymethyl ether and 1-methoxyethyl ether; optionally substituted aryl ethers such as phenyl ether, tosyl ether, t-butylphenyl ether, salicyl ether, 3,4-di-methoxyphenyl ether and benzamidophenyl ether; and aryl(lower)alkyl ethers such as benzyl ether, trityl ether and benzhydryl ether.

Examples of the esters include aliphatic esters, for example, lower alkyl esters such as methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester and 1-cyclopropylethyl ester; lower alkenyl esters such as vinyl ester and allyl ester; lower alkynyl esters such as ethynyl ester and propynyl ester; hydroxy(lower)alkyl ester such as hydroxyethyl ester; lower alkoxy (lower)alkyl esters such as methoxymethyl ester and 1-methoxyethyl ester; and optionally substituted aryl esters such as, for example, phenyl ester, tolyl ester, t-butylphenyl ester, salicyl ester, 3,4-di-methoxyphenyl ester and benzamidophenyl ester; and aryl(lower)alkyl ester such as benzyl ester, trityl ester and benzhydryl ester.

The amide of A means a group represented by the formula -CONR'R", wherein each of R' and R" is hydrogen, lower alkyl, aryl, alkyl- or aryl-sulfonyl, lower alkenyl and lower alkynyl, and include for example lower alkyl amides such as methylamide, ethylamide, dimethylamide and diethylamide; arylamides such as anilide and toluidide; and alkyl- or aryl-



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sulfonylamides such as methylsulfonylamide, ethylsulfonylamide and tolylsulfonylamide.

Preferred examples of L and M include hydroxy and oxo, and especially, M is hydroxy and L is oxo which has a 5-membered ring structure of, so called, PGE type.

Preferred example of A is  $-\text{COOH}$ , its pharmaceutically acceptable salt, ester or amide thereof.

Preferred example of B is  $-\text{CH}_2-\text{CH}_2-$ , which provide the structure of so-called, 13,14-dihydro type.

Preferred example of  $X_1$  and  $X_2$  is that at least one of them is halogen, more preferably, both of them are halogen, especially, fluorine that provides a structure of, so called 16,16-difluoro type.

Preferred  $R_1$  is a hydrocarbon residue containing 1-10 carbon atoms, preferably 6 to 10 carbon atoms. Further, at least one carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur.

Examples of  $R_1$  include, for example, the following groups:

$-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ ,  
 $-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ ,  
 $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}=\text{CH}-$ ,  
 $-\text{CH}_2-\text{C}\equiv\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ ,  
 $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}(\text{CH}_3)-\text{CH}_2-$ ,  
 $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_2-$ ,  
 $-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_2-\text{O}-\text{CH}_2-$ ,  
 $-\text{CH}_2-\text{C}\equiv\text{C}-\text{CH}_2-\text{O}-\text{CH}_2-$ ,  
 $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ ,  
 $-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ ,  
 $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}=\text{CH}-$ ,  
 $-\text{CH}_2-\text{C}\equiv\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ ,  
 $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}(\text{CH}_3)-\text{CH}_2-$ ,  
 $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ ,  
 $-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ ,  
 $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}=\text{CH}-$ ,  
 $-\text{CH}_2-\text{CH}=\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ , and  
 $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}(\text{CH}_3)-\text{CH}_2-$ .

Preferred  $R_a$  is a hydrocarbon containing 1 to 10 carbon atoms, more preferably, 1 to 8 carbon atoms.  $R_a$  may have one or two side chains having one carbon atom.

The configuration of the ring and the  $\alpha$ - and/or  $\omega$  chains in the above formula (I) and (II) may be the same as or different from that of the primary PGs. However, the present invention also includes a mixture of a compound having a primary type configuration and a compound of a non-primary type configuration.

The typical example of the present compounds are 13, 14-dihydro-15-keto-16-mono- or 16, 16-di-fluoro PGE compound and its derivative or analogue.

In the present invention, the 15-keto-PG compound may be in the keto-acetal equilibrium by formation of a hemiacetal between hydroxy at position 11 and keto at position 15.

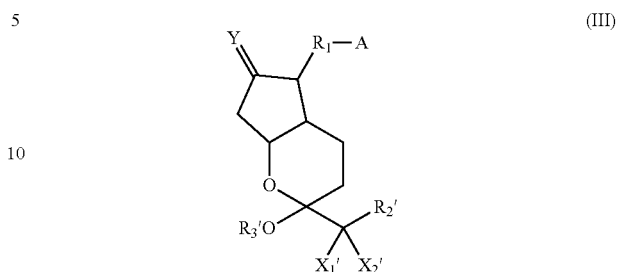
For example, it has been revealed that when both of  $X_1$  and  $X_2$  are halogen atoms, especially, fluorine atoms, the compound contains a tautomeric isomer, bi-cyclic compound.

If such tautomeric isomers as above are present, the proportion of both tautomeric isomers varies with the structure of the rest of the molecule or the kind of the substituent present. Sometimes one isomer may predominantly be present in comparison with the other. However, it is to be appreciated that the present invention includes both isomers.

Further, the 15-keto-PG compounds used in the invention include the bi-cyclic compound and analogs or derivatives thereof.

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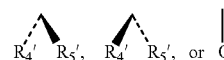
The bi-cyclic compound is represented by the formula (III):



wherein, A is  $-\text{CH}_3$ , or  $-\text{CH}_2\text{OH}$ ,  $-\text{COCH}_2\text{OH}$ ,  $-\text{COOH}$  or a functional derivative thereof;

$X_1'$  and  $X_2'$  are hydrogen, lower alkyl, or halogen;

Y is



wherein  $R_4'$  and  $R_5'$  are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl,

wherein  $R_4'$  and  $R_5'$  are not hydroxy and lower alkoxy at the same time;

$R_1$  is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, lower alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur;

$R_2'$  is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocycloxy group; lower alkyl; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic group; heterocycloxy group; and

$R_3'$  is hydrogen, lower alkyl, cyclo(lower)alkyl, aryl or heterocyclic group.

Furthermore, while the compounds used in the invention may be represented by a formula or name based on keto-type regardless of the presence or absence of the isomers, it is to be noted that such structure or name does not intend to exclude the acetal type compound.

In the present invention, any of isomers such as the individual tautomeric isomers, the mixture thereof, or optical isomers, the mixture thereof, a racemic mixture, and other steric isomers may be used in the same purpose.

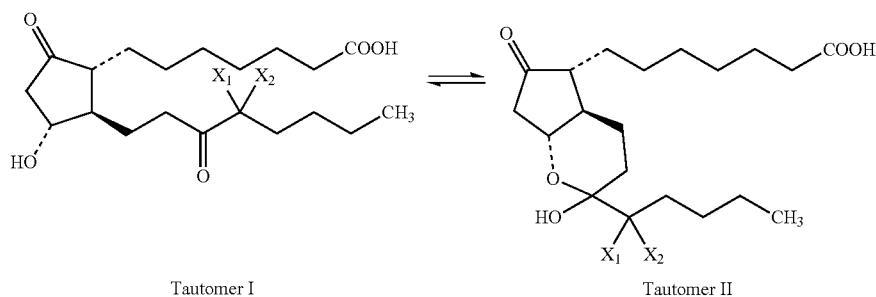
Some of the compounds used in the present invention may be prepared by the method disclosed in U.S. Pat. Nos. 5,073,569, 5,166,174, 5,221,763, 5,212,324, 5,739,161 and 6,242,485, the contents of these references are herein incorporated by reference.

It has been known that 13,14-dihydro-15-keto-prostaglandin compound having the formula as shown below (Tautomer I) may be in equilibrium with its tautomeric isomer (tautomer II) (See U.S. Pat. Nos. 5,166,174, 5,225,439, 5,284,858, 5,380,709, 5,428,062 and 5,886,034, the contents of these references are herein incorporated by reference.)

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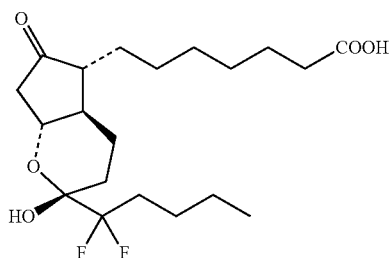
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It is considered that the halogen atom(s) at  $X_1$  and/or  $X_2$  promote bi-cyclic ring formation, such as the compound 1 or 2 below. In addition, in the absence of water, the tautomeric compounds as above exist predominantly in the form of the bi-cyclic compound. In aqueous media, it is supposed that hydrogen bonding occurs between the water molecule and, for example, the keto group on the hydrocarbon chain, thereby hindering bi-cyclic ring formation. The bi-cyclic/mono-cyclic structures, for example, may be present in a ratio of 6:1 in  $D_2O$ ; 10:1 in  $CD_3OD-D_2O$  and 96:4 in  $CDCl_3$ . In the instant specification and claims, tautomeric mixture containing the bi-cyclic compound in a ratio even greater to substantially 100% bi-cyclic compound is within this invention.

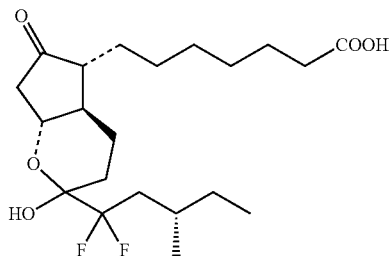
Embodiment of the bi-cyclic compound of the present invention include the Compounds 1 and 2 shown below.

Compound 1:



7-[(2R, 4aR, 5R, 7aR)-2-(1, 1-difluoropentyl)-2-hydroxy-6-oxooctahydrocyclopenta[b]pyran-5-yl]heptanoic acid

Compound 2:



7-[(4aR, 5R, 7aR)-2-[(3S)-1,1-difluoro-3-methylpentyl]-2-hydroxy-6-oxooctahydrocyclopenta[b]pyran-5-yl]heptanoic acid

15 According to the present invention, the pharmaceutically acceptable vehicle is not specifically limited as long as the vehicle can disperse the 15-keto-PG therein and does not significantly deteriorate the stability of the compound. In view of manufacturing soft gelatin capsule formulation, a solvent which is liquid at the room temperature. A solution, dispersion or mixture of the 15-keto-PG in the solvent may be filled in the capsule.

20 Examples of the pharmaceutically acceptable vehicles preferably used in the instant invention may be fatty acid esters, i.e. an ester of fatty acid and an alcohol, and polyols.

25 Preferred fatty acid which consists the fatty acid ester is a medium or higher chain fatty acid having at least C6, preferably C6-24 carbon atoms, for example caproic acid (C6), caprylic acid(C8), capric acid(C10), lauric acid(C12) and myristic acid (C14), palmitic acid(C16), palmitoleic acid (C16), stearic acid(C18), oleic acid(C18), linoleic acid(C18), linolenic acid(C18), ricinolic acid(C18) and arachic acid (O20). Preferred alcohols which consists the fatty acid ester may comprise C1-6 monovalent alcohol and polyols such as glycerin, polyethylene glycol and propylene glycol.

30 Preferred fatty acid esters may include a glyceride of a saturated or unsaturated fatty acid which may have a branched chain and a propylene glycol fatty acid ester. Two or more glycerides may be used as a mixture.

35 Examples of the mixture of glycerides are mixture of caprylic acid triglyceride and capric acid triglyceride, vegetable oils such as castor oil, corn oil, olive oil, sesame oil, rape oil, salad oil, cottonseed oil, camellia oil, peanut oil, palm oil and sunflower oil.

40 A fatty acid ester derived from a fatty acid and a monovalent alcohol is also preferably used as a pharmaceutically acceptable vehicle. The fatty acid ester may preferably be an ester of C8-20 fatty acid and a C2-3 monovalent alcohol, such as isopropyl myristate, isopropyl palmitate, ethyl linoleate and ethyl oleate.

45 Examples of polyols may preferably include alcohols having two or three hydroxy groups such as glycerin, polyethylene glycol and propylene glycol.

50 According to the present invention, the mixture which is filled in the soft-gelatin capsule shell may be obtained by dissolving or dispersing the above-described 15-keto-prostaglandin compound in the above described pharmaceutically acceptable vehicle which is liquid at the room temperature. When it is difficult to dissolve the 15-keto-PG compound directly in the vehicle, each of them may be dissolved in a solvent in which both of them are soluble respectively, and then the solutions may be combined.

55 The amount of the solvent in the mixture relative to the amount of the 15-keto-PG compound is not limited as long as

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the 15-keto-PG is stable in the final formulation. In general, the amount of the vehicle per one part of the 15-keto-PG compound may be 1-5,000,000, preferably, 5-1,000,000 and most preferably, 10-500,000 parts by weight.

The mixture used in the invention may further comprise an oil solvent such as mineral oil, liquid paraffin, and tocopherol. The mixture of the present invention may further comprise another pharmaceutically active ingredient.

In a preferred embodiment, the composition of the present invention is substantially free of water. The term "substantially free of water" means that the composition does not contain water that is intentionally added. It is understood that many materials contain water that is taken up from the atmosphere or is present as a coordination complex in its normal state. Water taken up by hygroscopic materials or present as a hydrate is permissibly present in the compositions of this embodiment. According to the embodiment, any water that is present in the composition should not be present in amounts such that the water will have a deleterious effect to the composition of the present invention.

According to the present invention, the shell of the soft gelatin capsule is manufactured from gelatin and a sugar alcohol as a plasticizer.

Sugar alcohol used in the present invention is an alcohol obtained by hydrogen reduction of the aldehyde group of a saccharide. For example, sorbitol, mannitol, maltitol, lactitol, palatinit, xylitol, erythritol, sugar alcohol solution derived from corn starch, i.e. a mixture of sorbitol, sorbitan, mannitol and hydrogenated starch hydrolysate, hydrogenated maltose starch syrup, i.e. a mixture of maltitol, sorbitol and oligosaccharide alcohol. Preferred sugar alcohols may include sorbitol, maltitol, sugar alcohol solution derived from corn starch and hydrogenated maltose starch syrup. Especially, sugar alcohol solution derived from corn starch and available on market under the name "Anidrisorb™" or "Polysorb™" is preferably used.

According to the invention, the amount of the sugar alcohol used for preparing the shell of the soft gelatin capsule is not specifically limited as long as the physical properties of the resulting capsule is not deteriorated. In general, the amount of sugar alcohol plasticizer is 20 to 60 parts by weight, preferably, 30 to 50 parts by weight per 100 parts by weight of gelatin.

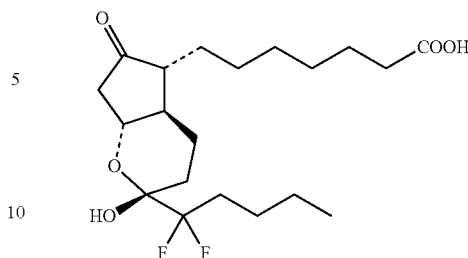
The soft gelatin capsule formulation of the 15-keto-PG compound may be manufactured according to a conventional manner using the above described liquid mixture and a mixture of gelatin and the plasticizer.

The present invention will be explained in more detail by means of the following examples, which are illustrated by way of example only and never intended to limit the scope of the present invention.

#### REFERENCE EXAMPLE 1

Compound 1 was dissolved in a vehicle shown in table 1 below to give 240 µg/g solution (sample). The precise concentration of compound 1 in the sample was determined by means of HPLC (day 0). Then, the sample was put in a hard glass container and kept at 55° C. for 10 days, and then the precise concentration of the compound 1 in the sample was determined by means of HPLC (day 10).

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Compound 1

The determination of the concentration of the compound in the sample was carried out as follows. About 0.2 g of the sample was mixed with exactly 2 ml of internal standard solution and then with a dissolving agent shown in Table 1 to give 5 mL of sample solution. About 12 mg of the reference standard compound 1 was weighted precisely and added with acetonitrile to give exactly 100 ml solution. Exactly 0.8 ml of the solution was obtained and added with exactly 4 ml of the internal standard solution, and then added with the dissolving agent to give 10 ml of standard solution.

The fluorescent labeling agent was added to the respective solution, stirred and stood at room temperature. Then, respective solution in an amount that theoretically gives 3.6 ng of compound 1 was loaded on the column and analyzed under the condition as follows:

HPLC analysis condition:

Column: 5mm×25 cm stainless steel column packed with octadecylsilane treated silica gel for HPLC (511m)

Mobile phase: mixture of acetonitrile HPLC grade: methanol HPLC grade: ammonium acetate (0.05 mol/L)

Temperature: 35° C.

Detector: spectrophotofluorometer

Results are shown in Table 1:

TABLE 1

Assay results of compound 1 after 55° C. storage				
	vehicle	dissolving agent	concentration of compound 1 <sup>1)</sup>	
			day 0	day 10
1	hydrogenated maltose starch syrup	acetonitrile/Water (1:1)	—	24.4%
2	Sugar alcohol solution derived from corn starch <sup>2)</sup>	methanol	—	26.2%
3	glycerin	methanol	92.0%	78.0%
4	propylene glycol	acetonitrile	97.8%	88.6%
5	polyethylene glycol 400	acetonitrile	98.2%	90.1%

<sup>1)</sup>Percentage based on a theoretical amount (240 µg/g)

<sup>2)</sup>Polysorb 85/70/00™, ROQUETTE AMERICA, Inc.

#### EXAMPLE 1

One hundred (100) parts by weight of gelatin (type A, high bloom, SKW Biosystems #195F) and 35 parts by weight of a plasticizer shown in Table 2 were mixed in water and dried to give gelatin piece. Compound 1 was dissolved in medium



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chain fatty acid triglyceride (USP/NF grade) to give a liquid mixture comprising 60 µg/g of the compound. 0.5 g of the liquid mixture and 0.5 g of each gelatin piece were put together in a sealed container and kept at 40° C. for 21 days. Then, the concentration of compound 1 contained in the liquid mixture was determined in the same manner as Reference Example 1. Results are shown in Table 2:

TABLE 2

Stability data of compound 1/medium chain fatty acid triglyceride (MCT) solution (60 µg/g)		
gelatin piece		concentration
plasticizer	water content (after dried)	of compound 1 after storage <sup>1)</sup>
glycerin	23%	86.8%
sugar alcohol solution derived from corn starch <sup>2)</sup>	25%	92.0%

<sup>1)</sup>Percentage based on a theoretical amount (60 µg/g)

<sup>2)</sup>Polysorb 85/70/00™, ROQUETTE AMERICA, Inc.

According to the reference example 1, in case the 15-keto-prostaglandin compound of the invention and the sugar alcohol were contacted directly, stability of the compound was significantly lowered. In contrast, in case the 15-keto-PG compound was directly contacted with a polyol such as glycerin, the stability of the compound was maintained. It has surprisingly revealed by Example 1 that the stability of the 15-keto-prostaglandin contacted with gelatin piece prepared using sugar alcohol as a plasticizer was better than that contacted with gelatin piece with glycerin as a plasticizer.

## EXAMPLE 2

Sugar alcohol solution derived from corn starch in an amount shown in Table 3 was added in an appropriate amount of water, stirred and heated. Then, gelatin 100 parts by weight was added thereto to give gelatin solution. Compound 1 was dissolved in medium chain fatty acid triglyceride (USP/NF grade) to give a fill solution containing 240 µg/g of compound 1. The gelatin solution and the liquid mixture were loaded on capsule forming and filling machine to give capsule containing the fill solution therein, and the capsule was dried to give soft gelatin capsule.

The capsule was put in a sealed container and kept at 40° C. for 3 months. The concentration of compound 1 in the fill solution contained in the capsule was determined after 1, 2 and 3 months storage in the same manner as Reference Example 1.

TABLE 3

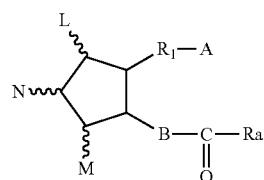
Stability of soft gelatin capsule of compound 1						
soft gelatin capsule (parts by weight)		conc. (% of Initial) 40° C.				
		1 mo	2 mo	3 mo		
gelatin	100	sugar	35	99.9%	100.3%	99.2%
		alcohol	45	—	100.5%	100.0%
		solution <sup>1)</sup>	55	—	99.3%	100.0%

<sup>1)</sup>Polysorb 85/70/00™, ROQUETTE AMERICA, Inc., derived from corn starch

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What is claimed is:

1. A soft gelatin capsule formulation of a 15-keto-prostaglandin compound, which comprises:
  - a soft gelatin capsule shell comprising gelatin and a sugar alcohol as a plasticizer, and
  - a mixture comprising a 15-keto-prostaglandin compound and a pharmaceutically acceptable vehicle, which is filled in the shell,
 wherein the pharmaceutically acceptable vehicle is a fatty acid ester or a polyol,
 wherein the 15-keto-prostaglandin compound is a compound of the formula (I):



wherein L, M and N are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is —CH<sub>3</sub>, or —CH<sub>2</sub>OH, —COCH<sub>2</sub>OH, —COOH or a functional derivative thereof;

B is —CH<sub>2</sub>—CH<sub>2</sub>—, —CH=CH— or —C=C—;

R<sub>1</sub> is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, lower alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur; and

R<sub>a</sub> is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocycloxy group; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic group; heterocycloxy group.

2. The formulation of claim 1, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-prostaglandin compound.
3. The formulation of claim 1, wherein the 15-keto-prostaglandin compound is a 15-keto-16-mono or 16,16-di-halogen-prostaglandin compound.
4. The formulation of claim 1, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16-mono or 16,16-di-halogen-prostaglandin compound.
5. The formulation of claim 1, wherein the 15-keto-prostaglandin compound is a 15-keto-16-mono- or 16,16-di-fluoro-prostaglandin compound.
6. The formulation of claim 1, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16-mono or 16,16-di-fluoro-prostaglandin compound.

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7. The formulation of claim 1, wherein the 15-keto-prostaglandin compound is a 15-keto-prostaglandin E compound.

8. The formulation of claim 1, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E<sub>1</sub>.

9. The formulation of claim 1, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16,16-difluoro-18S-methyl-prostaglandin E<sub>1</sub>.

10. The formulation of claim 1, wherein the sugar alcohol is selected from the group consisting of sorbitol, maltitol, sugar alcohol solution derived from corn starch, hydrogenated maltose syrup and a mixture thereof.

11. The formulation of claim 1, wherein the sugar alcohol comprises sorbitol and sorbitan as its major component.

12. The formulation of claim 1, wherein the pharmaceutically acceptable vehicle is a fatty acid ester.

13. The formulation of claim 1, wherein the pharmaceutically acceptable vehicle is a polyol.

14. The formulation of claim 1, wherein the pharmaceutically acceptable vehicle is glycerin or propylene glycol.

15. The formulation of claim 10, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E<sub>1</sub>.

16. The formulation of claim 11, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E<sub>1</sub>.

17. The formulation of claim 12, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E<sub>1</sub>.

18. The formulation of claim 13, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E<sub>1</sub>.

19. The formulation of claim 14, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E<sub>1</sub>.

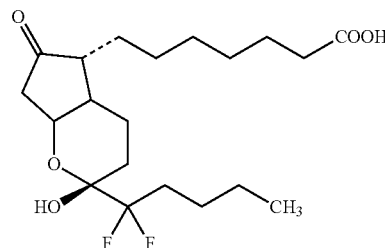
20. The formulation of claim 1, wherein the sugar alcohol comprises sorbitol,

wherein the pharmaceutically acceptable vehicle comprises a fatty acid ester, and

wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E<sub>1</sub>.

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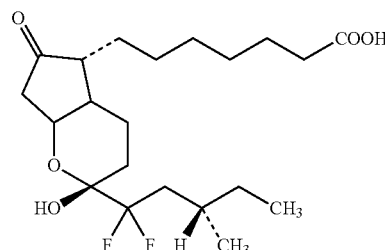
21. A soft gelatin capsule formulation comprising: a soft gelatin capsule shell comprising gelatin and a sugar alcohol as a plasticizer, and a mixture comprising



and a pharmaceutically acceptable vehicle, which is filled in the shell,

wherein the pharmaceutically acceptable vehicle is a fatty acid ester or a polyol.

22. A soft gelatin capsule formulation comprising: a soft gelatin capsule shell comprising gelatin and a sugar alcohol as a plasticizer, and a mixture comprising



and a pharmaceutically acceptable vehicle, which is filled in the shell,

wherein the pharmaceutically acceptable vehicle is a fatty acid ester or a polyol.

23. The formulation of claim 1, wherein M is a group other than hydrogen.

\* \* \* \* \*

# **EXHIBIT F**

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

(10) **Patent No.:** **US 8,779,187 B2**  
 (45) **Date of Patent:** **Jul. 15, 2014**

(54)	<b>SOFT-GELATIN CAPSULE FORMULATION</b>	5,073,569 A	12/1991	Ueno et al.	
		5,106,869 A	4/1992	Ueno et al.	
(71)	Applicants: <b>Sucampo AG</b> , Zug (CH); <b>R-Tech Ueno, Ltd.</b> , Tokyo (JP)	5,137,820 A	8/1992	Maeda et al.	
		5,164,415 A	11/1992	Ueno	
		5,166,174 A	11/1992	Ueno et al.	
		5,212,324 A	5/1993	Ueno	
(72)	Inventors: <b>Yukiko Hashitera</b> , Kobe (JP); <b>Ryu Hirata</b> , Sanda (JP); <b>Yasuhiro Harada</b> , Sanda (JP); <b>Ryuji Ueno</b> , Potomac, MD (US)	5,221,763 A	6/1993	Ueno et al.	
		5,225,439 A	7/1993	Ueno et al.	
		5,254,588 A	10/1993	Ueno et al.	
		5,284,858 A	2/1994	Ueno et al.	
		5,317,032 A	5/1994	Ueno et al.	
		5,380,709 A	1/1995	Ueno et al.	
(73)	Assignees: <b>Sumcampo AG</b> , Zug (CH); <b>R-Tech Ueno, Ltd.</b> , Tokyo (JP)	5,428,062 A	6/1995	Ueno et al.	
		5,534,547 A	7/1996	Ueno et al.	
		5,591,887 A	1/1997	Ueno et al.	
(*)	Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.	5,739,161 A	4/1998	Ueno	
		5,770,759 A	6/1998	Ueno et al.	
		5,886,034 A	3/1999	Ueno et al.	
		5,998,438 A	12/1999	Slassi et al.	
(21)	Appl. No.: <b>13/679,005</b>	6,207,699 B1	3/2001	Rothman	
		6,242,485 B1	6/2001	Ueno	
(22)	Filed: <b>Nov. 16, 2012</b>	6,265,440 B1	7/2001	Ueno et al.	
		6,583,174 B1	6/2003	Ueno et al.	
		8,026,393 B2 *	9/2011	Hashitera et al. ....	562/504
		8,338,639 B2 *	12/2012	Hashitera et al. ....	562/504
(65)	<b>Prior Publication Data</b>	2009/0022787 A1	1/2009	Harada et al.	

US 2013/0078303 A1 Mar. 28, 2013

**Related U.S. Application Data**

- (63) Continuation of application No. 13/210,556, filed on Aug. 16, 2011, now Pat. No. 8,338,639, which is a continuation of application No. 11/656,476, filed on Jan. 23, 2007, now Pat. No. 8,026,393.
- (60) Provisional application No. 60/761,360, filed on Jan. 24, 2006.
- (51) **Int. Cl.**  
**C07C 61/06** (2006.01)  
**C07C 61/20** (2006.01)
- (52) **U.S. Cl.**  
 USPC ..... **562/504**; 514/513
- (58) **Field of Classification Search**  
 None  
 See application file for complete search history.

(56) **References Cited**

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(57) **ABSTRACT**

The present invention discloses a soft gelatin capsule formulation of a 15-keto-prostaglandin compound, which comprises: a soft gelatin capsule shell comprising gelatin and sugar alcohol as a plasticizer, and a mixture comprising a 15-keto-prostaglandin compound and a pharmaceutically acceptable vehicle which is filled in the shell. By encapsulating the 15-keto-prostaglandin compound in the specified soft gelatin capsule shell, stability of the compound is significantly improved.

**17 Claims, No Drawings**

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**SOFT-GELATIN CAPSULE FORMULATION****CROSS REFERENCE TO RELATED APPLICATIONS**

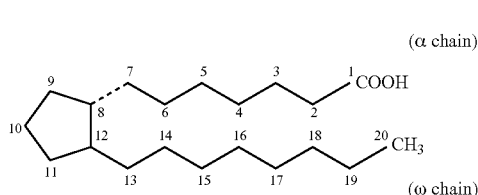
This is a continuation of application Ser. No. 13/210,556 filed Aug. 16, 2011, which is a continuation of application Ser. No. 11/656,476 filed Jan. 23, 2007, issued as U.S. Pat. No. 8,026,393 on Sep. 27, 2011, and claims the benefit of U.S. Provisional Application No. 60/761,360 filed Jan. 24, 2006. The disclosures of application Ser. Nos. 13/210,556 and 11/656,476 are all hereby incorporated by reference.

**FIELD OF THE INVENTION**

The present invention relates to a soft-gelatin capsule formulation of a therapeutically effective 15-keto-prostaglandin compound.

**BACKGROUND ART**

Prostaglandins (hereinafter, referred to as PGs) are members of class of organic carboxylic acids, which are contained in tissues or organs of human and other mammals, and exhibit a wide range of physiological activities. PGs found in nature (primary PGs) have, as a general structural property thereof, a prostanic acid skeleton as shown in the formula (A):



On the other hand, some synthetic analogues have modified skeletons. The primary PGs are classified into PGAs, PGBs, PGCs, PGDs, PGEs, PGFs, PGGs, PGHs, PGI and PGJs on the basis of the structural property of the five membered ring moiety, and further classified into the following three types by the number and position of the unsaturated bond in the carbon chain moiety.

Type 1 (subscript 1): 13,14-unsaturated-15-OH

Type 2 (subscript 2): 5,6- and 13,14-diunsaturated-15-OH

Type 3 (subscript 3): 5,6-, 13,14-, and 17,18-triunsaturated-15-OH.

Further, PGFs are classified on the basis of the configuration of the hydroxyl group at the 9-position into a type (wherein the hydroxyl group is of the  $\alpha$ -configuration) and  $\beta$  type (wherein the hydroxyl group is of the  $\beta$ -configuration).

In addition, some 15-keto-PGs (PGs having an oxo group at position 15 in place of the hydroxy group) and 13,14-dihydro-15-keto-PGs have been known as substances naturally produced by enzymatic actions during metabolism of the primary PGs and have some therapeutic effect. 15-keto-PGs have been disclosed in U.S. Pat. Nos. 5,073,569, 5,534,547, 5,225,439, 5,166,174, 5,428,062, 5,380,709, 5,886,034, 6,265,440, 5,106,869, 5,221,763, 5,591,887, 5,770,759 and 5,739,161. The contents of these publications are herein incorporated by reference.

For example, 15-keto-16-halogen prostaglandin compounds are useful as cathartics (U.S. Pat. No. 5,317,032, the contents of the reference is herein incorporated by reference). For treating gastrointestinal diseases, the agent is preferably

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formulated as an orally administrable dosage form. In general, PG compounds are less soluble in water and become significantly unstable under the presence of water. A capsulated formulation comprises a 15-keto-16-halogen PG compound and a solvent which can maintain the stability of the compound such as glyceride had been proposed (WO01/027099 (U.S. Pat. No. 6,583,174), the contents of the cited reference is herein incorporated by reference.

Elastic shell of a soft gelatin capsule, in general, incorporates a plasticizer in addition to gelatin. Examples of plasticizer include glycerin, propylene glycol, sorbitol, maltitol, sugar alcohol solution derived from corn starch (Anidrisorb™, Polysorb™), i.e. a mixture of sorbitol, sorbitane, mannitol and hydrogenated starch hydrolysate, hydrogenated maltose starch syrup, i.e. a mixture of maltitol, sorbitol and oligosaccharide alcohol.

**SUMMARY OF THE INVENTION**

An object of the present invention is to provide an orally administrable dosage form of a 15-keto-prostaglandin compound which has an excellent shelf stability.

Accordingly, the instant application provides a soft gelatin capsule formulation of a 15-keto-prostaglandin compound, which comprises:

- a soft gelatin capsule shell comprising gelatin and a sugar alcohol as a plasticizer, and
- a mixture comprising a 15-keto-prostaglandin compound and a pharmaceutically acceptable vehicle, which is filled in the shell.

The invention is also provides a method for improving stability of a 15-keto-prostaglandin compound which comprises, dissolving the 15-keto-prostaglandin in a pharmaceutically acceptable solvent and incorporating the solution in a soft-gelatin capsule whose shell comprises gelatin and a sugar alcohol as a plasticizer.

**DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS**

The nomenclature of the PG compounds used herein is based on the numbering system of prostanic acid represented in the above formula (A).

The formula (A) shows a basic skeleton of the C-20 PG compound, but the present invention is not limited to those having the same number of carbon atoms. In the formula (A), the numbering of the carbon atoms which constitute the basic skeleton of the PG compounds starts at the carboxylic acid (numbered 1), and carbon atoms in the  $\alpha$ -chain are numbered 2 to 7 towards the five-membered ring, those in the ring are 8 to 12, and those in the  $\omega$ -chain are 13 to 20. When the number of carbon atoms is decreased in the  $\alpha$ -chain, the number is deleted in the order starting from position 2; and when the number of carbon atoms is increased in the  $\alpha$ -chain, compounds are named as substitution compounds having respective substituents at position 2 in place of carboxy group (C-1). Similarly, when the number of carbon atoms is decreased in the  $\omega$ -chain, the number is deleted in the order starting from position 20; and when the number of carbon atoms is increased in the  $\omega$ -chain, compounds are named as substitution compounds having respective substituents at position 20. Stereochemistry of the compounds is the same as that of the above formula (A) unless otherwise specified.

In general, each of PGD, PGE and PGF represents a PG compound having hydroxy groups at positions 9 and/or 11, but in the present specification and claims they also include those having substituents other than the hydroxyl groups at

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positions 9 and/or 11. Such compounds are referred to as 9-dehydroxy-9-substituted-PG compounds or 11-dehydroxy-11-substituted-PG compounds. A PG compound having hydrogen in place of the hydroxy group is simply named as 9- or 11-dehydroxy compound.

As stated above, the nomenclature of PG compounds is based on the prostanic acid skeleton. However, in case the compound has a similar partial construction as a prostaglandin, the abbreviation of "PG" may be used. Thus, a PG compound of which  $\alpha$ -chain is extended by two carbon atoms, that is, having 9 carbon atoms in the  $\alpha$ -chain is named as 2-decarboxy-2-(2-carboxyethyl)-PG compound. Similarly, a PG compound having 11 carbon atoms in the  $\alpha$ -chain is named as 2-decarboxy-2-(4-carboxybutyl)-PG compound. Further, a PG compound of which  $\omega$ -chain is extended by two carbon atoms, that is, having 10 carbon atoms in the  $\omega$ -chain is named as 20-ethyl-PG compound. These compounds, however, may also be named according to the IUPAC nomenclatures.

The 15-keto-PG compound used in the present invention may be any derivative of a PG insofar as having an oxo group at position 15 in place of the hydroxy group, and may further include a compound having one double bond between positions 13 and 14 (15-keto-PG type 1 compound), two double bonds between positions 13 and 14, and positions 5 and 6 (15-keto-PG type 2 compound), and three double bonds between positions 5 and 6, positions 13' and 14, and positions 17 and 18 (15-keto-PG type 3 compound), and a derivative thereof wherein the bond between the positions and 14 is single bond, in place of the double bond (13,14-dihydro-15-keto-PG compound).

Examples of the analogue including substitution compounds or derivatives include a PG compound of which the carboxy group at the end of the alpha chain is esterified; physiologically acceptable salt thereof; an unsaturated derivative having a double bond between positions 2 and 3 or a triple bond between positions 5 and 6; PG compounds having substituent(s) on carbon atom(s) at position(s) 3, 5, 6, 16, 17, 18, 19 and/or 20; and PG compounds having lower alkyl or a hydroxy (lower) alkyl group at position 9 and/or 11 in place of the hydroxy group.

According to the present invention, preferred substituents on the carbon atom at position(s) 3, 17, 18 and/or 19 include alkyl having 1 to 6 carbon atoms, especially methyl and ethyl. Preferred substituents on the carbon atom at position 16 include lower alkyl such as methyl and ethyl, hydroxy, halogen atom such as chlorine and fluorine, and aryloxy such as trifluoromethylphenoxy. Preferred substituents on the carbon atom at position 17 include halogen atom such as chlorine and fluorine. Preferred substituents on the carbon atom at position 20 include saturated or unsaturated lower alkyl such as  $C_{1-4}$  alkyl, lower alkoxy such as  $C_{1-4}$  alkoxy, and lower alkoxy alkyl such as  $C_{1-4}$  alkoxy- $C_{1-4}$  alkyl. Preferred substituents on the carbon atom at position 5 include halogen atoms such as chlorine and fluorine. Preferred substituents on the carbon atom at position 6 include an oxo group forming a carbonyl group. Stereochemistry of PGs having hydroxy, lower alkyl or hydroxy(lower)alkyl substituent on the carbon atom at positions 9 and 11 may be  $\alpha$ ,  $\beta$  or a mixture thereof.

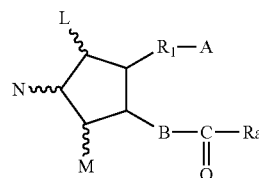
Further, the above described derivatives may have a  $\omega$  chain shorter than that of the primary PGs and a substituent such as alkoxy, cyclohexyl, cyclohexyloxy, phenoxy and phenyl at the end of the truncated  $\omega$ -chain.

Especially preferred compounds include a 13,14-dihydro-15-keto-PG compound that has a single bond between positions 13 and 14; a 15-keto-16-mono or 16,16-di-halogen PG compound that has at least one halogen atom, especially

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fluorine, at carbon atom of position 16; a 15-keto-PGE compound that has hydroxy group at position 9 and oxo group at position 11 of the five membered ring.

A preferred prostaglandin compound used in the present invention is represented by the formula (I):



(I)

wherein L, M and N are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

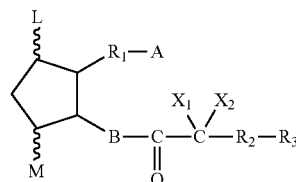
A is  $-\text{CH}_3$ , or  $-\text{CH}_2\text{OH}$ ,  $-\text{COCH}_2\text{OH}$ ,  $-\text{COOH}$  or a functional derivative thereof;

B is  $-\text{CH}_2-\text{CH}_2-$ ,  $-\text{CH}=\text{CH}-$  or  $-\text{C}\equiv\text{C}-$ ;

R<sub>1</sub> is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, lower alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur; and

Ra is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocycloxy group; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic group; heterocycloxy group.

A more preferred prostaglandin compound used in the present invention is represented by the formula (II):



(II)

wherein L and M are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have one or more double bonds;

A is  $-\text{CH}_3$ , or  $-\text{CH}_2\text{OH}$ ,  $-\text{COCH}_2\text{OH}$ ,  $-\text{COOH}$  or a functional derivative thereof;

B is  $-\text{CH}_2-\text{CH}_2-$ ,  $-\text{CH}=\text{CH}-$  or  $-\text{C}\equiv\text{C}-$ ;

X<sub>1</sub> and X<sub>2</sub> are hydrogen, lower alkyl, or halogen;

R<sub>1</sub> is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, lower alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur;



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R<sub>2</sub> is a single bond or lower alkylene; and

R<sub>3</sub> is lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo (lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocycloxy group.

In the above formula, the term "unsaturated" in the definitions for R<sub>1</sub> and Ra is intended to include at least one or more double bonds and/or triple bonds that are isolatedly, separately or serially present between carbon atoms of the main and/or side chains. According to the usual nomenclature, an unsaturated bond between two serial positions is represented by denoting the lower number of the two positions, and an unsaturated bond between two distal positions is represented by denoting both of the positions.

The term "lower or medium aliphatic hydrocarbon" refers to a straight or branched chain hydrocarbon group having 1 to 14 carbon atoms (for a side chain, 1 to 3 carbon atoms are preferable) and preferably 1 to 10, especially 6 to 10 carbon atoms for R<sub>1</sub> and 1 to 10, especially, 1 to 8 carbon atoms for Ra.

The term "halogen" covers fluorine, chlorine, bromine and iodine.

The term "lower" is intended to include a group having 1 to 6 carbon atoms unless otherwise specified.

The term "lower alkyl" refers to a straight or branched chain saturated hydrocarbon group containing 1 to 6 carbon atoms and includes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl and hexyl.

The term "lower alkoxy" refers to a group of lower alkyl-O—, wherein lower alkyl is as defined above.

The term "hydroxy(lower)alkyl" refers to a lower alkyl as defined above which is substituted with at least one hydroxy group such as hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 1-methyl-1-hydroxyethyl.

The term "lower alkanoyloxy" refers to a group represented by the formula RCO—O—, wherein RCO— is an acyl group formed by oxidation of a lower alkyl group as defined above, such as acetyl.

The term "cyclo(lower)alkyl" refers to a cyclic group formed by cyclization of a lower alkyl group as defined above but contains three or more carbon atoms, and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "cyclo(lower)alkyloxy" refers to the group of cyclo(lower)alkyl-O—, wherein cyclo(lower)alkyl is as defined above.

The term "aryl" may include unsubstituted or substituted aromatic hydrocarbon rings (preferably monocyclic groups), for example, phenyl, tolyl, xylyl.

Examples of the substituents are halogen atom and halo (lower)alkyl, wherein halogen atom and lower alkyl are as defined above.

The term "aryloxy" refers to a group represented by the formula ArO—, wherein Ar is aryl as defined above.

The term "heterocyclic group" may include mono- to tricyclic, preferably monocyclic heterocyclic group which is 5 to 14, preferably 5 to 10 membered ring having optionally substituted carbon atom and 1 to 4, preferably 1 to 3 of 1 or 2 type of hetero atoms selected from nitrogen, oxygen and sulfur. Examples of the heterocyclic group include furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, 2-pyrrolinyl, pyrrolidinyl, 2-imidazolyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, piperidino, piperazinyl, morpholino, indolyl, benzothienyl, quinolyl, isoquinolyl, purinyl, quinazoliny, carbazolyl, acridinyl, phenanthridinyl, benzimidazolyl, benzimidazoliny, benzothiazolyl, phenothiazinyl. Examples of the substituent in this case include halogen, and halogen substituted lower alkyl group, wherein halogen atom and lower alkyl group are as described above.

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The term "heterocycloxy group" means a group represented by the formula HcO—, wherein Hc is a heterocyclic group as described above.

The term "functional derivative" of A includes salts, preferably pharmaceutically acceptable salts, ethers, esters and amides.

Suitable "pharmaceutically acceptable salts" include salts formed with non-toxic bases conventionally used in pharmaceutical field, for example a salt with an inorganic base such as an alkali metal salt (such as sodium salt and potassium salt), an alkaline earth metal salt (such as calcium salt and magnesium salt), an ammonium salt; or a salt with an organic base, for example, an amine salt including such as methylamine salt, dimethylamine salt, cyclohexylamine salt, benzylamine salt, piperidine salt, ethylenediamine salt, ethanolamine salt, diethanolamine salt, triethanolamine salt, tris (hydroxymethylamino)ethane salt, monomethylmonoethanolamine salt, procaine salt and caffeine salt), a basic amino acid salt (such as arginine salt and lysine salt), tetraalkyl ammonium salt and the like. These salts may be prepared by a conventional process, for example from the corresponding acid and base or by salt interchange.

Examples of the ethers include alkyl ethers, for example, lower alkyl ethers such as methyl ether, ethyl ether, propyl ether, isopropyl ether, butyl ether, isobutyl ether, t-butyl ether, pentyl ether and 1-cyclopropyl ether; and medium or higher alkyl ethers such as octyl ether, diethylhexyl ether, lauryl ether and cetyl ether; unsaturated ethers such as oleyl ether and linolenyl ether; lower alkenyl ethers such as vinyl ether, allyl ether; lower alkynyl ethers such as ethynyl ether and propynyl ether; hydroxy(lower)alkyl ethers such as hydroxyethyl ether and hydroxyisopropyl ether; lower alkoxy (lower)alkyl ethers such as methoxymethyl ether and 1-methoxyethyl ether; optionally substituted aryl ethers such as phenyl ether, tosyl ether, t-butylphenyl ether, salicyl ether, 3,4-di-methoxyphenyl ether and benzamidophenyl ether; and aryl(lower)alkyl ethers such as benzyl ether, trityl ether and benzhydryl ether.

Examples of the esters include aliphatic esters, for example, lower alkyl esters such as methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester and 1-cyclopropylethyl ester; lower alkenyl esters such as vinyl ester and allyl ester; lower alkynyl esters such as ethynyl ester and propynyl ester; hydroxy(lower)alkyl ester such as hydroxyethyl ester; lower alkoxy (lower)alkyl esters such as methoxymethyl ester and 1-methoxyethyl ester; and optionally substituted aryl esters such as, for example, phenyl ester, tolyl ester, t-butylphenyl ester, salicyl ester, 3,4-di-methoxyphenyl ester and benzamidophenyl ester; and aryl(lower)alkyl ester such as benzyl ester, trityl ester and benzhydryl ester.

The amide of A means a group represented by the formula —CONR'R", wherein each of R' and R" is hydrogen, lower alkyl, aryl, alkyl- or aryl-sulfonyl, lower alkenyl and lower alkynyl, and include for example lower alkyl amides such as methylamide, ethylamide, dimethylamide and diethylamide; arylamides such as anilide and toluidide; and alkyl- or aryl-sulfonylamides such as methylsulfonylamide, ethylsulfonylamide and tolylsulfonylamide.

Preferred examples of L and M include hydroxy and oxo, and especially, M is hydroxy and L is oxo which has a 5-membered ring structure of, so called, PGE type.

Preferred example of A is —COOH, its pharmaceutically acceptable salt, ester or amide thereof.

Preferred example of B is —CH<sub>2</sub>—CH<sub>2</sub>—, which provide the structure of so-called, 13,14-dihydro type.

Preferred example of X<sub>1</sub> and X<sub>2</sub> is that at least one of them is halogen, more preferably, both of them are halogen, especially, fluorine that provides a structure of, so called 16,16-difluoro type.

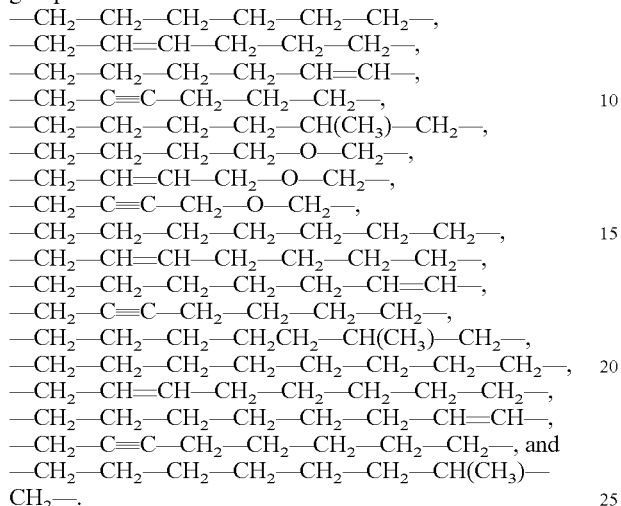


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Preferred R<sub>1</sub> is a hydrocarbon residue containing 1-10 carbon atoms, preferably 6 to 10 carbon atoms. Further, at least one carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur.

Examples of R<sub>1</sub> include, for example, the following groups:



Preferred R<sub>a</sub> is a hydrocarbon containing 1 to 10 carbon atoms, more preferably, 1 to 8 carbon atoms. R<sub>a</sub> may have one or two side chains having one carbon atom.

The configuration of the ring and the α- and/or ω chains in the above formula (I) and (II) may be the same as or different from that of the primary PGs. However, the present invention also includes a mixture of a compound having a primary type configuration and a compound of a non-primary type configuration.

The typical example of the present compounds are 13,14-dihydro-15-keto-16-mono- or 16,16-di-fluoro PGE compound and its derivative or analogue.

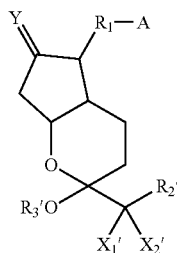
In the present invention, the 15-keto-PG compound may be in the keto-acetal equilibrium by formation of a hemiacetal between hydroxy at position 11 and keto at position 15.

For example, it has been revealed that when both of X<sub>1</sub> and X<sub>2</sub> are halogen atoms, especially, fluorine atoms, the compound contains a tautomeric isomer, bi-cyclic compound.

If such tautomeric isomers as above are present, the proportion of both tautomeric isomers varies with the structure of the rest of the molecule or the kind of the substituent present. Sometimes one isomer may predominantly be present in comparison with the other. However, it is to be appreciated that the present invention includes both isomers.

Further, the 15-keto-PG compounds used in the invention include the bi-cyclic compound and analogs or derivatives thereof.

The bi-cyclic compound is represented by the formula (III):

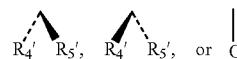


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wherein, A is  $\text{—CH}_3$ , or  $\text{—CH}_2\text{OH}$ ,  $\text{—COCH}_2\text{OH}$ ,  $\text{—COOH}$  or a functional derivative thereof;

X<sub>1</sub>' and X<sub>2</sub>' are hydrogen, lower alkyl, or halogen;

Y is



wherein R<sub>4</sub>' and R<sub>5</sub>' are hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or hydroxy(lower)alkyl,

wherein R<sub>4</sub>' and R<sub>5</sub>' are not hydroxy and lower alkoxy at the same time;

R<sub>1</sub>' is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, lower alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur;

R<sub>2</sub>' is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocycloxy group; lower alkyl; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic group; heterocycloxy group; and

R<sub>3</sub>' is hydrogen, lower alkyl, cyclo(lower)alkyl, aryl or heterocyclic group.

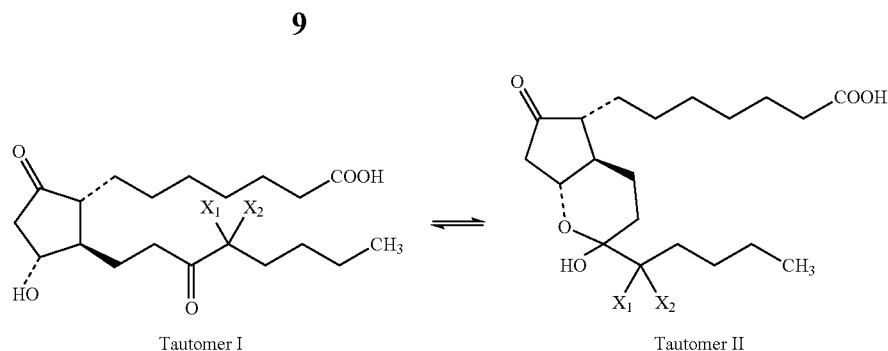
Furthermore, while the compounds used in the invention may be represented by a formula or name based on keto-type regardless of the presence or absence of the isomers, it is to be noted that such structure or name does not intend to exclude the acetal type compound.

In the present invention, any of isomers such as the individual tautomeric isomers, the mixture thereof, or optical isomers, the mixture thereof, a racemic mixture, and other steric isomers may be used in the same purpose.

Some of the compounds used in the present invention may be prepared by the method disclosed in U.S. Pat. Nos. 5,073, 569, 5,166,174, 5,221,763, 5,212,324, 5,739,161 and 6,242, 485, the contents of these references are herein incorporated by reference.

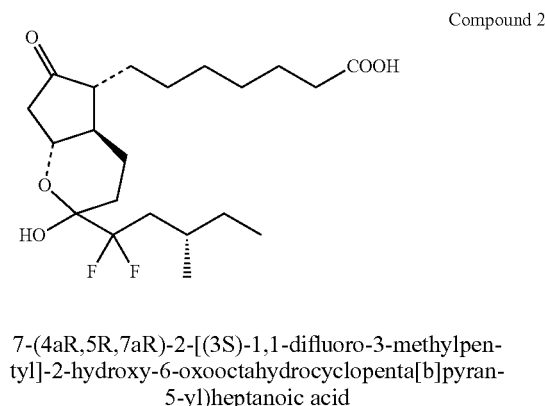
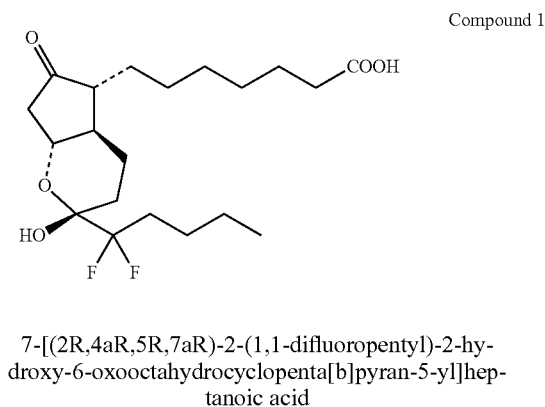
It has been known that 13,14-dihydro-15-keto-prostaglandin compound having the formula as shown below (Tautomer I) may be in equilibrium with its tautomeric isomer (tautomer II) (See U.S. Pat. No. 5,166,174, U.S. Pat. No. 5,225,439, U.S. Pat. No. 5,284,858, U.S. Pat. No. 5,380,709, U.S. Pat. No. 5,428,062 and U.S. Pat. No. 5,886,034, the contents of these references are herein incorporated by reference.)

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It is considered that the halogen atom(s) at  $X_1$  and/or  $X_2$  promote bi-cyclic ring formation, such as the compound 1 or 2 below. In addition, in the absence of water, the tautomeric compounds as above exist predominantly in the form of the bi-cyclic compound. In aqueous media, it is supposed that hydrogen bonding occurs between the water molecule and, for example, the keto group on the hydrocarbon chain, thereby hindering bi-cyclic ring formation. The bi-cyclic/mono-cyclic structures, for example, may be present in a ratio of 6:1 in  $D_2O$ ; 10:1 in  $CD_3OD-D_2O$  and 96:4 in  $CDCl_3$ . In the instant specification and claims, tautomeric mixture containing the bi-cyclic compound in a ratio even greater to substantially 100% bi-cyclic compound is within this invention.

Embodiment of the bi-cyclic compound of the present invention include the Compounds 1 and 2 shown below.



According to the present invention, the pharmaceutically acceptable vehicle is not specifically limited as long as the

vehicle can disperse the 15-keto-PG therein and does not significantly deteriorate the stability of the compound. In view of manufacturing soft gelatin capsule formulation, a solvent which is liquid at the room temperature. A solution, dispersion or mixture of the 15-keto-PG in the solvent may be filled in the capsule.

Examples of the pharmaceutically acceptable vehicles preferably used in the instant invention may be fatty acid esters, i.e. an ester of fatty acid and an alcohol, and polyols.

Preferred fatty acid which consists the fatty acid ester is a medium or higher chain fatty acid having at least C6, preferably C6-24 carbon atoms, for example caproic acid (C6), caprylic acid (C8), capric acid (C10), lauric acid (C12) and myristic acid (C14), palmitic acid (C16), palmitoleic acid (C16), stearic acid (C18), oleic acid (C18), linoleic acid (C18), linolenic acid (C18), ricinolic acid (C18) and arachic acid (C20). Preferred alcohols which consists the fatty acid ester may comprise C1-6 monovalent alcohol and polyols such as glycerin, polyethylene glycol and propylene glycol.

Preferred fatty acid esters may include a glyceride of a saturated or unsaturated fatty acid which may have a branched chain and a propylene glycol fatty acid ester. Two or more glycerides may be used as a mixture.

Examples of the mixture of glycerides are mixture of caprylic acid triglyceride and capric acid triglyceride, vegetable oils such as castor oil, corn oil, olive oil, sesame oil, rape oil, salad oil, cottonseed oil, camellia oil, peanut oil, palm oil and sunflower oil.

A fatty acid ester derived from a fatty acid and a monovalent alcohol is also preferably used as a pharmaceutically acceptable vehicle. The fatty acid ester may preferably be an ester of C8-20 fatty acid and a C2-3 monovalent alcohol, such as isopropyl myristate, isopropyl palmitate, ethyl linoleate and ethyl oleate.

Examples of polyols may preferably include alcohols having two or three hydroxy groups such as glycerin, polyethylene glycol and propylene glycol.

According to the present invention, the mixture which is filled in the soft-gelatin capsule shell may be obtained by dissolving or dispersing the above-described 15-keto-prostaglandin compound in the above described pharmaceutically acceptable vehicle which is liquid at the room temperature. When it is difficult to dissolve the 15-keto-PG compound directly in the vehicle, each of them may be dissolved in a solvent in which both of them are soluble respectively, and then the solutions may be combined.

The amount of the solvent in the mixture relative to the amount of the 15-keto-PG compound is not limited as long as the 15-keto-PG is stable in the final formulation. In general, the amount of the vehicle per one part of the 15-keto-PG compound may be 1-5,000,000, preferably, 5-1,000,000 and most preferably, 10-500,000 parts by weight.

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The mixture used in the invention may further comprise an oil solvent such as mineral oil, liquid paraffin, and tocopherol. The mixture of the present invention may further comprise another pharmaceutically active ingredient.

In a preferred embodiment, the composition of the present invention is substantially free of water. The term "substantially free of water" means that the composition does not contain water that is intentionally added. It is understood that many materials contain water that is taken up from the atmosphere or is present as a coordination complex in its normal state. Water taken up by hygroscopic materials or present as a hydrate is permissibly present in the compositions of this embodiment. According to the embodiment, any water that is present in the composition should not be present in amounts such that the water will have a deleterious effect to the composition of the present invention.

According to the present invention, the shell of the soft gelatin capsule is manufactured from gelatin and a sugar alcohol as a plasticizer.

Sugar alcohol used in the present invention is an alcohol obtained by hydrogen reduction of the aldehyde group of a saccharide. For example, sorbitol, mannitol, maltitol, lactitol, palatinit, xylitol, erithyritol, sugar alcohol solution derived from corn starch, i.e. a mixture of sorbitol, sorbitan, mannitol and hydrogenated starch hydrolysate, hydrogenated maltose starch syrup, i.e. a mixture of maltitol, sorbitol and oligosaccharide alcohol. Preferred sugar alcohols may include sorbitol, maltitol, sugar alcohol solution derived from corn starch and hydrogenated maltose starch syrup. Especially, sugar alcohol solution derived from corn starch and available on market under the name "Anidrisorb™" or "Polysorb™" is preferably used.

According to the invention, the amount of the sugar alcohol used for preparing the shell of the soft gelatin capsule is not specifically limited as long as the physical properties of the resulting capsule is not deteriorated. In general, the amount of sugar alcohol plasticizer is 20 to 60 parts by weight, preferably, 30 to 50 parts by weight per 100 parts by weight of gelatin.

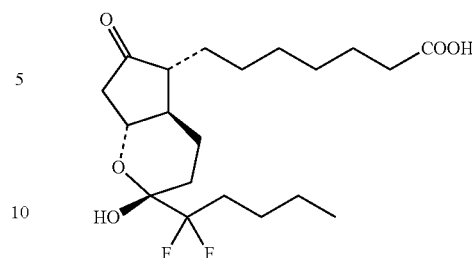
The soft gelatin capsule formulation of the 15-keto-PG compound may be manufactured according to a conventional manner using the above described liquid mixture and a mixture of gelatin and the plasticizer.

The present invention will be explained in more detail by means of the following examples, which are illustrated by way of example only and never intended to limit the scope of the present invention.

#### Reference Example 1

Compound 1 was dissolved in a vehicle shown in table 1 below to give 240 µg/g solution (sample). The precise concentration of compound 1 in the sample was determined by means of HPLC (day 0). Then, the sample was put in a hard glass container and kept at 55° C. for 10 days, and then the precise concentration of the compound 1 in the sample was determined by means of HPLC (day 10).

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Compound 1

The determination of the concentration of the compound in the sample was carried out as follows. About 0.2 g of the sample was mixed with exactly 2 ml of internal standard solution and then with a dissolving agent shown in Table 1 to give 5 mL of sample solution. About 12 mg of the reference standard compound 1 was weighted precisely and added with acetonitrile to give exactly 100 ml solution. Exactly 0.8 ml of the solution was obtained and added with exactly 4 ml of the internal standard solution, and then added with the dissolving agent to give 10 ml of standard solution.

The fluorescent labeling agent was added to the respective solution, stirred and stood at room temperature. Then, respective solution in an amount that theoretically gives 3.6 ng of compound 1 was loaded on the column and analyzed under the condition as follows:

HPLC Analysis Condition:

Column: 5 mm×25 cm stainless steel column packed with octadecylsilane treated silica gel for HPLC (5 µm)

Mobile phase: mixture of acetonitrile HPLC grade: methanol HPLC grade: ammonium acetate (0.05 mol/L)

Temperature: 35° C.

Detector: spectrophotofluorometer

Results are shown in Table 1:

TABLE 1

Assay results of compound 1 after 55° C. storage				
			concentration of compound 1 <sup>1)</sup>	
	vehicle	dissolving agent	day 0	day 10
1	hydrogenated maltose starch syrup	acetonitrile/Water (1:1)	—	24.4%
2	Sugar alcohol solution derived from corn starch <sup>2)</sup>	methanol	—	26.2%
3	glycerin	methanol	92.0%	78.0%
4	propylene glycol	acetonitrile	97.8%	88.6%
5	polyethylene glycol 400	acetonitrile	98.2%	90.1%

<sup>1)</sup>Percentage based on a theoretical amount (240 µg/g)

<sup>2)</sup>Polysorb 85/70/00™, ROQUETTE AMERICA, Inc.

#### Example 1

One hundred (100) parts by weight of gelatin (type A, high bloom, SKW Biosystems #195F) and 35 parts by weight of a plasticizer shown in Table 2 were mixed in water and dried to give gelatin piece. Compound 1 was dissolved in medium chain fatty acid triglyceride (USP/NF grade) to give a liquid mixture comprising 60 µg/g of the compound. 0.5 g of the liquid mixture and 0.5 g of each gelatin piece were put together in a sealed container and kept at 40° C. for 21 days. Then, the concentration of compound 1 contained in the liquid mixture was determined in the same manner as Reference Example 1. Results are shown in Table 2:

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TABLE 2

Stability data of compound 1/medium chain fatty acid triglyceride (MCT) solution (60 µg/g)		
gelatin piece		concentration
plasticizer	water content (after dried)	of compound 1 after storage <sup>1)</sup>
glycerin	23%	86.8%
sugar alcohol solution derived from corn starch <sup>2)</sup>	25%	92.0%

<sup>1)</sup>Percentage based on a theoretical amount (60 µg/g)<sup>2)</sup>Polysorb 85/70/00™, ROQUETTE AMERICA, Inc.

According to the reference example 1, in case the 15-keto-prostaglandin compound of the invention and the sugar alcohol were contacted directly, stability of the compound was significantly lowered. In contrast, in case the 15-keto-PG compound was directly contacted with a polyol such as glycerin, the stability of the compound was maintained. It has surprisingly revealed by Example 1 that the stability of the 15-keto-prostaglandin contacted with gelatin piece prepared using sugar alcohol as a plasticizer was better than that contacted with gelatin piece with glycerin as a plasticizer.

## Example 2

Sugar alcohol solution derived from corn starch in an amount shown in Table 3 was added in an appropriate amount of water, stirred and heated. Then, gelatin 100 parts by weight was added thereto to give gelatin solution. Compound 1 was dissolved in medium chain fatty acid triglyceride (USP/NF grade) to give a fill solution containing 240 µg/g of compound 1. The gelatin solution and the liquid mixture were loaded on capsule forming and filling machine to give capsule containing the fill solution therein, and the capsule was dried to give soft gelatin capsule.

The capsule was put in a sealed container and kept at 40° C. for 3 months. The concentration of compound 1 in the fill solution contained in the capsule was determined after 1, 2 and 3 months storage in the same manner as Reference Example 1.

TABLE 3

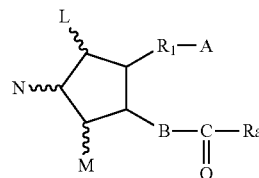
Stability of soft gelatin capsule of compound 1						
soft gelatin capsule (parts by weight)		conc. (% of Initial) 40° C.				
		1 mo	2 mo	3 mo		
gelatin	100	sugar	35	99.9%	100.3%	99.2%
		alcohol	45	—	100.5%	100.0%
		solution <sup>1)</sup>	55	—	99.3%	100.0%

<sup>1)</sup>Polysorb 85/70/00™, ROQUETTE AMERICA, Inc., derived from corn starch

The invention claimed is:

1. A soft gelatin capsule formulation of a 15-keto-prostaglandin compound, which comprises:
  - a soft gelatin capsule shell comprising gelatin and sugar alcohol as a sole plasticizer, and
  - a mixture comprising a 15-keto-prostaglandin compound and a pharmaceutically acceptable vehicle, which is filled in the shell.
2. The formulation of claim 1, wherein the 15-keto-prostaglandin compound is a compound of the formula (I):

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wherein L, M and N are hydrogen, hydroxy, halogen, lower alkyl, hydroxy(lower)alkyl, lower alkanoyloxy or oxo, wherein at least one of L and M is a group other than hydrogen, and the five-membered ring may have at least one double bond;

A is —CH<sub>3</sub>, or —CH<sub>2</sub>OH, —COCH<sub>2</sub>OH, —COOH or a functional derivative thereof;

B is —CH<sub>2</sub>—CH<sub>2</sub>—, —CH=CH— or —C≡C—;

R<sub>1</sub> is a saturated or unsaturated bivalent lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, lower alkyl, hydroxy, oxo, aryl or heterocyclic group, and at least one of carbon atom in the aliphatic hydrocarbon is optionally substituted by oxygen, nitrogen or sulfur; and

R<sub>a</sub> is a saturated or unsaturated lower or medium aliphatic hydrocarbon residue, which is unsubstituted or substituted with halogen, oxo, hydroxy, lower alkyl, lower alkoxy, lower alkanoyloxy, cyclo(lower)alkyl, cyclo(lower)alkyloxy, aryl, aryloxy, heterocyclic group or heterocycloxy group; lower alkoxy; lower alkanoyloxy; cyclo(lower)alkyl; cyclo(lower)alkyloxy; aryl; aryloxy; heterocyclic group; heterocycloxy group.

3. The formulation of claim 1, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-prostaglandin compound.

4. The formulation of claim 1, wherein the 15-keto-prostaglandin compound is a 15-keto-16-mono or 16,16-di-halogen-prostaglandin compound.

5. The formulation of claim 1, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16-mono- or 16,16-di-halogen-prostaglandin compound.

6. The formulation of claim 1, wherein the 15-keto-prostaglandin compound is a 15-keto-16-mono- or 16,16-di-fluoro-prostaglandin compound.

7. The formulation of claim 1, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16-mono- or 16,16-di-fluoro-prostaglandin compound.

8. The formulation of claim 1, wherein the 15-keto-prostaglandin compound is a 15-keto-prostaglandin E compound.

9. The formulation of claim 1, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16,16-difluoro-prostaglandin E<sub>1</sub>.

10. The formulation of claim 1, wherein the 15-keto-prostaglandin compound is a 13,14-dihydro-15-keto-16,16-difluoro-18S-methyl-prostaglandin E<sub>1</sub>.

11. The formulation of claim 1, wherein the pharmaceutically acceptable vehicle is a fatty acid ester or a polyol.

12. The formulation of claim 1, wherein the fatty acid ester is a glyceride.

13. The formulation of claim 1, wherein the sugar alcohol is selected from the group consisting of sorbitol, maltitol, sugar alcohol solution derived from corn starch, hydrogenated maltose syrup and a mixture thereof.

14. The formulation of claim 1, wherein the sugar alcohol comprises sorbitol and sorbitan as its major component.

15. A method for stabilizing a 15-keto-prostaglandin compound, which comprises: dissolving, dispersing or mixing the

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15-keto-prostaglandin in a pharmaceutically acceptable vehicle to give a liquid mixture, and incorporating the liquid mixture in a soft gelatin capsule which comprises gelatin and sugar alcohol as a sole plasticizer.

**16.** The method of claim **15**, wherein the sugar alcohol is selected from the group consisting of sorbitol, maltitol, sugar alcohol solution derived from corn starch, hydrogenated maltose syrup and a mixture thereof. 5

**17.** The method of claim **15**, wherein the sugar alcohol comprises sorbitol and sorbitan as its major component. 10

\* \* \* \* \*

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# **EXHIBIT G**



(12) **United States Patent**  
**Ueno**

(10) **Patent No.:** **US 8,748,481 B2**  
 (45) **Date of Patent:** **Jun. 10, 2014**

(54) **METHOD FOR TREATING GASTROINTESTINAL DISORDER**

(75) Inventor: **Ryuji Ueno**, Montgomery, MD (US)

(73) Assignee: **Sucampo AG**, Zug (CH)

(\* ) 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.: **11/216,012**

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

(65) **Prior Publication Data**  
 US 2006/0063830 A1 Mar. 23, 2006

**Related U.S. Application Data**

(60) Provisional application No. 60/606,521, filed on Sep. 2, 2004, provisional application No. 60/666,317, filed on Mar. 30, 2005, provisional application No. 60/666,593, filed on Mar. 31, 2005.

(51) **Int. Cl.**  
**A61K 31/352** (2006.01)

(52) **U.S. Cl.**  
 USPC ..... **514/456**; 514/892

(58) **Field of Classification Search**  
 None  
 See application file for complete search history.

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*Assistant Examiner* — Gregg Polansky  
 (74) *Attorney, Agent, or Firm* — Sughrue Mion, PLLC

(57) **ABSTRACT**

The present invention relates to a method for the long term treatment of gastrointestinal disorders in a human subject, which comprises administering an effective amount of a halogenated prostaglandin compound and/or its tautomer to the subject. The method induces substantially no electrolyte shifting during the term of the treatment. The compound used in the present invention can improve quality of life in the human subjects with gastrointestinal disorders, are similarly effective in treating male and female subjects, and also effective in a human subject aged even 65 years and older.

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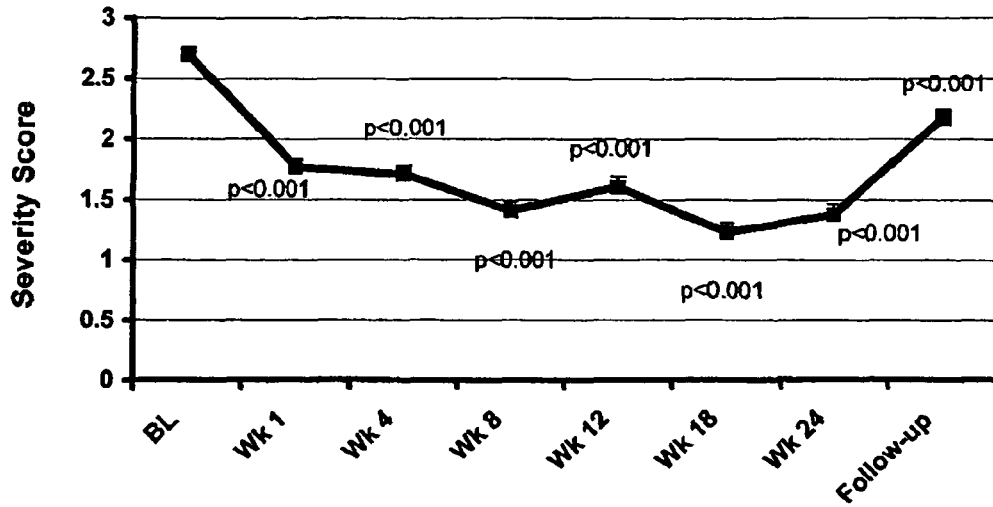
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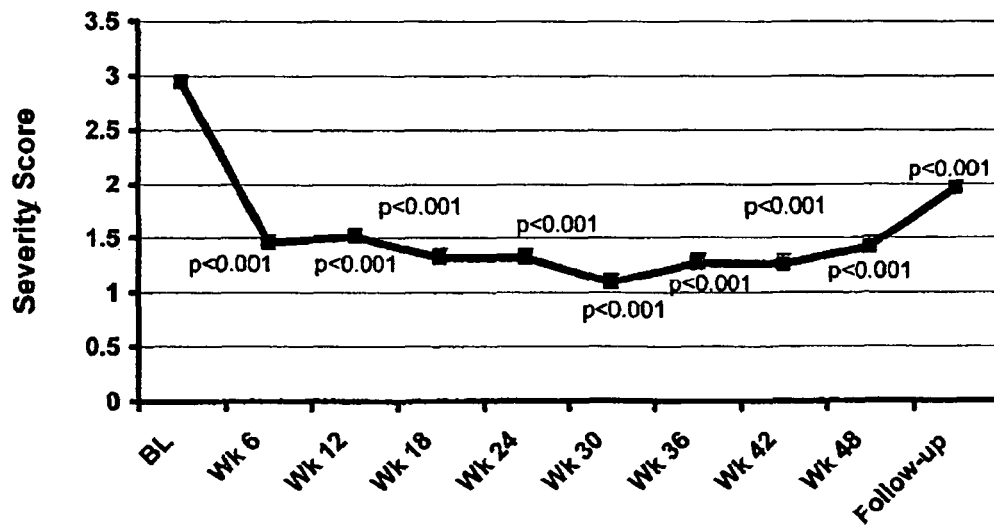
**FIG. 1**

**6 month Severity of Constipation**  
(Efficacy Evaluable Population)

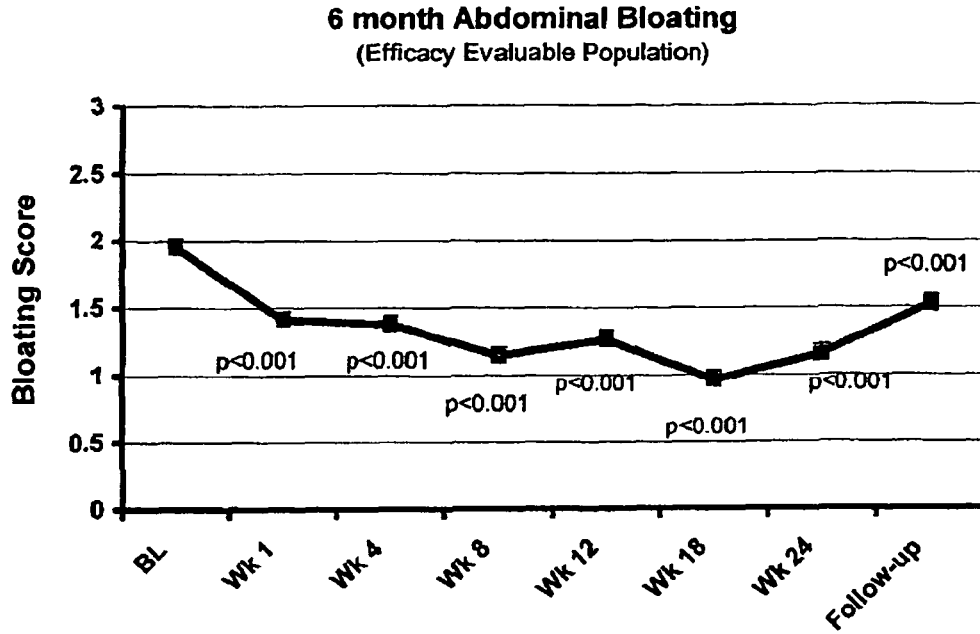


**FIG. 2**

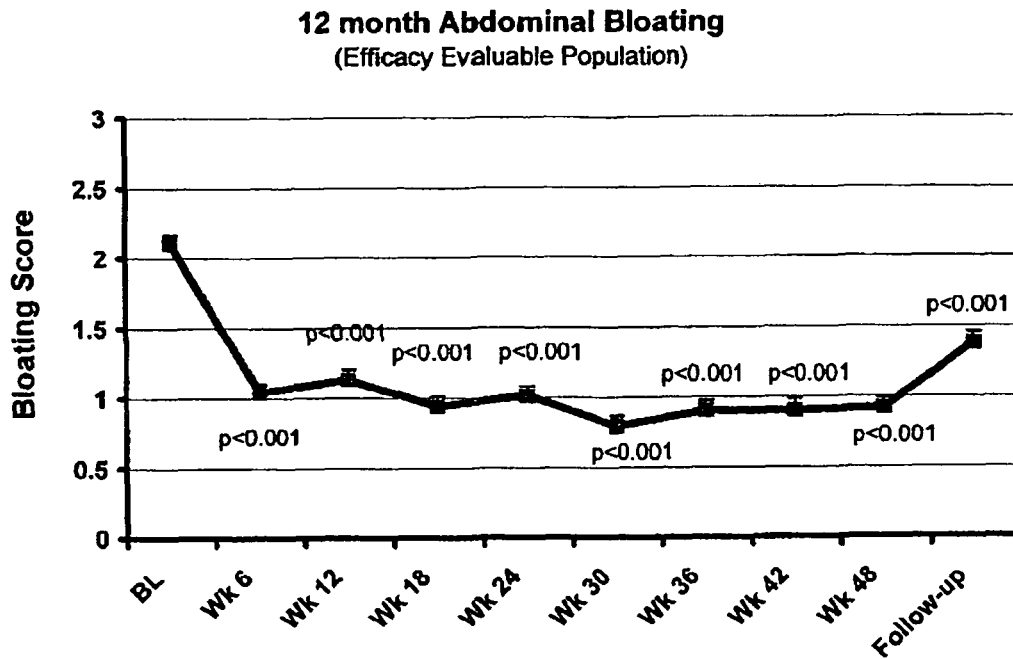
**12 month Severity of Constipation**  
(Efficacy Evaluable Population)



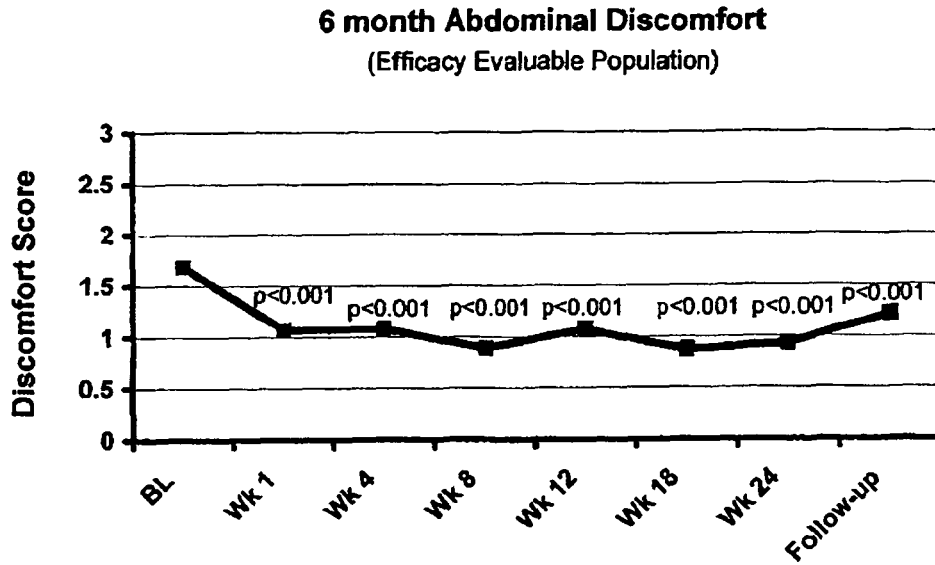
**FIG. 3**



**FIG. 4**



**FIG. 5**



**FIG. 6**

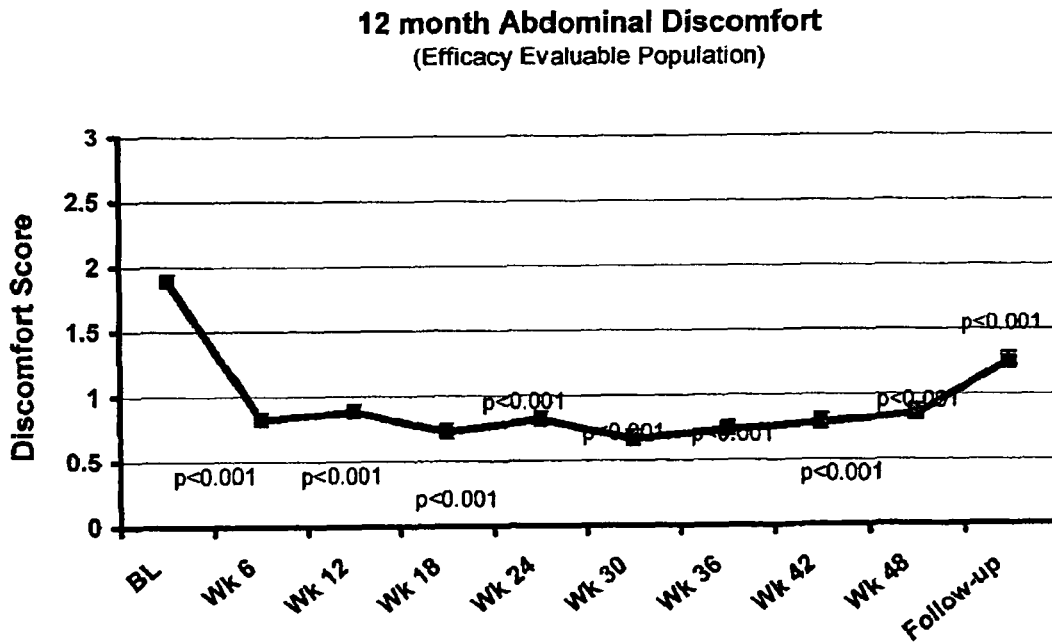


FIG. 7

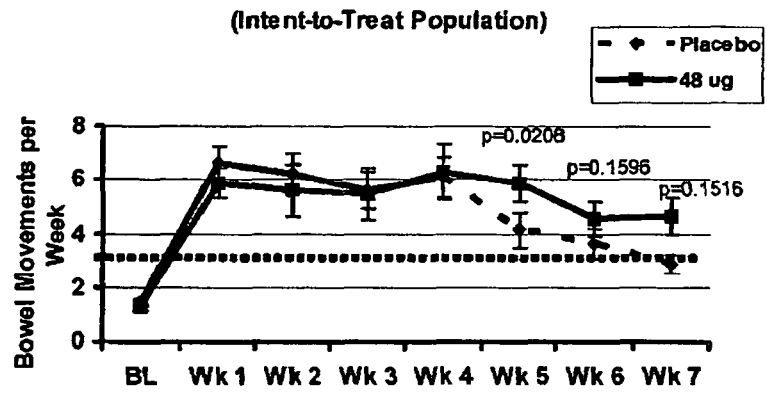


FIG. 8

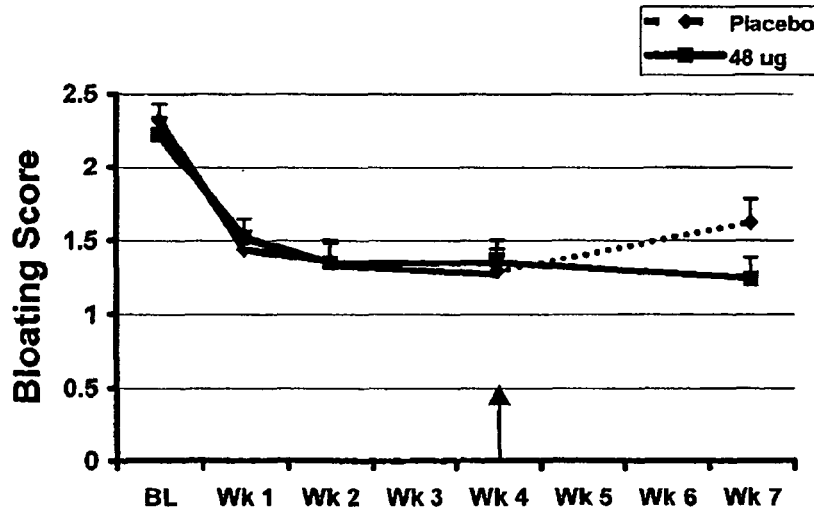




FIG. 9

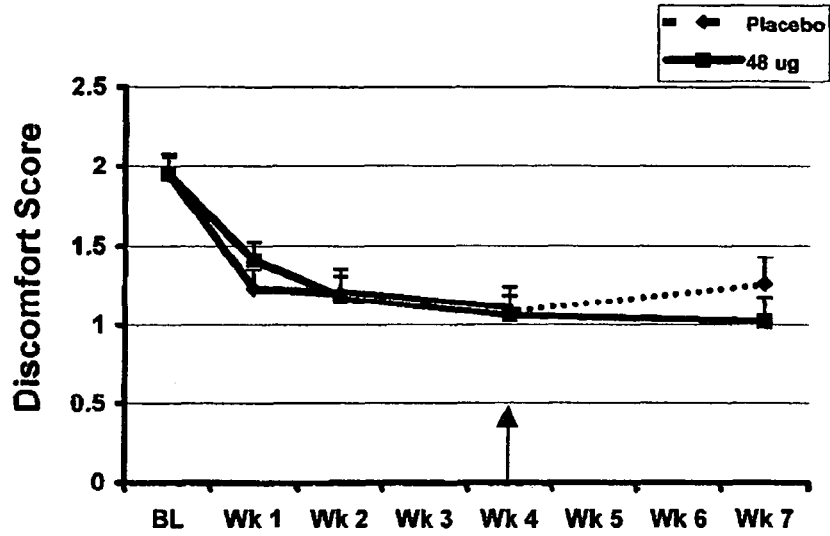


FIG. 10

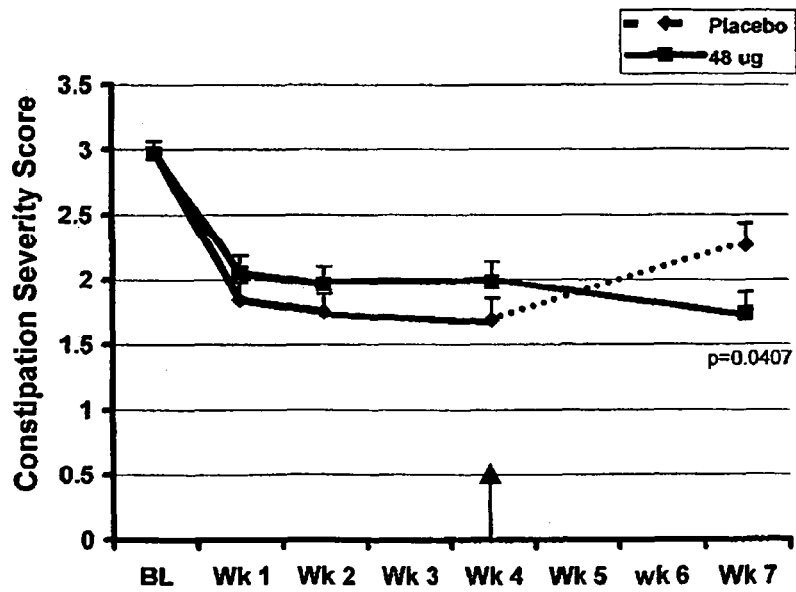


FIG. 11

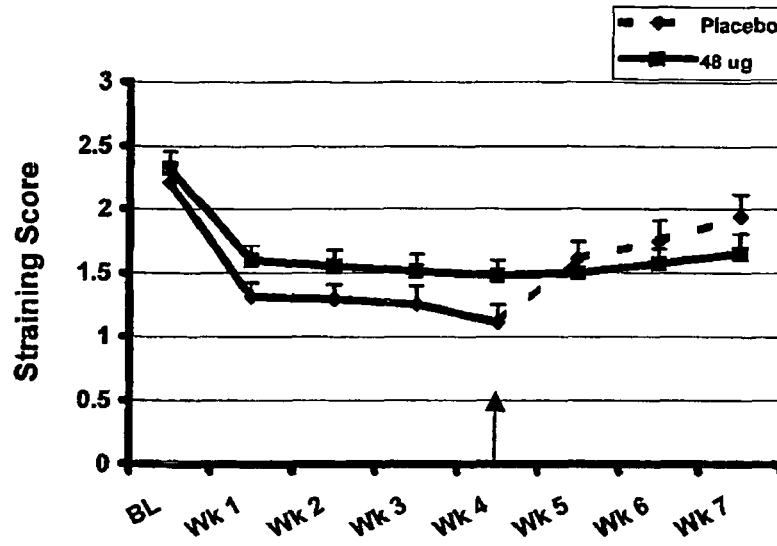
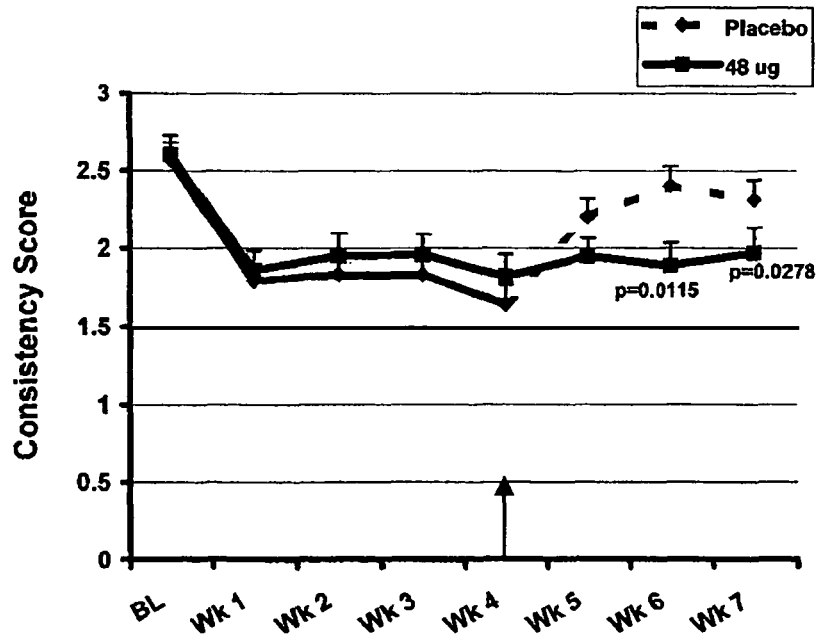
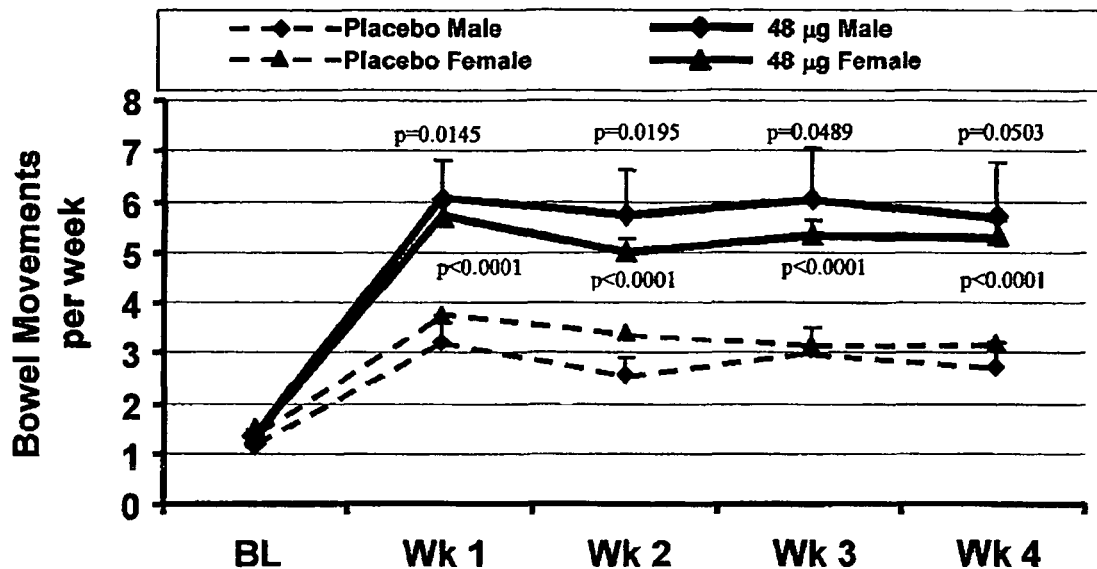


FIG. 12



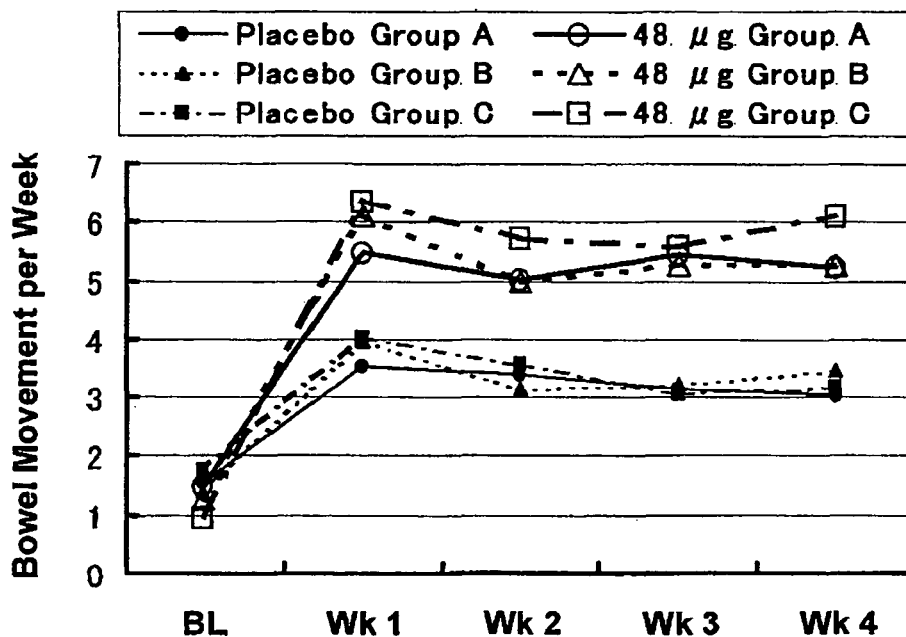
**FIG. 13**

**Effects on male vs female patients in bowel movement**



**FIG. 14**

**Effects by age in bowel movement**



Group A: 18≤Age<50, Group B: 50≤Age<65, Group C: 65≤Age

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## METHOD FOR TREATING GASTROINTESTINAL DISORDER

### CROSS REFERENCE TO RELATED APPLICATIONS

This application claims benefit from U.S. Provisional Application No. 60/606,521 filed on Sep. 2, 2004, U.S. Provisional Application No. 60/666,317 filed on Mar. 30, 2005, and U.S. Provisional Application No. 60/666,593 filed on Mar. 31, 2005 in the United States Patent and Trademark Office, the disclosures of which are incorporated herein in their entirety by reference.

### TECHNICAL FIELD

The present invention relates to a method and composition for the long-term treatment of gastrointestinal disorders in a human subject.

The present invention also relates to a method and composition for the treatment of gastrointestinal disorders in both male and female human subject.

The present invention further relates to a method and composition for the treatment of gastrointestinal disorders in a human subject aged 65 years and older.

Furthermore, the present invention relates to a method and composition for the improvement of quality of life in a human subject with gastrointestinal disorders.

### BACKGROUND ART

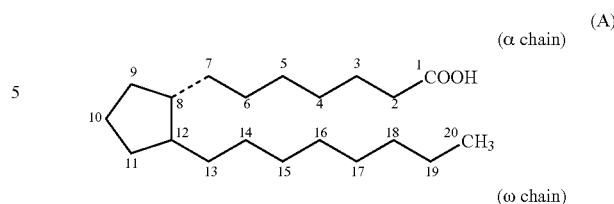
Constipation is generally defined as infrequent and difficult passage of stool. Medical reporting estimates that one of every 50 people in the United States suffers from constipation. That is, one of the most common disorders among Americans. Constipation is more likely to affect females than males and more likely to occur in older adults, showing an exponential increase after the age of 65. The actual occurrence of constipation is likely higher than reported, as many individuals suffer at home without seeking professional care.

Although in some instances constipation may be caused by obstruction, most constipation can be associated with factors such as a diet low in soluble and insoluble fibers, inadequate exercise, medication use (in particular, opiate analgesics, anticholinergic antidepressants, antihistamines, and vinca alkaloids), bowel disorders, neuromuscular disorders, metabolic disorders, poor abdominal pressure or muscular atony.

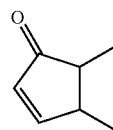
A precise quantitative definition of constipation has been difficult to establish due to the wide range of perceived "normal" bowel habits, as well as the diverse array of symptoms and signs associated with constipation. The FDA has recognized a need for prescriptive treatment of occasional constipation.

Prostaglandins (hereinafter, referred to as PGs) are members of class of organic carboxylic acids, which are contained in tissues or organs of human or other mammals, and exhibit a wide range of physiological activity. PGs found in nature (primary PGs) generally have a prostanoid acid skeleton as shown in the formula (A):

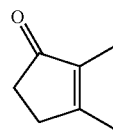
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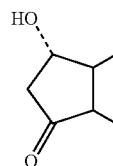
PGs are classified into several types according to the structure and substituents on the five-membered ring, for example, Prostaglandins of the A series (PGAs);



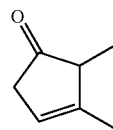
Prostaglandins of the B series (PGBs);



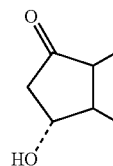
Prostaglandins of the C series (PGCs);



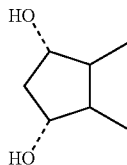
Prostaglandins of the D series (PGDs);



Prostaglandins of the E series (PGEs);



Prostaglandins of the F series (PGFs);



and the like. Further, they are classified into PG<sub>1</sub>s containing a 13,14-double bond; PG<sub>2</sub>s containing, 5,6- and 13,14-double bonds; and PG<sub>3</sub>s containing 5,6-, 13,14- and 17,18-double bonds. PGs are known to have various pharmacological and physiological activities, for example, vasodilatation, inducing of inflammation, platelet aggregation, stimulating uterine muscle, stimulating intestinal muscle, anti-ulcer effect and the like. The major prostaglandins produced in the human gastrointestinal (GI) system are those of the E, I and F series (Sellin, *Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, and Management*. (WB Saunders Company, 1998); Robert, *Physiology of the Gastrointestinal Tract 1407-1434* (Raven, 1981); Rampton, *Prostaglandins: Biology and Chemistry of Prostaglandins and Related Eicosanoids 323-344* (Churchill Livingstone, 1988); Hawkey, et al., *Gastroenterology*, 89: 1162-1188 (1985); Eberhart, et al., *Gastroenterology*, 109: 285-301 (1995)).

Under normal physiological conditions, endogenously produced prostaglandins play a major role in maintaining GI function, including regulation of intestinal motility and transit, and regulation of fecal consistency. (Sellin, *Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, and Management*. (WB Saunders Company, 1998); Robert, *Physiology of the Gastrointestinal Tract 1407-1434* (Raven, 1981); Rampton, *Prostaglandins: Biology and Chemistry of Prostaglandins and Related Eicosanoids 323-344* (Churchill Livingstone, 1988); Hawkey, et al., *Gastroenterology*, 89: 1162-1188 (1985); Eberhart, et al., *Gastroenterology*, 109: 285-301 (1995); Robert, *Adv Prostaglandin Thromboxane Res*, 2:507-520 (1976); Main, et al., *Postgrad Med J*, 64 Suppl 1: 3-6 (1988); Sanders, *Am J Physiol*, 247: G117 (1984); Pairet, et al., *Am J Physiol*, 250 (3 pt 1): G302-G308 (1986); Gaginella, *Textbook of Secretory Diarrhea 15-30* (Raven Press, 1990)). When administered in pharmacological doses, both PGE<sub>2</sub> and PGF<sub>2α</sub> have been shown to stimulate intestinal transit and to cause diarrhea (Robert, *Physiology of the Gastrointestinal Tract 1407-1434* (Raven, 1981); Rampton, *Prostaglandins: Biology and Chemistry of Prostaglandins and Related Eicosanoids 323-344* (Churchill Livingstone, 1988); Robert, *Adv Prostaglandin Thromboxane Res*, 2:507-520 (1976)). Furthermore, the most commonly reported side effect of misoprostol, a PGE<sub>1</sub> analogue developed for the treatment of peptic ulcer disease, is diarrhea (Monk, et al., *Drugs* 33 (1): 1-30 (1997)).

PGE or PGF can stimulate the intestines and cause intestinal contraction, but the enteropooling effect is poor. Accordingly, it is impossible to use PGEs or PGFs as cathartics because of side effects such as stomachache caused by the intestinal contraction.

Multiple mechanisms, including modifying enteric nerve responses, altering smooth muscle contraction, stimulating mucous secretion, stimulating cellular ionic (in particular electrogenic Cl<sup>-</sup> transport) and increasing intestinal fluid volume have been reported to contribute to the GI effects of prostaglandins (Robert, *Physiology of the Gastrointestinal Tract 1407-1434* (Raven, 1981); Rampton, *Prostaglandins:*

*Biology and Chemistry of Prostaglandins and Related Eicosanoids 323-344* (Churchill Livingstone, 1988); Hawkey, et al., *Gastroenterology*, 89: 1162-1188 (1985); Eberhart, et al., *Gastroenterology*, 109: 285-301 (1995); Robert, *Adv Prostaglandin Thromboxane Res*, 2:507-520 (1976); Main, et al., *Postgrad Med J*, 64 Suppl 1: 3-6 (1988); Sanders, *Am J Physiol*, 247: G117 (1984); Pairet, et al., *Am J Physiol*, 250 (3 pt 1): G302-G308 (1986); Gaginella, *Textbook of Secretory Diarrhea 15-30* (Raven Press, 1990); Federal Register Vol. 50, No. 10 (GPO,1985); Pierce, et al., *Gastroenterology* 60 (1): 22-32 (1971); Beubler, et al., *Gastroenterology*, 90: 1972 (1986); Clarke, et al., *Am J Physiol* 259: G62 (1990); Hunt, et al., *J Vet Pharmacol Ther*, 8 (2): 165-173 (1985); Dajani, et al., *Eur J Pharmacol*, 34(1): 105-113 (1975); Sellin, *Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, and Management 1451-1471* (WB Saunders Company, 1998)). Prostaglandins have additionally been shown to have cytoprotective effects (Sellin, *Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, and Management*. (WB Saunders Company, 1998); Robert, *Physiology of the Gastrointestinal Tract 1407-1434* (Raven, 1981); Robert, *Adv Prostaglandin Thromboxane Res 2:507-520* (1976); Wallace, et al., *Aliment Pharmacol Ther* 9: 227-235 (1995)).

U.S. Pat. No. 5,317,032 to Ueno et al. describes prostaglandin analog cathartics, including the existence of bicyclic tautomers of the same and U.S. Pat. No. 6,414,016 to Ueno describes bicyclic tautomers of a prostaglandin analog as having pronounced activity as anti-constipation agents. The bicyclic tautomers of a prostaglandin analog, which is substituted at the C-16 position by one or more halogen atoms, especially fluorine atoms, can be employed in small doses for relieving constipation.

U.S. Patent publication No. 2003/0130352 to Ueno et al. describes that prostaglandin compound opens and activates chloride channels, especially ClC channels, more especially ClC-2 channel.

U.S. Patent publication No. 2003/0119898 to Ueno et al. describes specific composition of a halogenated prostaglandin analog for the treatment and prevention of constipation.

U.S. Patent publication No. 2004/0138308 to Ueno et al. describes that a chloride channel opener, especially a prostaglandin compound can be used for the treatment of abdominal discomfort, and for the treatment of functional gastrointestinal disorders such as irritable bowel syndrome and functional dyspepsia.

MiraLax™ (polyethylene Glycol 3350, NF Powder for solution) is synthetic polyglycol having an average molecular weight of 3350, and used for the treatment of occasional constipation. This product is basically used for up to two weeks. Prolonged, frequent or excessive use of MiraLax™ may result in electrolyte imbalance and dependence on laxatives (MiraLax™ Package insert). MiraLax™ acts as an osmotic agent, which creates an imbalance in the lumen of the gut and draws fluid osmotically into the lumen. The increased fluid level softens the stool and promotes bowel movements.

Likewise, the aforesaid ClC-2 chloride channel activators are believed to function by stimulating chloride secretion into the lumen of the gut, which draws water through an osmotic mechanism into the lumen that, in turn, promotes bowel movements. Given that a specific prostaglandin compound is an ion channel activator and is believed to work essentially in an osmotic manner, like MiraLax™, one would expect that long term use of said prostaglandin compound would also have the disadvantages found in MiraLax™. Therefore, its use would be limited practically to a couple of weeks, just like MiraLax™.

Zelnorm® (tegaserod maleate) is indicated for the short-term treatment of women with irritable bowel syndrome (IBS), whose primary bowel symptom is constipation. In two

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randomized, placebo-controlled, double-blind studies enrolling 288 males, there were no significant differences between placebo and Zelnorm® response rates. The safety and effectiveness of Zelnorm® in men with IBS with constipation has not been established. In addition, Subgroup analyses of patients aged 65 years and older showed no significant treatment effect for Zelnorm® over placebo. That is, the effectiveness of Zelnorm® in patients aged 65 years and older with chronic idiopathic constipation has not been established. Further, if the patients stop taking Zelnorm®, the symptoms may return within 1 or 2 weeks. (Zelnorm® Package insert)

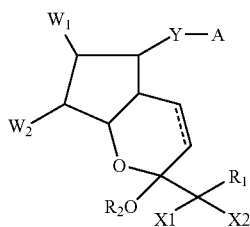
## SUMMARY OF THE INVENTION

Despite the essentially osmotic mechanism of action, however, the inventor has found surprisingly that there is no electrolyte shifting on using certain halogenated prostaglandin compounds in human patients during long term use.

The inventor has also found that halogenated prostaglandin compounds are effective in a long-term treatment and that substantially no rebound effect is seen after the discontinuation of even the long-term treatment with said compound.

Furthermore, the inventor has found that halogenated prostaglandin compounds improve the quality of life in the patients with gastrointestinal disorders and are similarly effective in treating male and female human patients, and even 65 years and older patients.

Namely, the present invention provides a method for the long term treatment of gastrointestinal disorders in a human subject, which comprises administering an effective amount of a prostaglandin compound represented by Formula (I) and/or its tautomer:



wherein  $W_1$  and  $W_2$  are



$R_3$  and  $R_4$  are hydrogen; or one of them is OH and the other is hydrogen;

$X_1$  and  $X_2$  are hydrogen, lower alkyl or halogen, provided that at least one of them is halogen;

$R_2$  is hydrogen or alkyl;

$Y$  is a saturated or unsaturated  $C_{2-10}$  hydrocarbon chain, which is unsubstituted or substituted by oxo, halogen, alkyl, hydroxy or aryl;

$A$  is  $-CH_2OH$ ,  $-COCH_2OH$ ,  $-COOH$  or its functional derivative;

$R_1$  is a saturated or unsaturated, straight chain-, branched chain- or ring-forming lower hydrocarbon, which is unsubstituted or substituted by halogen, oxo, hydroxy, lower alkyl, lower alkoxy, lower alkanoyloxy, lower cycloalkyl, lower cycloalkyloxy, aryl, or aryloxy; lower cycloalkyl; lower cycloalkyloxy; aryl; or aryloxy;

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the bond between C-13 and C-14 positions is double or single bond, and the steric configuration at C-15 position is R, S or a mixture thereof

to the subject in need thereof.

The present invention also provides a method for the treatment of gastrointestinal disorders in a male human subject, or a human subject aged 65 years and older, which comprises administering an effective amount of a prostaglandin compound represented by Formula (I) and/or its tautomer to the subject in need thereof.

The present invention further provides a method for the improvement of quality of life in a human subject with gastrointestinal disorders, which comprises administering an effective amount of a prostaglandin compound represented by Formula (I) and/or its tautomer to the subject in need thereof.

In each embodiment of the method of the present invention, total daily dose of the PG compound may preferably be 6-96  $\mu g$ .

The method of the present invention can be carried out by administering a pharmaceutical composition which comprises the above-identified prostaglandin compound and/or its tautomer to the subject to be treated. Accordingly, in another aspect of the present invention, a pharmaceutical composition for the long term treatment of gastrointestinal disorders in a human subject comprising (i) an effective amount of a prostaglandin compound represented by Formula (I) and/or its tautomer and (ii) a pharmaceutically suitable excipient is provided.

The present invention further provides a

(I) Pharmaceutical composition for the treatment of gastrointestinal disorder in both male and female patients or in a human subject aged 65 years and older, which comprises (i) an effective amount of a prostaglandin compound represented by Formula (I) and/or its tautomer and (ii) a pharmaceutically suitable excipient.

The present invention still further provides a pharmaceutical composition for the improvement of quality of life in a human subject with gastrointestinal disorders, which comprises (i) an effective amount of a prostaglandin compound represented by Formula (I) and/or its tautomer and (ii) a pharmaceutically suitable excipient.

In another aspect of the present invention, use of a prostaglandin compound represented by Formula (I) and/or its tautomer for the manufacture of a pharmaceutical composition as defined above is provided.

## BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph showing severity of constipation during the treatment for 6 months.

FIG. 2 is a graph showing severity of constipation during the treatment for 12 months.

FIG. 3 is a graph showing abdominal bloating during the treatment for 6 months.

FIG. 4 is a graph showing abdominal bloating during the treatment for 12 months.

FIG. 5 is a graph showing abdominal discomfort during the treatment for 6 months.

FIG. 6 is a graph showing abdominal discomfort during the treatment for 12 months.

FIG. 7 is a graph showing effects on bowel movements per week.

FIG. 8 is a graph showing effects on abdominal bloating.

FIG. 9 is a graph showing effects on abdominal discomfort.



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FIG. 10 is a graph showing effects on severity of Constipation.

FIG. 11 is a graph showing effects on straining.

FIG. 12 is a graph showing effects on Consistency.

FIG. 13 is a graph showing effects on male vs. female patients in bowel movement.

FIG. 14 is a graph showing effects by age in bowel movement.

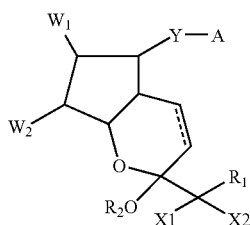
#### DETAILED DESCRIPTION OF THE INVENTION

In the present invention, the "effective amount" may be determined based on the age, body weight, conditions of the patient to be treated, desired therapeutic effect, administration route, treatment period and the like. According to the present invention, the amount of the prostaglandin compound to be administered may be 0.001-1000  $\mu\text{g}/\text{kg}$  body weight, more preferably, 0.01-100  $\mu\text{g}/\text{kg}$  body weight and most preferably, 0.1-10  $\mu\text{g}/\text{kg}$  body weight per day. The frequency of administration may be one or more times per day, preferably, two or more times per day. Typical administration amount to a patient is about 6-96  $\mu\text{g}$  per day. According to the specification and claims, the administration amount or dose is determined based on a patient having body weight of approximately 60 kg.

As used herein, the term "about" when used in conjunction with a unit of measure can be defined as  $\pm 30\%$ , preferably  $\pm 20\%$ , and especially  $\pm 10\%$ . For example, the total daily dose of about 6-96  $\mu\text{g}$  preferably means the range of 5.4-105.6  $\mu\text{g}$ . The preferred dose is in the range of about 6-72  $\mu\text{g}$ . In a more preferred embodiment, the dose is in the range of about 6-60  $\mu\text{g}$ . For example, the dose of said halogenated compound can be about 8-48  $\mu\text{g}$ .

(i) Prostaglandin Compound of Formula (I)

The instant invention utilizes a prostaglandin compound represented by formula (I):



wherein  $W_1$  and  $W_2$  are



$R_3$  and  $R_4$  are hydrogen; or one of them is OH and the other is hydrogen;

$X_1$  and  $X_2$  are hydrogen, lower alkyl or halogen, provided that at least one of them is halogen;

$R_2$  is hydrogen or alkyl;

$Y$  is a saturated or unsaturated  $C_{2-10}$  hydrocarbon chain, which is unsubstituted or substituted by oxo, halogen, alkyl, hydroxy or aryl;

$A$  is  $-\text{CH}_2\text{OH}$ ,  $-\text{COCH}_2\text{OH}$ ,  $-\text{COOH}$  or its functional derivative;

$R_1$  is a saturated or unsaturated, straight chain-, branched chain- or ring-forming lower hydrocarbon, which is unsub-

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stituted or substituted by halogen, oxo, hydroxy, lower alkyl, lower alkoxy, lower alkanoyloxy, lower cycloalkyl, lower cycloalkyloxy, aryl, or aryloxy; lower cycloalkyl; lower cycloalkyloxy; aryl; or aryloxy;

the bond between C-13 and C-14 positions is double or single bond, and

the steric configuration at C-15 position is R, S or a mixture thereof.

In the above formula, the term "halogen" is used to include fluorine, chlorine, bromine, and iodine atoms. Particularly preferable halogen atoms for  $X_1$  and  $X_2$  are fluorine atoms.

The term "unsaturated" in the definitions for  $R_1$  and  $Y$  is intended to include at least one or more double bonds and/or triple bonds that are isolatedly, separately or serially present between carbon atoms of the main and/or side chains. According to the usual nomenclature, an unsaturated bond between two serial positions is represented by denoting the lower number of the two positions, and an unsaturated bond between two distal positions is represented by denoting both of the positions.

The term "lower" throughout the specification and claims is intended to include a group having 1 to 6 carbon atoms unless otherwise specified.

The term "ring" refers to lower cycloalkyl, lower cycloalkyloxy, aryl or aryloxy.

The term "lower alkyl" refers to a straight or branched chain saturated hydrocarbon group containing 1 to 6 carbon atoms and includes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl and hexyl.

The term "lower alkoxy" refers to a group of lower alkyl-O—, wherein lower alkyl is as defined above.

The term "lower alkanoyloxy" refers to a group represented by the formula  $\text{RCO}-\text{O}-$ , wherein  $\text{RCO}-$  is an acyl group formed by oxidation of a lower alkyl group as defined above, such as acetyl.

The term "lower cycloalkyl" refers to a cyclic group formed by cyclization of a lower alkyl group as defined above but contains three or more carbon atoms, and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "lower cycloalkyloxy" refers to the group of lower cycloalkyl-O—, wherein lower cycloalkyl is as defined above.

The term "aryl" refers to unsubstituted or substituted aromatic carbocyclic or heterocyclic groups (preferably monocyclic groups), for example, phenyl, naphthyl, tolyl, xylyl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, furzanyl, pyranyl, pyridyl, pyridazyl, pyrimidyl, pyrazyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidino, piperazinyl, morpholino, indolyl, benzothienyl, quinolyl, isoquinolyl, puryl, quinazolinyl, carbazolyl, acridinyl, phenathridinyl, benzimidazolyl, benzimidazolonyl, benzothiazolyl and phenothiazinyl. Examples of substituents are halogen atom and halo (lower)alkyl, wherein halogen atom and lower alkyl are as defined above.

The term "aryloxy" refers to a group represented by the formula  $\text{ArO}-$ , wherein Ar is aryl as defined above.

The term "functional derivative" of A includes salts (preferably pharmaceutically acceptable salts), ethers, esters and amides.

Suitable "pharmaceutically acceptable salts" include conventionally used non-toxic salts, for example a salt with an inorganic base such as an alkali metal salt (such as sodium salt and potassium salt), an alkaline earth metal salt (such as calcium salt and magnesium salt), an ammonium salt; or a salt with an organic base, for example, an amine salt (such as

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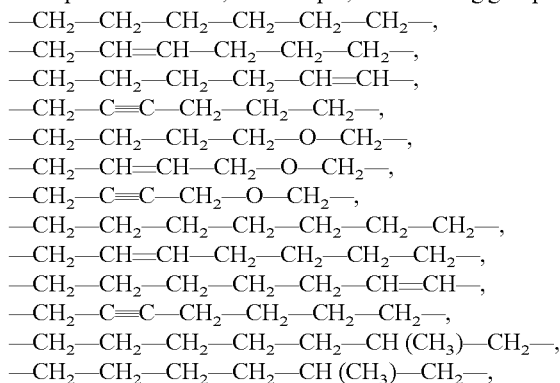
methylamine salt, dimethylamine salt, cyclohexylamine salt, benzylamine salt, piperidine salt, ethylenediamine salt, ethanolamine salt, diethanolamine salt, triethanolamine salt, tris (hydroxymethylamino)ethane salt, monomethyl-monoethanolamine salt, procaine salt and caffeine salt), a basic amino acid salt (such as arginine salt and lysine salt), tetraalkyl ammonium salt and the like. These salts may be prepared by a conventional process, for example from the corresponding acid and base or by salt interchange.

Examples of the ethers include alkyl ethers, for example, lower alkyl ethers such as methyl ether, ethyl ether, propyl ether, isopropyl ether, butyl ether, isobutyl ether, t-butyl ether, pentyl ether and 1-cyclopropyl ethyl ether; and medium or higher alkyl ethers such as octyl ether, diethylhexyl ether, lauryl ether and cetyl ether; unsaturated ethers such as oleyl ether and linolenyl ether; lower alkenyl ethers such as vinyl ether, allyl ether; lower alkynyl ethers such as ethynyl ether and propynyl ether; hydroxy(lower)alkyl ethers such as hydroxyethyl ether and hydroxyisopropyl ether; lower alkoxy (lower)alkyl ethers such as methoxymethyl ether and 1-methoxyethyl ether; optionally substituted aryl ethers such as phenyl ether, tosyl ether, t-butylphenyl ether, salicyl ether, 3,4-di-methoxyphenyl ether and benzamidophenyl ether; and aryl(lower)alkyl ethers such as benzyl ether, trityl ether and benzhydryl ether.

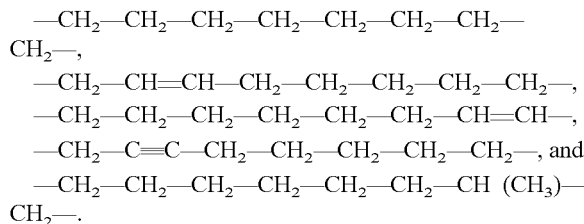
Examples of the esters include aliphatic esters, for example, lower alkyl esters such as methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester and 1-cyclopropylethyl ester; lower alkenyl esters such as vinyl ester and allyl ester; lower alkynyl esters such as ethynyl ester and propynyl ester; hydroxy(lower) alkyl ester such as hydroxyethyl ester; lower alkoxy (lower) alkyl esters such as methoxymethyl ester and 1-methoxyethyl ester; and optionally substituted aryl esters such as, for example, phenyl ester, tolyl ester, t-butylphenyl ester, salicyl ester, 3,4-di-methoxyphenyl ester and benzamidophenyl ester; and aryl(lower)alkyl ester such as benzyl ester, trityl ester and benzhydryl ester.

The amide of A means a group represented by the formula —CONR'R", wherein each of R' and R" is hydrogen, lower alkyl, aryl, alkyl- or aryl-sulfonyl, lower alkenyl and lower alkynyl, and includes for example, lower alkyl amides such as methylamide, ethylamide, dimethylamide and diethylamide; arylamides such as anilide and toluidide; and alkyl- or aryl-sulfonylamides such as methylsulfonylamide, ethylsulfonylamide and tolylsulfonylamide.

Examples of Y include, for example, the following groups:



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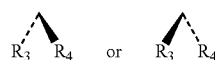
Further, at least one carbon atom in the aliphatic hydrocarbon of Y is optionally substituted by oxygen, nitrogen or sulfur.

Preferred A is —COOH or its pharmaceutically acceptable salt or ester.

Preferred X<sub>1</sub> and X<sub>2</sub> are both being halogen atoms, and more preferably, fluorine atoms.

Preferred W<sub>1</sub> is =O.

Preferred W<sub>2</sub> is



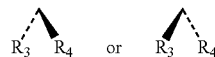
where R<sub>3</sub> and R<sub>4</sub> are both hydrogen atoms.

Preferred Y is an unsubstituted, saturated or unsaturated hydrocarbon chain having 6-8 carbon atoms.

Preferred R<sub>1</sub> is a hydrocarbon containing 1-6 carbon atoms, more preferably, 1-4 carbon atoms. R<sub>1</sub> may have one or two side chains having one carbon atom.

R<sub>2</sub> is preferably hydrogen.

Most preferred embodiment is a prostaglandin compound of formula (I) in which A is —COOH; Y is (CH<sub>2</sub>)<sub>6</sub>; W<sub>1</sub> is =O; W<sub>2</sub> is

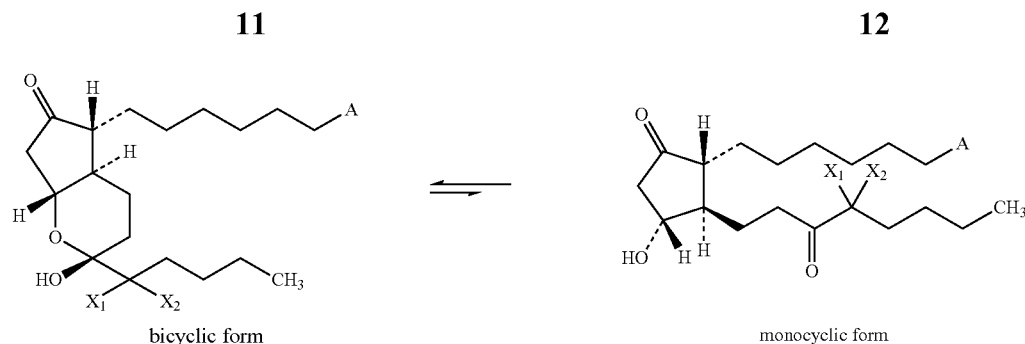


wherein R<sub>3</sub> and R<sub>4</sub> are both hydrogen; R<sub>2</sub> is hydrogen; X<sub>1</sub> and X<sub>2</sub> are fluorine; and R<sub>1</sub> is (CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub> or CH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>.

The active agent of this invention or the PG compound of formula (I) exists as a bicyclic compound in a solid state, but when dissolved in a solvent, a part of the compound forms a tautomer. In the absence of water, compound represented by formula (I) exists predominantly in the form of the bicyclic structure. In aqueous media, it is believed that hydrogen bonding occurs between the water molecule and, for example, the keto moiety at the C-15 position, thereby hindering bicyclic ring formation. In addition, it is believed that the halogen atoms at the C-16 position promote bicyclic ring formation. The tautomerism between the hydroxy at the C-11 position and the keto moiety at the C-15 position, shown below, is especially significant in the case of compounds having a 13,14 single bond and two fluorine atoms at the C-16 position.

Accordingly, the present invention may comprise isomers of the halogenated prostaglandin compounds. For example, mono-cyclic tautomers having a keto group at the C-15 position and halogen atoms at the C-16 position is shown as follows.

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A preferred compound according to the invention in its monocyclic form can be named as 13,14-dihydro-15-keto-16,16-difluoro-PGE<sub>1</sub>, according to conventional prostaglandin nomenclature.

(ii) The Pharmaceutically Suitable Excipient

According to the invention, the pharmaceutical composition may be formulated in any form. The pharmaceutically suitable excipient may be, therefore, selected depending on the desired form of the composition. According to the invention, "pharmaceutically suitable excipient" means an inert substance, which is combined with the active ingredient of the invention and suitable for preparing the desired form.

For example, a solid composition for oral administration of the present invention may include tablets, preparations, granules and the like. In such a solid composition, one or more active ingredients may be mixed with at least one inactive diluent, for example, lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinyl pyrrolidone, magnesium aluminate metasilicate and the like. According to the usual work-up, the composition may contain additives other than inactive diluent, for example, lubricant such as magnesium stearate; disintegrant such as fibrous calcium gluconate; stabilizer such as cyclodextrin, for example,  $\alpha$ , $\beta$ - or  $\gamma$ -cyclodextrin; etherified cyclodextrin such as dimethyl- $\alpha$ -, dimethyl- $\beta$ -, trimethyl- $\beta$ -, or hydroxypropyl- $\beta$ -cyclodextrin; branched cyclodextrin such as glucosyl-, maltosyl-cyclodextrin; formylated cyclodextrin, cyclodextrin containing sulfur; phospholipid and the like. When the above cyclodextrins are used, inclusion compound with cyclodextrins may be sometimes formed to enhance stability. Alternatively, phospholipid may be sometimes used to form liposome, resulting in enhanced stability.

Tablets or pills may be coated with film soluble in the stomach or intestine such as sugar, gelatin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose phthalate as needed. Further, they may be formed as capsules with absorbable substances such as gelatins. Preferably, the composition is formulated in a soft gelatin capsule with liquid contents of the halogenated prostaglandin compound and a medium chain fatty acid triglyceride. Examples of the medium chain fatty acid triglyceride used in the present invention include a triglyceride of a saturated or unsaturated fatty acid having 6-14 carbon atoms which may have a branched chain. A preferred fatty acid is a straight chain saturated fatty acid, for example caproic acid (C6), caprylic acid (C8), capric acid (C10), lauric acid (C12) and myristic acid (C14). In addition, two or more medium chain fatty acid triglycerides may be used in combination. Further suitable excipients are disclosed in the published PCT application WO 01/27099.

A liquid composition for oral administration may be in the form of emulsion, solution, suspension, syrup or elixir comprising a generally used inactive diluent. Such composition may contain, in addition to the inactive diluent, additives such

as lubricants, sweetening agents, flavoring agents, preservatives, solubilizers, anti-oxidants and the like. The additives may be selected from those described in any general textbooks in the pharmaceutical field. Such liquid compositions may be directly enclosed in soft capsules. The composition of the present invention may be suppository, enema or the like. They may be in the form of, for example, sterile aqueous or non-aqueous solution, suspension, emulsion, and the like. Examples of the excipients for the aqueous solution, suspension or emulsion may include, for example, distilled water, physiological saline and Ringer's solution.

Examples of excipients for non-aqueous solution, suspension or emulsion may include, for example, propylene glycol, polyethylene glycol, fatty acid triglyceride, vegetable oil such as olive oil, alcohols such as ethanol, polysorbate and the like. Such composition may contain additives such as preservatives, wetting agent, emulsifier, dispersant, anti-oxidants and the like.

According to the present invention, the pharmaceutical composition may be either for parenteral or oral administration and an orally applicable composition is preferred. In an example, the active ingredient is preferably dissolved medium chain fatty acid triglyceride and filled in a capsule.

According to the method of the invention, the composition of the present invention can be administered systemically or locally by means of oral or parenteral administration, including parenteral administration using suppository, enema and the like. The composition of the present invention may be administered once to several times per day.

Preferably, the total daily dose of the prostaglandin compound of the present invention is in the range of about 6-96  $\mu$ g, more preferably about 6-72  $\mu$ g, still more preferably about 6-60  $\mu$ g and especially, 8-48  $\mu$ g. The dose may vary somewhat, at the discretion of the physician, depending the age and body weight of the patient, conditions, therapeutic effect, administration route, treatment period and the like.

The term "substantially no electrolyte shifting" used herein means that electrolyte imbalance during the term of the treatment is far less than that induced by a known electrolyte imbalance inducing agent. Moreover, the term "substantially no electrolyte shifting" refers to serum electrolyte levels in a treated patient that are within clinically normal ranges as they would be understood by the clinician. As described above, MiraLax™, that is used for the treatment of constipation may induce electrolyte imbalance, which can result in, among other things, dangerous cardiac problems. On the other hand, as shown in the following example, the prostaglandin compound used in the instant invention induces substantially no electrolyte shifting even if it is administered for long term.

The following examples also show that the pharmaceutical composition of the present invention induces substantially no rebound constipation or the other disadvantage after stopping the prolonged treatment with the composition. Accordingly, it

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can be resulted in that the composition of the present invention is useful for long term treatment.

Furthermore, the assessment of quality of life in both constipation and IBS patients observed that the present compounds improved the quality of life in the patients.

According to the present invention, the present compounds are useful for the long-term treatment of gastrointestinal disorders. It is similarly effective in treating male and female patients. In addition it is useful in treating a patient aged 65 years and older.

The "gastrointestinal disorders" used herein include for example, but not limited to, acute or chronic constipation, functional gastrointestinal disorders such as irritable bowel syndrome and functional dyspepsia, gastric ulcer, large or small intestinal ulcer and abdominal discomfort.

Included in the types of constipation to be treated, although not particularly limited, are functional constipation such as relaxing constipation, spastic constipation, rectal constipation and post operative ileus; organic constipation caused by intestinal diseases and stenosis due to postoperative adhesion; and constipation induced by a drug such as opioid.

In addition to relieving or preventing constipation, the present composition may be used for preventing a patient with hernia or cardiovascular diseases from straining at stool, or for softening feces of a patient with anorectal diseases. Moreover, the present composition may be used for cleansing the gastrointestinal tract in preparation for endoscopic examination or for diagnostic or surgical procedures such as colonoscopy, barium enema X-rays and intravenous pyelography, and emergency procedures such as emergency gastrointestinal flush for poison removal and the like. Accordingly the invention covers embodiments wherein the composition of the present invention is used for cleansing the gastrointestinal tract in a human male subject or a human subject aged 65 years and older in need thereof.

The term "treatment" used herein includes any means of control such as prevention, care, relief of symptoms, attenuation of symptoms and arrest of progression. The term "long term treatment" used herein means administering the compound for at least two weeks. The compound may be administered everyday for the whole term of the treatment or with an interval of one to several days. In a particular embodiment of

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another particular embodiment, the prostaglandin compound is administered for at least 6 months.

The further details of the present invention will follow with reference to test examples, which, however, are not intended to limit the present invention.

#### Example 1

##### (Method)

Multi-center, open-label study was performed to evaluate the safety of 48 µg of Compound A (13,14-dihydro-15-keto-16,16-difluoro-PGE<sub>1</sub>) (24 µg of Compound A b.i.d) when administered daily for 24 weeks (6 months) or 48 weeks (12 months) to subjects with occasional constipation. Patients who demonstrated history of chronic constipation for at least 3 months (having less than three SBMs per week) and at least one associated symptom such as hard stools, incomplete evacuation, straining were enrolled. After 14-day drug-free washout period, they received 48 µg of Compound A (24 µg of Compound A b.i.d) orally for 48 weeks.

In this study, the following parameters were evaluated.

##### 1) Electrolyte Balance

Sodium, potassium, chloride, calcium, magnesium and phosphorus ion concentrations in serum of patients (n=299) were measured before, and at 6, 12, 18, 24, 30, 36, 48 and 50 weeks after the start of the Compound A treatment.

The laboratory standard values for the panel of electrolytes were taken from the normal reference ranges for the central laboratory.

##### 2) Severity of Constipation, 3) Abdominal Bloating and 4) Abdominal Discomfort

Each parameter (Severity of Constipation, Abdominal bloating or Abdominal discomfort) was evaluated on the scale of: 0 (absent), 1 (mild), 2 (moderate), 3 (severe) and 4 (very severe) in the patients during 6 months (n=246) or 12 months (n=304) treatments.

##### (Results)

##### 1) Electrolyte Balance

As shown in Table 1, treatment with compound A had no effect on sodium, potassium, chloride, calcium, magnesium and phosphorus ion concentration in serum of the patients. The results demonstrate that Compound A does not induce substantial shift of electrolyte over long-term administration.

TABLE 1

Mean Serum Chemistry Results						
Week	Sodium (mmol/L)	Potassium (mmol/L)	Chloride (mmol/L)	Calcium (mg/dL)	Magnesium (mg/dL)	Phosphorus (mg/dL)
0	141.00	4.28	103.08	9.61	2.18	3.65
6	142.25	4.28	103.00	9.90	2.23	3.20
12	139.78	4.20	103.08	9.71	2.24	3.57
18	141.50	4.40	105.50	9.30	2.35	3.55
24	139.21	4.19	102.56	9.77	2.21	3.61
30	136.00	4.30	100.00	9.10	2.30	2.50
36	138.94	4.18	102.51	9.67	2.19	3.58
48	139.59	4.20	102.88	9.66	2.14	3.50
50	139.11	4.49	102.67	9.47	2.31	3.54
Laboratory Standard	135-148	3.5-5.5	96-109	8.5-10.6	1.6-2.6	*

\*Female: 15-19 year 2.5-5.3 mg/dL, ≥20 year 2.5-4.5 mg/dL  
Male: 15-19 year 2.5-5.6 mg/dL, ≥20 year 2.5-4.5 mg/dL

the present invention, the prostaglandin compound is administered for at least three weeks. In another particular embodiment, the prostaglandin compound is administered for at least four weeks. In another particular embodiment, the prostaglandin compound is administered for at least 2 months. In

2) Severity of Constipation (6 and 12 months), 3) Abdominal bloating (6 and 12 months) and 4) Abdominal discomfort (6 and 12 months) were shown in FIG. 1 to FIG. 6 respectively.

As shown in FIGS. 1 to 6, Compound A is effective during the 6 months and 12 months treatment.



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Example 2

(Method)

Multi-center, double-blind, randomized, placebo-controlled study was performed to assess post-treatment response, in a portion of the total population, after four (4) weeks of active treatment (48 µg Compound A total daily dose) and three (3) weeks randomized withdrawal period. Patients who demonstrated history of chronic constipation for at least 6 months (having less than three SBMs per week) and at least one associated symptom such as hard stools, incomplete evacuation, straining were enrolled. After 14-day drug-free washout period, they received orally 48 µg (total daily dose) of Compound A for 28 days followed by either 0 or 48 µg (total daily dose) of Compound A for 21 days.

In this study, the following parameters were evaluated.

- 1) Bowel movements per week
- 2) Abdominal bloating
- 3) Abdominal discomfort
- 4) Severity of Constipation
- 5) Straining
- 6) Consistency

Each parameter (Abdominal bloating, Abdominal discomfort, Severity of Constipation or Straining) was evaluated on the scale of: 0 (absent), 1 (mild), 2 (moderate), 3 (severe) and 4 (very severe) in the patients. Consistency was evaluated on a scale of: 0 (very loose), 1 (loose), 2 (normal), 3 (hard) and 4 (very hard, little balls)

(Results)

1) Bowel movements per week, 2) Abdominal bloating, 3) Abdominal discomfort, 4) Severity of Constipation, 5) Straining and 6) Consistency were shown in FIG. 7 to FIG. 12 respectively.

As shown in FIGS. 7 to 12, substantially no rebound effect after the discontinuation of the treatment with Compound A was observed, and the efficacy of the compound A was sustained even after stopping the treatment.

This result indicates that the quality of life of the patients is improved by the administration of compound A.

Example 3

(Method)

Patients with irritable bowel syndrome (IBS) were treated with 48 µg of Compound A (24 µg of Compound A b.i.d) for 48 weeks.

In this study, we evaluated the following parameters.

- 1) Abdominal discomfort
- 2) Abdominal bloating
- 3) Severity of Constipation

Each of Abdominal discomfort and Abdominal bloating was evaluated on a scale of: 0 (absent), 1 (mild), 2 (moderate), 3 (severe) and 4 (very severe) in the patients. Severity of Constipation was evaluated on a scale of: 0 (very loose), 1: (loose), 2: (normal), 3 (hard), 4 (very hard) in the patients.

(Results)

1) Abdominal discomfort, 2) Abdominal bloating and 3) Severity of Constipation were shown in Table 2 to Table 4 respectively.

As shown in Tables 2 to 4, Compound A is effective during the 12 months treatment in IBS patients.

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TABLE 2

Analysis of Abdominal discomfort		
Week	Compound A Mean ± SD (N) Median Range	Compound A Mean ± SD (N) Median Range p-Value*
Baseline	1.95 ± 0.850 (183) 2.00 0.00-4.00	Change from Baseline
Week 12	1.16 ± 0.836 (135) 1.00 0.00-4.00	-0.79 ± 0.993 (135) -1.00 -3.00-2.00 <0.001#
Week 18	0.98 ± 0.874 (111) 1.00 0.00-3.00	-0.97 ± 1.031 (111) -1.00 -4.00-3.00 <0.001#
Week 24	1.09 ± 0.917 (107) 1.00 0.00-4.00	-0.82 ± 1.035 (107) -1.00 -4.00-3.00 <0.001#
Week 36	0.93 ± 0.799 (57) 1.00 0.00-3.00	-0.77 ± 0.926 (57) -1.00 -4.00-2.00 <0.001#
Week 48	0.87 ± 0.929 (52) 1.00 0.00-4.00	-0.81 ± 0.908 (52) -1.00 -2.00-2.00 <0.001#
End of Treatment	1.28 ± 1.020 (183) 1.00 0.00-4.00	-0.66 ± 1.112 (183) -1.00 -4.00-2.00 <0.001#
Follow-Up	1.40 ± 0.996 (121) 1.00 0.00-4.00	-0.55 ± 1.080 (121) -1.00 -4.00-2.00 <0.001#

\*P-value is from a Wilcoxon signed-rank test.

TABLE 3

Analysis of Abdominal bloating		
Week	Compound A Mean ± SD (N) Median Range	Compound A Mean ± SD (N) Median Range p-Value*
Baseline	2.23 ± 0.927 (183) 2.00 0.00-4.00	Change from Baseline
Week 12	1.43 ± 0.919 (135) 1.00 0.00-4.00	-0.84 ± 1.045 (135) -1.00 -3.00-3.00 <0.001#
Week 18	1.19 ± 0.837 (111) 1.00 0.00-3.00	-1.07 ± 1.068 (111) -1.00 -3.00-3.00 <0.001#
Week 24	1.26 ± 0.915 (107) 1.00 0.00-4.00	-0.95 ± 1.102 (107) -1.00 -4.00-3.00 <0.001#
Week 36	1.05 ± 0.854 (57) 1.00 0.00-3.00	-1.00 ± 1.134 (57) -1.00 -4.00-2.00 <0.001#
Week 48	1.12 ± 0.832 (52) 1.00 0.00-4.00	-0.94 ± 0.802 (52) -1.00 -3.00-1.00 <0.001#
End of Treatment	1.50 ± 1.005 (183) 1.00 0.00-4.00	-0.73 ± 1.075 (183) -1.00 -4.00-2.00 <0.001#

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TABLE 3-continued

Analysis of Abdominal bloating		
Week	Compound A Mean $\pm$ SD (N) Median Range	Compound A Mean $\pm$ SD (N) Median Range p-Value*
Follow-Up	1.55 $\pm$ 0.957 (121) 2.00 0.00-4.00	-0.69 $\pm$ 1.109 (121) -1.00 -3.00-3.00 <0.001#

\*P-value is from a Wilcoxon signed-rank test.

TABLE 4

Analysis of Severity of Constipation		
Week	Compound A Mean $\pm$ SD (N) Median Range	Compound A Mean $\pm$ SD (N) Median Range p-Value*
Baseline	2.95 $\pm$ 0.751 (183) 3.00 1.00-4.00	Change from Baseline
Week 12	1.76 $\pm$ 1.003 (135) 2.00 0.00-4.00	-1.16 $\pm$ 1.099 (135) -1.00 -4.00-2.00 <0.001#
Week 18	1.33 $\pm$ 0.985 (111) 1.00 0.00-4.00	-1.59 $\pm$ 1.148 (111) -2.00 -4.00-3.00 <0.001#
Week 24	1.50 $\pm$ 0.965 (107) 1.00 0.00-4.00	-1.40 $\pm$ 1.036 (107) -1.00 -3.00-2.00 <0.001#
Week 36	1.39 $\pm$ 0.921 (57) 1.00 0.00-4.00	-1.33 $\pm$ 1.123 (57) -1.00 -4.00-2.00 <0.001#
Week 48	1.37 $\pm$ 0.894 (51) 1.00 0.00-3.00	-1.37 $\pm$ 1.095 (51) -1.00 -3.00-1.00 <0.001#
End of Treatment	1.84 $\pm$ 1.120 (183) 2.00 0.00-4.00	-1.11 $\pm$ 1.148 (183) -1.00 -4.00-2.00 <0.001#
Follow-Up	2.07 $\pm$ 0.946 (121) 2.00 0.00-4.00	-0.88 $\pm$ 1.122 (121) -1.00 -4.00-2.00 <0.001#

\*P-value is from a Wilcoxon signed-rank test.

## Example 4

## (Method)

Multi-center, parallel-group, double-blind, placebo-controlled study was performed to compare the effect of Compound A on the weekly number of spontaneous bowel movements in male and female patients. Male and female patients with occasional constipation were received 48  $\mu$ g (total daily dose) of Compound A (24  $\mu$ g of Compound A b.i.d) for 4 weeks. The bowel movements in the patient were recorded during the treatment.

## (Results)

The effect of 48  $\mu$ g of Compound A on the weekly number of spontaneous bowel movements in male vs. female patients is shown in FIG. 13.

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As shown in FIG. 13, Compound A was significantly effective for both male and female patients. There was no significant difference between the effects in male and female patients.

## Example 5

## (Method)

Multi-center, parallel-group, double-blind, placebo-controlled study was performed to compare the effect of Compound A on improving weekly number of spontaneous bowel movements among different aged patients with occasional constipation. The patients were received 48  $\mu$ g (total daily dose) of Compound A (24  $\mu$ g of Compound A b.i.d) for 4 weeks. The bowel movements in the patient were recorded during the treatment.

## (Results)

The result is shown in FIG. 14. As shown in FIG. 14, Compound A was significantly effective in all aged groups, and even 65 years and older patients.

## Example 6

## (Method)

A 48-week multi-center study was performed to assess the safety and efficacy of 48  $\mu$ g (total daily dose) of Compound A to subjects with occasional constipation. Patients who demonstrated history of constipation for at least 3 months (having less than three SBMs per week) and at least one associated symptom such as hard stools, incomplete evacuation, straining were enrolled. After 14-day drug-free washout period, they received orally 48  $\mu$ g of Compound A (24  $\mu$ g of Compound 1, b.i.d) daily for 48 weeks.

The subjects completed the Medical Outcomes Study (MOS) 36-item short form (SF-36), i.e., a conventionally used QOL assessment form, at enrollment (baseline) and end of treatment (Week 48). Components of the MOS SF-36 (Med Care 30(6),473-483, 1992) are outlined below:

Physical component: Physical Function; Role-Physical, Bodily Pain and General Health

Mental component: Vitality, Social Function, Role-Emotional and Mental Health

Each of the 8 components was scored within the guidelines of the publisher, including the publisher's guidelines for imputing missing variables. The change from baseline in each of the 8 component scores at the end of treatment (Week 48) were recorded and evaluated with paired t-tests.

## (Results)

As shown in Table 5, for each of the 8 component scores, the mean baseline score was between 47 and 52, indicating that the subject population was generally healthy. The mean change from baseline for each component score at Week 48 represented a small increase, which is indicative of an improvement in the respective categories. Improvements that were significantly different from zero were observed at Week 48 for the components of Physical Function, Role-Physical, Bodily Pain, General Health, Vitality, Social Function and Mental Health. The results indicate that Compound A improves the QOL of the patients.

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TABLE 5

Summary of SF36 results								
Component/Scale Score								
	Physical Function	Role-Physical	Bodily Pain	General Health	Vitality	Social Function	Role-Emotional	Mental Health
<b>Baseline</b>								
N	320	320	319	319	319	320	319	319
Mean	49.04	49.75	47.53	51.52	50.61	50.12	49.52	50.60
(Std)	9.817	9.457	9.765	9.069	9.940	9.778	9.973	9.829
<b>Week 48<sup>a)</sup></b>								
N	153	153	151	151	151	152	151	151
Mean <sup>b)</sup>	2.48**	1.95**	3.38**	1.47*	2.89**	2.22**	1.22	1.97**
(Std)	8.431	7.403	9.883	7.827	9.163	8.973	9.560	9.201

<sup>a)</sup>Values represented at Week 48 are for the changes from baseline.<sup>b)</sup>\*p < 0.05, \*\*p < 0.01 (paired T-tests.)

## Example 7

## (Method)

A 12-week, double-blind, randomized study was performed to assess the safety and efficacy of oral 16 µg, 32 µg and 48 µg (total daily dose) of compound A to subjects with irritable bowel syndrome (IBS).

The patients answered the IBS QOL questionnaire at baseline, at week 4, Week 12 and at the end of study, and Questionnaire results were scored according to the IBS QOL User's Manual (A Quality of Life Measure for Persons with Irritable Bowel Syndrome (IBS-QOL): User's Manual and Scoring Diskette for United States Version. Seattle, Wash.: University of Washington; 1997). Scaled scores were used for

all analyses, and scores were calculated according to the User's Manual as follows:

$$\text{Scaled Score} = \left( \frac{\text{Sum of IBS-QOL items} - \text{lowest possible score}}{\text{Possible raw score range}} \right) \times 100$$

Changes from baseline at week 4, week 12 and at the End of Study were assessed for the mean overall score and for the mean domain scores (dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual, and relationship).

A summary of mean change from baseline in IBS-QOL scores analyzed without LOCF (Last observation carried forward) is shown in Table 6 to Table 8.

These data indicated that the change from baseline was significantly different from Zero in all groups. In general, the 16 µg of compound A group showed the greatest improvement from baseline of all the groups in every specific area and for QOL overall.

TABLE 6

Summary of change from Baseline in IBS QOL (16 µg)									
Component/Scaled Score									
	QOL Overall	Dysphoria	Interference with Activity	Body Image	Health Worry	Food Avoidance	Social Reaction	Sexual	Relationship
<b>Baseline</b>									
N	51	51	51	51	51	51	51	51	51
Mean	55.66	53.19	65.82	41.42	37.74	46.08	63.97	64.95	67.81
(Std)	21.165	27.333	22.544	22.877	23.113	30.016	24.546	33.913	25.387
<b>Week 4</b>									
N	45	45	45	45	45	45	45	45	45
Mean	14.7**	17.85**	10.87**	16.39**	22.41**	13.89**	11.94**	13.33**	10.74**
(Std)	14.842	18.483	14.899	19.867	20.241	22.332	19.439	25.057	17.463
<b>Week 12</b>									
N	42	42	42	42	42	42	42	42	42
Mean	18.54**	23.51**	13.95**	22.32**	23.81**	15.28**	14.58**	16.67**	15.47**
(Std)	17.698	20.949	18.392	21.701	22.129	26.792	21.548	29.82	21.897
<b>End of Study</b>									
N	49	49	49	49	49	49	49	49	49
Mean	16.82**	21.62**	11.95**	20.41**	21.94**	13.95**	13.78**	14.03**	14.28**
(Std)	17.145	20.451	18.348	21.491	21.562	25.762	20.57	28.485	20.692



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TABLE 7

Summary of change from Baseline in IBS QOL (32 µg)									
Component/Scale Score									
	QOL Overall	Dysphoria	Interference with Activity	Body Image	Health Worry	Food Avoidance	Social Reaction	Sexual	Relationship
<b>Baseline</b>									
N	49	49	49	49	49	49	49	49	49
Mean	60.14	59.69	69.82	43.37	44.38	52.21	66.84	68.62	70.23
(Std)	22.05	24.79	23.385	24.387	24.672	32.175	28.562	31.367	23.385
<b>Week 4</b>									
N	36	36	36	36	36	36	36	36	36
Mean	11.25**	14.58**	7.04*	15.28**	16.9**	8.33*	9.9**	8.68**	7.64*
(Std)	16.277	20.39	17.753	18.264	17.534	23.988	16.46	18.131	18.831
<b>Week 12</b>									
N	33	33	33	33	33	33	33	33	33
Mean	13.08**	15.25**	9.42**	17.99**	19.44**	11.36**	10.8**	10.98**	9.09*
(Std)	13.527	15.285	18.052	15.21	21.616	23.46	14.173	18.424	20.87
<b>End of Study</b>									
N	44	44	44	44	44	44	44	44	44
Mean	12.58**	14.77**	8.2**	17.47**	17.61**	10.79**	11.08**	10.23**	10.79**
(Std)	12.621	14.429	16.726	15.344	22.317	21.906	14.32	16.894	20.139

TABLE 8

Summary of change from Baseline in IBS QOL (48 µg)									
Component/Scaled Score									
	QOL Overall	Dysphoria	Interference with Activity	Body Image	Health Worry	Food Avoidance	Social Reaction	Sexual	Relationship
<b>Baseline</b>									
N	45	45	45	45	45	45	45	45	45
Mean	59.85	56.81	68.25	45.69	44.07	50.37	66.81	71.94	75.18
(Std)	21.664	26.802	23.396	21.396	23.274	31.927	27.074	30.404	22.365
<b>Week 4</b>									
N	34	34	34	34	34	34	34	34	34
Mean	12.43**	17.28**	9.14**	13.24**	19.61**	12.01**	8.82**	8.46**	6.87**
(Std)	11.619	16.842	14.477	13.568	18.562	19.59	14.028	15.607	12.558
<b>Week 12</b>									
N	30	30	30	30	30	30	30	30	30
Mean	14.8**	20.83**	10.95**	17.08**	23.33**	11.3**9	14.17**	5	6.95**
(Std)	13.65	18.863	15.091	18.419	18.098	22.153	21.143	18.159	12.202
<b>End of Study</b>									
N	43	43	43	43	43	43	43	43	43
Mean	11.54**	16.28**	7.97**	14.24**	17.05**	8.33**	12.06**	3.49	6.01**
(Std)	13.002	18.62	14.387	17.43	19.067	20.002	18.72	17.535	12.244

\*P &lt; 0.05,

\*\*P &lt; 0.01 (paired T-Tests)

The description of the invention is merely exemplary in nature and, thus, variations that do not depart from the gist of the invention are intended to be within the scope of the invention. Such variations are not to be regarded as a departure from the spirit and scope of the invention.

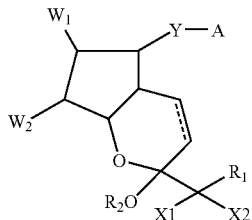
All patents and publications cited in this specification are herein incorporated by reference

What is claimed is:

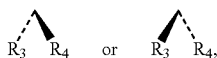
1. A method for the long term treatment of chronic constipation in a human subject, wherein the treatment comprises administering to the subject in need thereof an effective amount of a prostaglandin compound represented by Formula (I) and/or its tautomer:

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wherein  $W_1$  is =O; and  $W_2$  is



wherein  $R_3$  and  $R_4$  are hydrogen;  
 $X_1$  and  $X_2$  are halogen;  
 $R_2$  is hydrogen or alkyl;  
 $Y$  is a saturated or unsaturated  $C_{2-10}$  hydrocarbon chain;  
 $A$  is —COOH or its salt, ester or amide;  
 $R_1$  is a saturated or unsaturated, straight chain or branched chain lower hydrocarbon;  
the bond between C-13 and C-14 positions is double or single bond, and  
the steric configuration at C-15 position is R, S or a mixture thereof,  
wherein said prostaglandin compound is administered for over 4 weeks,  
wherein the treatment induces substantially no serum electrolyte shifting during the term of treatment,  
wherein the amount of said prostaglandin compound to be administered is in the range of about 6-48  $\mu\text{g}$  per day, and  
wherein the treatment improves quality of life of the subject.

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- (I) 2. The method of claim 1, wherein said prostaglandin compound is a monocyclic tautomer of formula (I).  
3. The method of claim 1, wherein the amount of said prostaglandin compound to be administered is in the range of about 6-32  $\mu\text{g}$  per day.  
5 4. The method of claim 1, wherein the amount of said prostaglandin compound to be administered is in the range of about 6-16  $\mu\text{g}$  per day.  
6. The method of claim 1, wherein the amount of said prostaglandin compound to be administered is in the range of about 8-48  $\mu\text{g}$  per day.  
10 7. The method of claim 1, wherein the prostaglandin compound is administered orally.  
8. The method of claim 1, wherein said prostaglandin compound is administered with an oil solvent as an excipient.  
15 9. The method of claim 1, wherein A is —COOH; Y is  $(\text{CH}_2)_6$ ; atoms;  $R_2$  is hydrogen atom;  $X_1$  and  $X_2$  are fluorine atoms; and  $R_1$  is  $(\text{CH}_2)_3\text{CH}_3$ .  
20 10. The method of claim 1, wherein said prostaglandin compound is administered for at least 6 months.  
11. The method of claim 1, wherein said prostaglandin compound is administered for at least 1 year.  
25 12. The method of claim 1, wherein said human subject is a male human subject.  
13. The method of claim 1, wherein said human subject is a human subject aged 65 years and older.  
30 14. The method of claim 1, wherein A is —COOH; Y is  $(\text{CH}_2)_6$ ; atoms;  $R_2$  is hydrogen atom;  $X_1$  and  $X_2$  are fluorine atoms; and  $R_1$  is  $\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$ .  
15. The method of claim 1, wherein said human subject is aged 18 years or older.  
16. The method of claim 1, wherein said prostaglandin compound is administered for at least 2 months.  
35 17. The method of claim 1, wherein the treatment improves quality of life of the subject that is confirmed by SF-36.

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