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Teijin Limited, Teijin Pharma Limited,
and Takeda Pharmaceuticals U.S.A., Inc.

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

TEIJIN LIMITED, TEIJIN PHARMA
LIMITED, and TAKEDA
PHARMACEUTICALS U.S.A., INC.,

Plaintiffs,

v.

SUNSHINE LAKE PHARMA CO., LTD. and
HEC PHARM USA INC.,

Defendants.

Civil Action No. _____

**COMPLAINT FOR
PATENT INFRINGEMENT**

(Filed Electronically)

COMPLAINT

Plaintiffs Teijin Limited (“Teijin Ltd.”), together with its subsidiary Teijin Pharma Limited (“Teijin Pharma Ltd.”) (collectively, “Teijin”), and Takeda Pharmaceuticals U.S.A., Inc. (“Takeda”) (together with Teijin, “Plaintiffs”), for their Complaint against Defendants Sunshine Lake Pharma Co., Ltd. (“Sunshine Lake”) and HEC Pharm USA Inc. (“HEC USA”) (collectively, “Defendants”), hereby allege as follows:

PARTIES

1. Plaintiff Teijin Ltd. is a Japanese corporation, having its principal place of business at 2-4, Nakanoshima 3-chome, Kita-ku, Osaka 530-8605, Japan.

2. Plaintiff Teijin Pharma Ltd. is a Japanese corporation, having its principal place of business at 2-1, Kasumigaseki 3-chome, Chiyoda-ku, Tokyo 100-8585, Japan.

3. Plaintiff Takeda is a Delaware corporation, having its principal place of business at 1 Takeda Parkway, Deerfield, Illinois 60015.

4. Upon information and belief, Sunshine Lake is a corporation organized and existing under the laws of China, having a place of business at Northern Industry Road 1#, Song Shan Lake, Dongguan, 523808 Guangdong, China.

5. Upon information and belief, HEC USA is a corporation organized and existing under the laws of the State of New Jersey, having a principal place of business at 116 Village Blvd, Suite 200, Princeton, NJ 08540.

6. Upon information and belief, Sunshine Lake is a subsidiary of HEC Pharm, a private company based in China.

7. Upon information and belief, HEC USA is a subsidiary of HEC Pharm and a corporate affiliate of Sunshine Lake.

8. Upon information and belief, Sunshine Lake, by itself and/or through, HEC USA, develops, manufactures, and/or imports generic versions of branded pharmaceutical products for sale and use throughout the United States, including in this Judicial District.

NATURE OF THE ACTION

9. This is a civil action for infringement of United States Patent Nos. 7,361,676 (“the ’676 patent”), 8,372,872 (“the ’872 patent”), and 9,107,912 (“the ’912 patent”)

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

JURISDICTION AND VENUE

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

11. This Court has personal jurisdiction over Sunshine Lake and HEC USA by virtue of, *inter alia*, the fact that Sunshine Lake and HEC USA have committed, or aided, abetted, contributed to, or participated in the commission of, the tortious act of patent infringement under 35 U.S.C. § 271(e)(2), which has led and/or will lead to foreseeable harm and injury to Plaintiffs. This Court has personal jurisdiction over Sunshine Lake and HEC USA for the additional reasons set forth below, including that HEC USA is a New Jersey corporation, and for other reasons that will be presented to the Court if jurisdiction is challenged.

12. Upon information and belief, Sunshine Lake and/or HEC USA have submitted, either directly or through an agent acting at their direction, numerous Abbreviated New Drug Applications (“ANDAs”) to the United States Food and Drug Administration (“FDA”).

13. Upon information and belief, Sunshine Lake and/or HEC USA have received numerous approvals for pharmaceutical products and sell pharmaceutical products throughout the United States, including in this Judicial District.

14. Upon information and belief, Sunshine Lake, alone and/or together with its affiliate and agent HEC USA, filed ANDA No. 213069 (“Sunshine Lake’s ANDA”) with the FDA seeking approval for their proposed oral tablets containing 40 mg and 80 mg of the active ingredient febuxostat (“Sunshine Lake’s Generic Products”).

15. Upon information and belief, Sunshine Lake and HEC USA are agents of each other, and are acting in concert with each other, with respect to formulating, manufacturing, packaging, marketing, and/or selling pharmaceutical products throughout the United States, including in the State of New Jersey, and will do the same with respect to Sunshine Lake's Generic Products that are the subject matter of Sunshine Lake's ANDA.

16. Upon information and belief, Sunshine Lake and HEC USA, in concert with each other and/or through their affiliates or agents, will market, offer for sale, and/or sell Sunshine Lake's Generic Products upon final approval of Sunshine Lake's ANDA by the FDA, with the reasonable expectation or knowledge and intent that such products will ultimately be purchased and used by consumers in the United States, including in this Judicial District.

17. This Court has personal jurisdiction over Sunshine Lake because Sunshine Lake generally and unconditionally accepted the personal jurisdiction of the courts of the State of New Jersey in Section 9 of its Offer of Confidential Access to Abbreviated New Drug Application Pursuant to 21 U.S.C. § 355(j)(5)(C)(i)(III).

18. This Court has personal jurisdiction over HEC USA because HEC USA is incorporated in the State of New Jersey. Furthermore, HEC USA has availed itself of the rights and benefits of the laws of New Jersey by engaging in systematic and continuous contacts with the State of New Jersey. This Court also has personal jurisdiction over HEC USA because HEC USA has previously affirmatively availed themselves of the jurisdiction of this Court by filing counterclaims in this district and did not contest personal jurisdiction or venue in actions brought in this Judicial District. *See, e.g., Boehringer Ingelheim Pharmaceuticals Inc., et al. v. Accord Healthcare, Inc., et al.*, 16-cv-0852; *Astrazeneca AB, et al. v. HEC Pharm Co., Ltd., et al.*, 15-

cv-6025; *Novartis AG, et al. v. HEC Pharm Co., Ltd., et al.*, 15-cv-1647; *Boehringer Ingelheim Pharmaceuticals Inc., et al. v. HEC Pharm Group, et al.*, 15-cv-5982.

19. Alternatively, should the Court find that the above facts do not establish personal jurisdiction over Sunshine Lake in this action, this Court may exercise jurisdiction over Sunshine Lake pursuant to Fed. R. Civil P. 4(k)(2) because (a) Plaintiffs' claims arise under federal law; (b) Sunshine Lake is a foreign defendant not subject to personal jurisdiction in the courts of any state; and (c) Sunshine Lake has sufficient contacts with the United States as a whole, including, but not limited to, submitting various ANDAs to the FDA and manufacturing and selling active pharmaceutical ingredients that are used in pharmaceutical products distributed throughout the United States, such that this Court's exercise of jurisdiction over Sunshine Lake satisfies due process.

20. Venue is proper in this Judicial District pursuant to 28 U.S.C. §§ 1391 and 1400(b). Specifically, venue is proper in New Jersey because HEC USA is a corporation organized and existing under the laws of the State of New Jersey, and because Sunshine Lake is not incorporated anywhere in the United States, does not have a regular and established place of business in the United States, and thus may be sued in any Judicial District.

THE PATENTS-IN-SUIT

21. On April 22, 2008, the '676 patent, titled "Solid Preparation Containing Single Crystal Form," was duly and legally issued. A copy of the '676 patent is attached as Exhibit A.

22. Teijin Ltd. is the owner of the '676 patent. Teijin Pharma Ltd. and Takeda hold exclusive licenses with respect to the '676 patent.

23. On February 12, 2013, the '872 patent, titled "Methods For Concomitant Treatment of Theophylline and Febuxostat," was duly and legally issued. A copy of the '872 patent is attached as Exhibit B.

24. Takeda is the owner of the '872 patent.

25. On August 18, 2015, the '912 patent, titled "Methods For Concomitant Treatment of Theophylline and Febuxostat," was duly and legally issued. A copy of the '912 patent is attached as Exhibit C.

26. Takeda is the owner of the '912 patent.

ACTS GIVING RISE TO THIS ACTION

27. Takeda holds New Drug Application ("NDA") No. 21-856 for oral tablets containing 40 mg or 80 mg of the active ingredient febuxostat. Takeda markets and sells these tablets in the United States under the brand name "Uloric[®]."

28. Pursuant to 21 U.S.C. § 355(b)(1), the patents-in-suit are listed in the FDA's publication titled, *Approved Drug Products with Therapeutic Equivalence Evaluations* (also known as the "Orange Book") as covering Uloric[®] or its use.

29. Upon information and belief, Defendants submitted ANDA No. 213069 to the FDA under § 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(j)). Upon information and belief, Sunshine Lake's ANDA seeks FDA approval to engage in the commercial manufacture, use, offer for sale, or sale of Sunshine Lake's Generic Products prior to the expiration of the patents-in-suit.

30. Upon information and belief, pursuant to § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act, Defendants certified in ANDA No. 213069 that the

claims of the patents-in-suit are invalid, unenforceable, or would not be infringed by the commercial manufacture, use, offer for sale, or sale of Sunshine Lake's Generic Products.

31. Plaintiffs received written notification of Sunshine Lake's ANDA and its accompanying § 505(j)(2)(A)(vii)(IV) certification by letter dated June 4, 2019 ("Sunshine Lake's Notice Letter").

32. Sunshine Lake's Notice Letter contains limited information about the crystal form or forms of the febuxostat materials for which Sunshine Lake filed ANDA No. 213069.

33. The information relating to Sunshine Lake's Generic Products provided to Plaintiffs does not demonstrate that the product Defendants are asking the FDA to approve for sale will not fall within the scope of an issued claim of the patents-in-suit.

34. This action is being commenced within 45 days of receipt of Sunshine Lake's Notice Letter.

INFRINGEMENT OF THE '676 PATENT

35. Plaintiffs re-allege paragraphs 1-34 as if fully set forth herein.

36. By seeking approval of Sunshine Lake's ANDA to engage in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States of Sunshine Lake's Generic Products prior to the expiration of the '676 patent, including filing its § 505(j)(2)(A)(vii)(IV) certification, Defendants have infringed one or more claims of the '676 patent under 35 U.S.C. § 271(e)(2)(A).

37. If Sunshine Lake manufactures, uses, offers to sell, or sells within the United States, or imports into the United States Sunshine Lake's Generic Products prior to the expiration of the '676 patent, subject to any patent term extension or exclusivity for the '676

patent to which Plaintiffs are or become entitled, Defendants will infringe one or more claims of the '676 patent under 35 U.S.C. § 271.

38. Plaintiffs are entitled to relief provided by 35 U.S.C. § 271(e)(4), including an order from this Court that the effective date of the approval of Sunshine Lake's ANDA be a date that is not earlier than the expiration date of the '676 patent, subject to any patent term extension or exclusivity for the '676 patent to which Plaintiffs are or become entitled.

39. Plaintiffs are entitled to a declaration that if Defendants commercially manufacture, use, offer for sale, or sell Sunshine Lake's Generic Products within the United States, import Sunshine Lake's Generic Products into the United States, or induce or contribute to such conduct, Defendants will infringe the '676 patent under 35 U.S.C. § 271.

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

41. Upon information and belief, Defendants were aware of the existence of the '676 patent and were aware that the filing of their ANDA and certification with respect to the '676 patent constituted an act of infringement of that patent.

INFRINGEMENT OF THE '872 and '912 PATENTS

42. Plaintiffs re-allege paragraphs 1-41 as if fully set forth herein.

43. By seeking approval of Sunshine Lake's ANDA to engage in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States of Sunshine Lake's Generic Products prior to the expiration of the '872 patent,

including filing its § 505(j)(2)(A)(vii)(IV) certification, Defendants have infringed the sole claim of the '872 patent under 35 U.S.C. § 271(e)(2)(A).

44. Takeda is entitled to relief provided by 35 U.S.C. § 271(e)(4), including an order from this Court that the effective date of the approval of Sunshine Lake's ANDA be a date that is not earlier than the expiration date of the '872 patent, subject to any patent term extension or exclusivity for the '872 patent to which Takeda is or becomes entitled.

45. By seeking approval of Sunshine Lake's ANDA to engage in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States of Sunshine Lake's Generic Products prior to the expiration of the '912 patent, including filing its § 505(j)(2)(A)(vii)(IV) certification, Defendants have infringed one or more claims of the '912 patent under 35 U.S.C. § 271(e)(2)(A).

46. Takeda is entitled to relief provided by 35 U.S.C. § 271(e)(4), including an order from this Court that the effective date of the approval of Sunshine Lake's ANDA be a date that is not earlier than the expiration date of the '912 patent, subject to any patent term extension or exclusivity for the '912 patent to which Takeda is or becomes entitled.

47. Uloric®, as of February 2009, was contraindicated for patients treated with theophylline. The prescribing information stated "CONTRAINDICATIONS. ULORIC is contraindicated in patients being treated with azathioprine, mercaptopurine, or theophylline," and "Do not take ULORIC if you: . . . take Theophylline (Theo-24®, Elixophyllin®, Theochron®, Theolair®, Uniphyll®)." Exhibit D.

48. The prescribing information for Uloric® as revised in February 2009 further stressed the contraindication. In this regard, the prescribing information stated, "*Xanthine Oxidase Substrate Drugs-Azathioprine, Mercaptopurine, and Theophylline: Febuxostat is an XO inhibitor. Drug interaction studies of ULORIC with drugs that are*

metabolized by XO (e.g., theophylline, mercaptopurine, azathioprine) have not been conducted. Inhibition of XO by ULORIC may cause increased plasma concentrations of these drugs leading to toxicity. ULORIC is contraindicated in patients being treated with azathioprine, mercaptopurine, and theophylline [*see Contraindications (4) and Drug Interactions (7)*].

...

Theophylline is a CYP1A2 and XO substrate. Although no ULORIC drug interaction study with theophylline has been conducted, concomitant administration of theophylline with allopurinol, a xanthine oxidase inhibitor at doses ≥ 600 mg per day, has been reported to increase theophylline plasma concentrations. Because ULORIC is a xanthine oxidase inhibitor and theophylline is a low therapeutic index drug, ULORIC could inhibit the XO-mediated metabolism of theophylline leading to increased plasma concentrations of theophylline that could induce severe theophylline toxicity.” Exhibit D.

49. Research leading to the ’872 patent and the ’912 patent reveals that there is no need to contraindicate co-administration of febuxostat and theophylline. Co-administration of febuxostat and theophylline can be carried out without adjusting the amount of theophylline administered for adverse drug interactions. The ’872 patent and the ’912 patent further disclose that dose adjustment of theophylline is required when it is co-administered with allopurinol.

50. As a result, Uloric[®] is no longer contraindicated for patients treated with theophylline. The prescribing information states “CONTRAINDICATIONS. ULORIC is contraindicated in patients being treated with azathioprine or mercaptopurine.” The prescribing information documents as revised in January 2011, November 2012, August 2017, February 2018, and February 2019 are attached as Exhibits E, F, G, H, and I respectively.

51. Upon information and belief, Defendants’ prescribing information provided with Sunshine Lake’s Generic Products is expected to carry the same or substantially same contraindications as quoted in paragraph 50.

52. The absence of the above-referenced contraindication in the prescribing information for Uloric[®] on Defendants’ prescribing information, aided by the fact that the use in such population was previously contraindicated, induces the practice of the invention of the ’872

patent and/or the '912 patent by a medical practitioner, a patient, or any other person to coadminister or cause the co-administration of febuxostat and theophylline without adjusting the amount of theophylline.

53. The recent and current revisions of Uloric® prescribing information contain express statements that no dose adjustment is necessary. The prescribing information states,

"Theophylline: No dose adjustment is necessary for theophylline when co-administered with ULORIC. Administration of ULORIC (80 mg once daily) with theophylline resulted in an increase of 6% in C_{max} and 6.5% in AUC of theophylline. These changes were not considered statistically significant. However, the study also showed an approximately 400-fold increase in the amount of 1-methylxanthine (one of the major theophylline metabolites) excreted in urine as a result of XO inhibition by ULORIC. The safety of long-term exposure to 1-methylxanthine has not been evaluated. This should be taken into consideration when deciding to co-administer ULORIC and theophylline.

...
ULORIC is an XO inhibitor. Based on a drug interaction study in healthy subjects, febuxostat altered the metabolism of theophylline (a substrate of XO) in humans [*see Clinical Pharmacology (12.3)*]. Therefore, use with caution when coadministering ULORIC with theophylline.

...
Xanthine Oxidase Substrate Drugs-Azathioprine, Mercaptopurine, and Theophylline: Febuxostat is an XO inhibitor. A drug-drug interaction study evaluating the effect of ULORIC upon the pharmacokinetics of theophylline (an XO substrate) in healthy subjects showed that coadministration of febuxostat with theophylline resulted in an approximately 400-fold increase in the amount of 1-methylxanthine, one of the major metabolites of theophylline, excreted in the urine. Since the long-term safety of exposure to 1-methylxanthine in humans is unknown, use with caution when coadministering febuxostat with theophylline." Exhibits E, F, G, H, and I.

54. Upon information and belief, Defendants' prescribing information to be provided with Sunshine Lake's Generic Products is expected to carry the same or substantially same affirmative statements as quoted in paragraph 53. As a result of the removal of theophylline from the contraindications and the addition of the language discussing the co-administration of Uloric® with theophylline, the prescribing information encourages the co-administration of febuxostat and theophylline without adjusting the amount of theophylline.

55. Further, the affirmative statements set forth in paragraph 53 induce the practice of the invention of the '872 patent and/or the '912 patent by a medical practitioner, a patient, or any other person to co-administer or cause the co-administration of febuxostat and theophylline without adjusting the amount of theophylline.

56. For "Dosage and Administration," the prescribing information for Uloric® states, *inter alia*, that:

"ULORIC is recommended at 40 mg or 80 mg once daily. The recommended starting dose of ULORIC is 40 mg once daily. For patients who do not achieve a serum uric acid (sUA) less than 6 mg/dL after 2 weeks with 40 mg, ULORIC 80 mg is recommended." Exhibits D, E, F, G and H. *See also* Exhibit I.

57. Upon information and belief, Defendants' prescribing information to be provided with Sunshine Lake's Generic Products is expected to carry the same or substantially same dosage and administration statements as quoted in paragraph 56.

58. Claim 1, the sole claim in the '872 patent, states, *inter alia*, that "administering to the hyperuricemic patient suffering from gout a therapeutically effective amount of febuxostat in a dose of 80 mg."

59. The affirmative statements set forth in paragraph 56 will induce the practice of the invention of the '872 patent by a medical practitioner, a patient, or any other person to increase the dosage of febuxostat to 80 mg, such as by administering one 80 mg pill, or two 40 mg pills at the same time.

60. Therefore, for the reasons alleged in paragraphs 47-59 and other reasons that may be subsequently developed, the commercial manufacture, use, offer to sell, sale, or importation of Sunshine Lake's Generic Products, if approved by the FDA, prior to the expiration of the '872 patent, subject to any patent term extension or exclusivity for the '872

patent to which Takeda or becomes entitled, would induce the infringement of the '872 patent under 35 U.S.C. § 271(b).

61. Takeda is entitled to a declaration that, if Defendants commercially manufacture, use, offer for sale, or sell Sunshine Lake's Generic Products within the United States, import Sunshine Lake's Generic Products into the United States, or induce or contribute to such conduct, Defendants will infringe the '872 patent under 35 U.S.C. § 271(b).

62. Claim 1, the sole independent claim in the '912 patent, states, *inter alia*, that "administering to a patient suffering from hyperuricemia and at least one second disease state, a therapeutically effective amount of [febuxostat] or a pharmaceutically acceptable salt thereof, wherein the subject is also receiving concomitant administration of theophylline to treat the at least one second disease state"

63. Therefore, for the reasons alleged in paragraphs 47-57 and 62 and other reasons that may be subsequently developed, the commercial manufacture, use, offer to sell, sale, or importation of Sunshine Lake's Generic Products, if approved by the FDA, prior to the expiration of the '912 patent, subject to any patent term extension or exclusivity for the '912 patent to which Takeda is or becomes entitled, would induce the infringement of the '912 patent under 35 U.S.C. § 271(b).

64. Takeda is entitled to a declaration that, if Defendants commercially manufacture, use, offer for sale, or sell Sunshine Lake's Generic Products within the United States, import Sunshine Lake's Generic Products into the United States, or induce or contribute to such conduct, Defendants will infringe the '912 patent under 35 U.S.C. § 271(b).

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

66. Upon information and belief, Defendants were aware of the existence of the '872 and '912 patents and were aware that the filing of their ANDA and certifications with respect the '872 and '912 patents constituted an act of infringement of those patents.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs pray for judgment as follows:

- A. That Defendants have infringed the '676, '872, and '912 patents;
- B. That, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of ANDA No. 213069 under § 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(j)) shall not be earlier than the expiration of the '676, '872, and '912 patents, including any applicable exclusivities or extensions to which Takeda and/or Teijin are or become entitled;
- C. That Defendants, their officers, agents, servants, and employees, and those persons in active concert or participation with any of them, be preliminarily and permanently enjoined from commercially manufacturing, using, offering to sell, selling, or importing into the United States Sunshine Lake's Generic Products and any other product that infringes or induces or contributes to the infringement of one or more claims of the '676, '872, and '912 patents prior to its expiration, including any exclusivities or extensions to which Takeda and/or Teijin are or become entitled;
- D. That Plaintiffs be awarded the attorneys' fees, costs, and expenses that they incur prosecuting this action; and

E. That Plaintiffs be awarded such other and further relief as this Court deems just and proper.

Dated: July 16, 2019

s/ Charles M. Lizza

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CERTIFICATION PURSUANT TO LOCAL CIVIL RULES 11.2 & 40.1

Pursuant to Local Civil Rules 11.2 and 40.1, I hereby certify that the matter captioned *Teijin Limited, et al. v. Alkem Laboratories Limited, et al.*, Civil Action No. 19-768-RGA (D. Del.) is related to the matter in controversy because the matter in controversy involves the same plaintiffs and the same patents, and because the defendants are seeking FDA approval to market generic versions of the same pharmaceutical product.

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: July 16, 2019

s/ Charles M. Lizza

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EXHIBIT A



US007361676B2

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

(10) **Patent No.:** **US 7,361,676 B2**
(45) **Date of Patent:** **Apr. 22, 2008**

(54) **SOLID PREPARATION CONTAINING SINGLE CRYSTAL FORM**

(75) Inventors: **Michio Iwai**, Osaka (JP); **Kazuhiro Nakamura**, Yamaguchi (JP); **Masahiko Dohi**, Tokyo (JP); **Hiroko Mochizuki**, Yamaguchi (JP); **Seiji Mochizuki**, Yamaguchi (JP)

(73) Assignee: **Teijin Limited**, Osaka (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 346 days.

(21) Appl. No.: **10/503,391**

(22) PCT Filed: **Mar. 28, 2003**

(86) PCT No.: **PCT/JP03/03962**

§ 371 (c)(1),
(2), (4) Date: **Aug. 3, 2004**

(87) PCT Pub. No.: **WO03/082279**

PCT Pub. Date: **Oct. 9, 2003**

(65) **Prior Publication Data**

US 2005/0043375 A1 Feb. 24, 2005

(30) **Foreign Application Priority Data**

Mar. 28, 2002 (JP) 2002-090889

(51) **Int. Cl.**

A61K 31/425 (2006.01)
C07D 277/00 (2006.01)

(52) **U.S. Cl.** **514/365; 548/201**

(58) **Field of Classification Search** **514/365; 548/201**
See application file for complete search history.

(56) **References Cited**

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M. Kitamura, et al., Effects of solvent composition and temperature on polymorphism and crystallization behavior of thiazole-derivative, Journal of Crystal Growth, Mar. 2002, vol. 236, No. 4, pp. 676 to 686.

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Primary Examiner—Rei-tsang Shiao

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

(57) **ABSTRACT**

There are provided a solid preparation containing a single crystal of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid, an excipient and a disintegrating agent, and a method for producing the same.

10 Claims, 5 Drawing Sheets

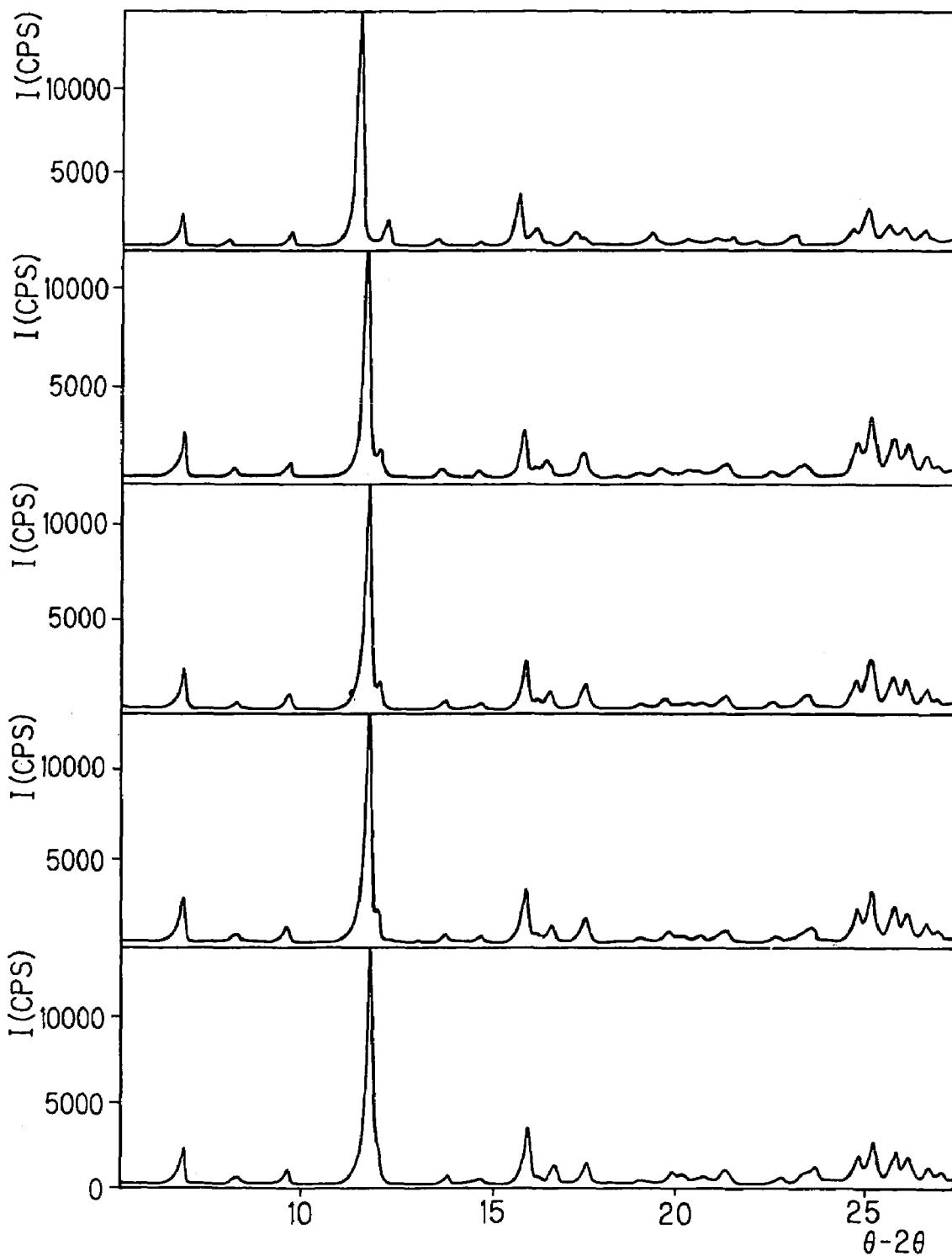
U.S. Patent

Apr. 22, 2008

Sheet 1 of 5

US 7,361,676 B2

Fig. 1



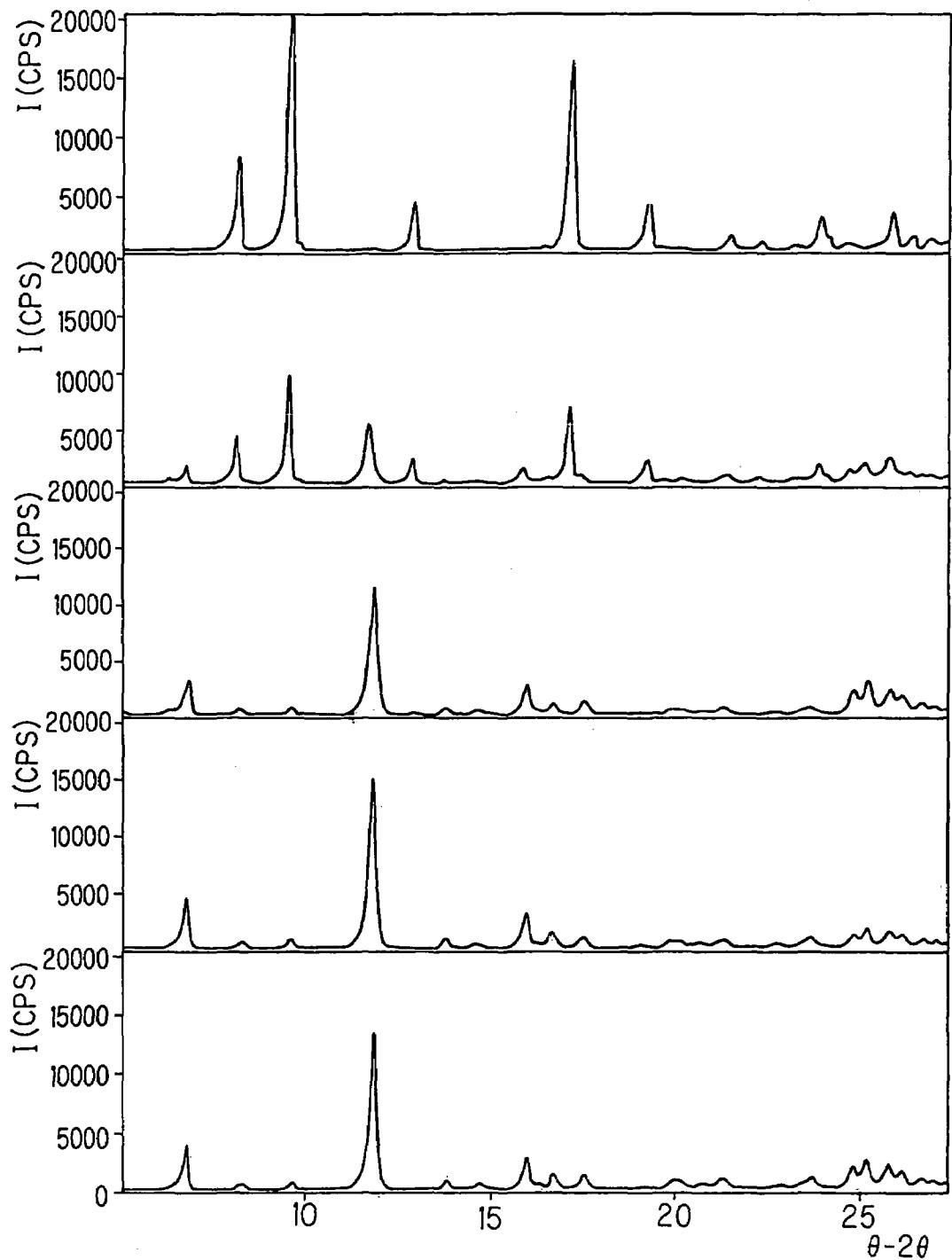
U.S. Patent

Apr. 22, 2008

Sheet 2 of 5

US 7,361,676 B2

Fig. 2



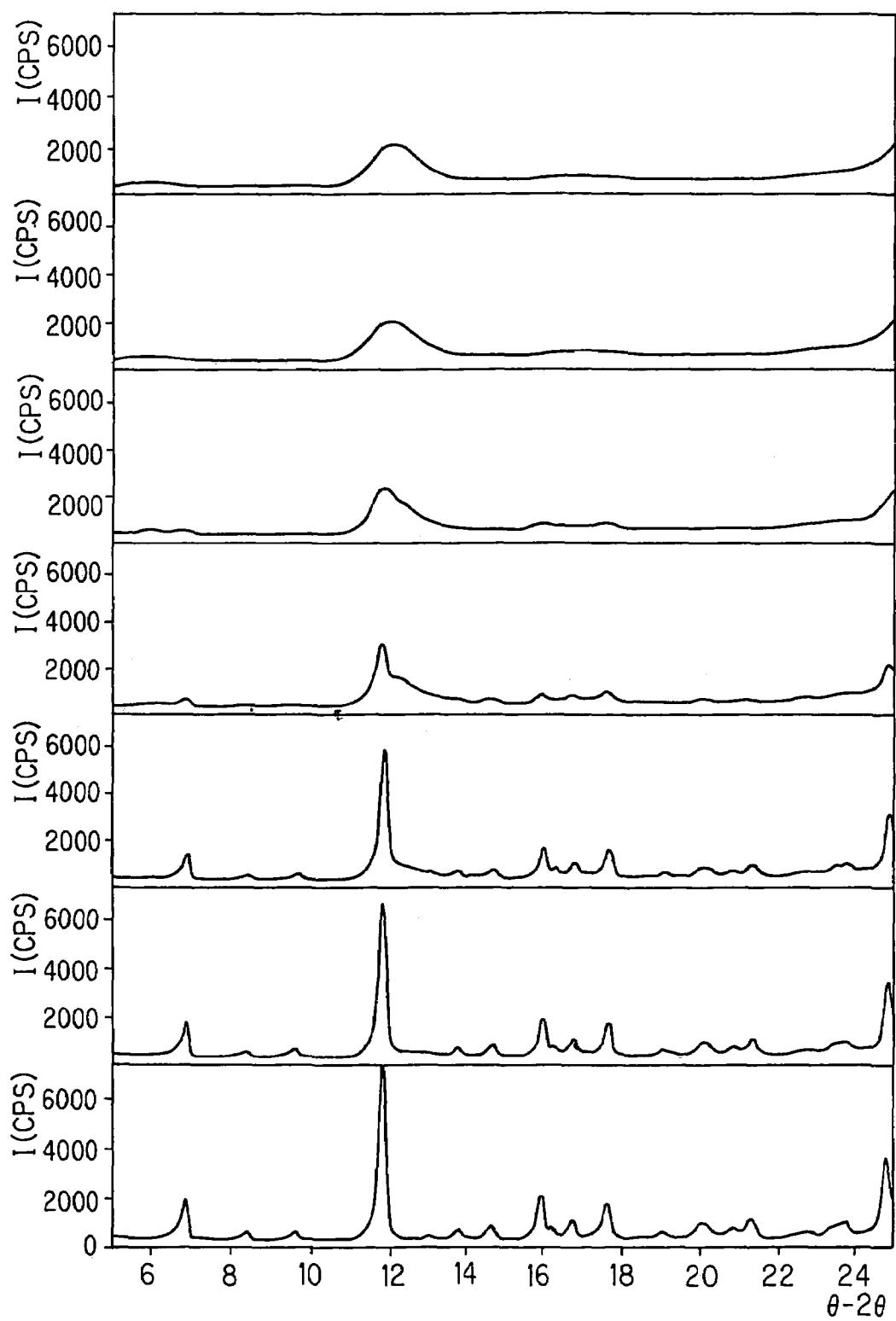
U.S. Patent

Apr. 22, 2008

Sheet 3 of 5

US 7,361,676 B2

Fig. 3



U.S. Patent

Apr. 22, 2008

Sheet 4 of 5

US 7,361,676 B2

Fig. 4

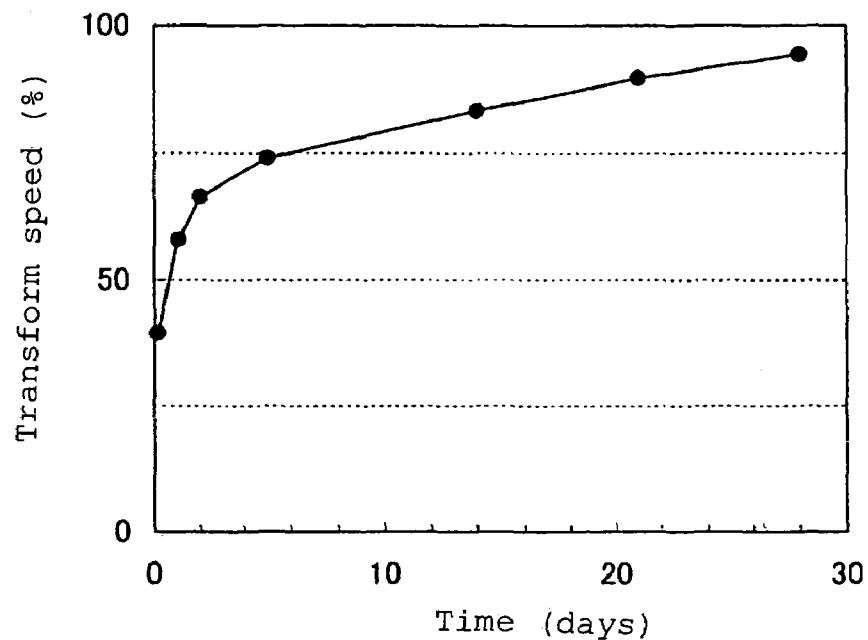
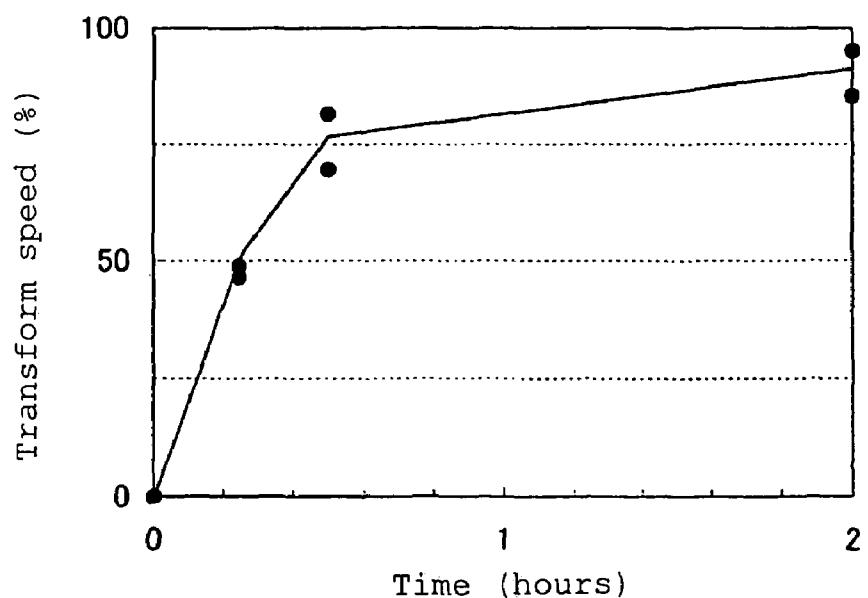


Fig. 5



U.S. Patent

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Sheet 5 of 5

US 7,361,676 B2

Fig. 6

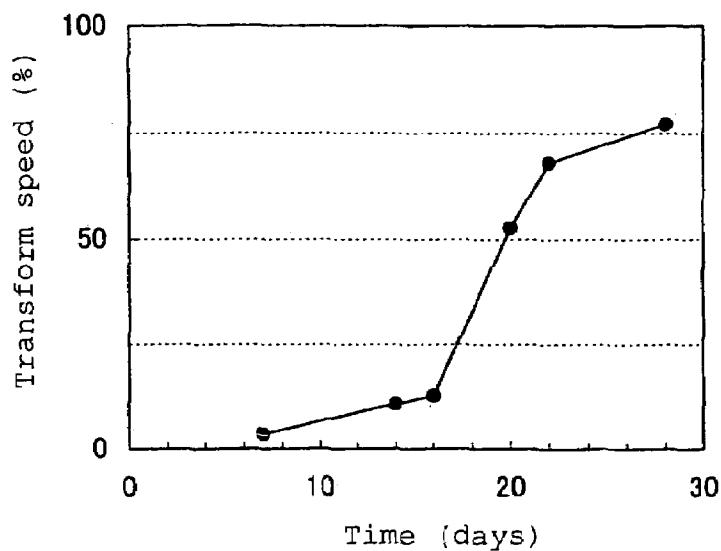
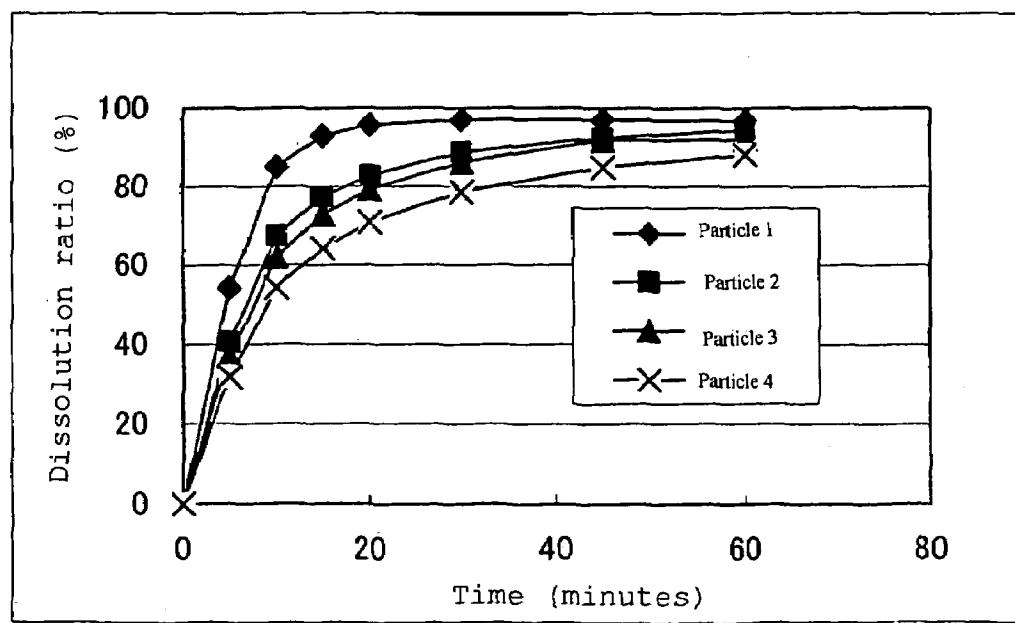


Fig. 7



US 7,361,676 B2

1**SOLID PREPARATION CONTAINING
SINGLE CRYSTAL FORM**

This application is a 371 of PCT/JP03/03962 filed on Mar. 28, 2003.

TECHNICAL FIELD

The present invention relates to a solid preparation of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazole carboxylic acid for oral administration. More particularly, it relates to a solid preparation comprising 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazole carboxylic acid as a single crystal form, and a method for producing the same.

BACKGROUND ART

2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazole carboxylic acid has a strong activity for inhibiting xanthine oxidase or a uric acid decreasing action, and it is expected to be a therapeutic agent for gout or hyperuricemia, as has been described in International Publication WO92/09279.

In International Publication WO99/65885, there are described following six crystal polymorphs of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazole carboxylic acid, i.e., a polymorph which shows an X-ray powder diffraction pattern having specific peaks at a reflection angle 2θ, of about 6.62°, 7.18°, 12.80°, 13.26°, 16.48°, 19.58°, 21.92°, 22.68°, 25.84°, 26.70°, 29.16° and 36.70° (crystal A);

a polymorph which has specific peaks at a reflection angle 2θ of about 6.76°, 8.08°, 9.74°, 11.50°, 12.22°, 13.56°, 15.76°, 16.20°, 17.32°, 19.38°, 21.14°, 21.56°, 23.16°, 24.78°, 25.14°, 25.72°, 26.12°, 26.68°, 27.68° and 29.36° (crystal B);

a polymorph which has specific peaks at a reflection angle 2θ of about 6.62°, 10.82°, 13.36°, 15.52°, 16.74°, 17.40°, 18.00°, 18.70°, 20.16°, 20.62°, 21.90°, 23.50°, 24.78°, 25.18°, 34.08°, 36.72° and 38.04° (crystal C);

a polymorph which has specific peaks at a reflection angle 2θ of about 8.32°, 9.68°, 12.92°, 16.06°, 17.34°, 19.38°, 21.56°, 24.06°, 26.00°, 30.06°, 33.60° and 40.34° (crystal D); and

a polymorph which has specific peaks at a reflection angle 2θ of about 8.86°, 8.36°, 9.60°, 11.76°, 13.74°, 14.60°, 15.94°, 16.74°, 17.56°, 20.00°, 21.26°, 23.72°, 24.78°, 25.14°, 25.74°, 26.06°, 26.64°, 27.92°, 28.60°, 29.66° and 29.98° (crystal G), and an amorphous (also referred to as crystal E).

In said International Publication WO99/65885, it is described that crystals A, C and G are useful in view of retention of a crystal form in long term storage. Among them, crystal A is preferred in view of industrial superiority.

However, the publication is silent about what the industrial superiority means. Further, the publication has no evidence (data) supporting the fact that the crystal A is preferred in view of industrial superiority.

The present inventors investigated this matter and found that, in formulating 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazole carboxylic acid, it is not possible to obtain preparations having no variation in the dissolution profiles of drugs, even if such a crystal form is used as is thought to be most stable in a physical stability test. Further, they found that there is a crystal form that is suitable for preparing preparations, independently from the characteristics of the crystals (including amorphous) of drug substances and have reached the invention.

2

An object of the invention is, therefore, to provide solid preparations of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid which is stable and which is little variation in the dissolution profiles.

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DISCLOSURE OF THE INVENTION

The invention provides solid preparations containing a single crystal form of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid, excipients and disintegrating agents.

Further, the invention provides a process for producing solid preparations containing a single crystal form of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid, excipients and disintegrating agents.

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BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is an X-ray powder diffraction pattern showing the transformation of crystal B in Reference Example 1.

FIG. 2 is an X-ray powder diffraction pattern showing the transformation of crystal D in Reference Example 1.

FIG. 3 is an X-ray powder diffraction pattern showing the transformation of crystal E in Reference Example 1.

FIG. 4 is a data showing the transformation speed of crystal B in Reference Example 1 (unsealed state at 40° C./75% RH).

FIG. 5 is a data showing the transformation speed of crystal D in Reference Example 1 (unsealed at 40° C./75% RH).

FIG. 6 is a data showing the transformation speed of crystal E in Reference example 1 (unsealed at 40° C./75% RH).

FIG. 7 shows dissolution profiles of tablets containing crystal A (particles 1 to 4) in Example 4 each having a different average particle size.

BEST MODE FOR CARRYING OUT THE INVENTION

The single crystal of the 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid (also referred to as the drug substance of the invention) of the invention is that which has a characteristic spectrum when the drug substance is analyzed by a solid NMR or that having specific peaks when analyzed by an X-ray powder diffraction.

The crystal of the invention, i.e., the crystal A of the drug substance of the invention has, when analyzed by a solid ¹⁵N-NMR a, a spectrum having specific signals at 226 ppm, 228 ppm, 276 ppm, and 282 ppm. When analyzed by a solid ¹³C-NMR, the crystal A has approximately equivalent doublet peak at 20 ppm.

Further, the crystal of the drug substance of the invention shows an X-ray powder diffraction pattern having specific peaks at a reflection angle 2θ, of about 6.62°, 7.18°, 12.80°, 13.26°, 16.48°, 19.58°, 21.92°, 22.68°, 25.84°, 26.70°, 29.16° and 36.70°.

The crystal of the drug substance of the invention can be produced by the method shown in, for example, International Publication WO 92/09279 and WO 99/65885.

The crystal of the drug substance of the invention is contained in the solid preparation of the invention preferably in an amount of 1 to 50 parts by weight based on 100 parts by weight of the solid preparation.

There are no particular restrictions to the average particle size of the crystal of the drug substance of the invention contained in the solid preparation of the invention. The

US 7,361,676 B2

3

average particle size is preferably 3 μm or greater and 50 μm or less, when it is determined by an image analysis.

Examples of the excipients for the solid preparation of the invention include lactose, lactose anhydride, crystalline cellulose, corn starch, pregelatinized starch, partly pregelatinized starch, D-mannitol and dibasic calcium phosphate. Particularly the lactose, crystalline cellulose, starches or their combination are preferable. The excipients are contained in an amount of 50 to 98 parts by weight, and more preferably 60 to 95 parts by weight, based on 100 parts by weight of the solid preparation.

Examples of the disintegrating agent for the solid preparation of the invention include carmellose sodium, carmellose calcium, low-substituted hydroxypropyl cellulose, crosscarmellose sodium, carboxymethyl starch sodium and crosspovidone. Particularly the crosscarmellose sodium and partly pregelatinized starch are preferable. The disintegrating agent is contained in an amount of 1 to 25 parts by weight, preferably 1.5 to 20 parts by weight, based on 100 parts by weight of the solid preparation.

There may be added known binders, lubricants, coating agents, plasticizers, diluents, colorants, preservatives, anti-septics or fragrance agents to the solid preparation of the invention to improve the physical properties, appearance, odor, etc. of the preparation.

The binders for the solid preparation of the invention may be those known to the persons in the art. Particularly preferable binders are hydroxypropyl cellulose, hydroxy propylmethyl cellulose, and polyvinyl pyrrolidone. The binder is contained in an amount of 0.5 to 25 parts by weight, and preferably 1 to 20 parts by weight, based on 100 parts by weight of the solid preparation of the invention.

The solid preparations of the invention can be produced by compressing a mixture of the crystals of the drug substance of the invention with excipients and disintegrating agents. For example, one method for the production includes mixing the crystals of the drug substance of the invention with the materials for the preparation by a suitable mixer, and directly compressing the mixture to tablets. Other methods include a dry granulating step to produce granules for tablets using dry granulating machines or roller compacters, and a wet granulating step to produce granules for tablets using water, ethanol and solutions containing binders when necessary.

There is no limitation to the dosage form of the solid preparation of the invention. An example is a tablet.

When the solid preparation is made in a form of a tablet, the tablet can be produced, for example, through granulating, sieving, mixing and tableting steps. Further, it is possible to coat the surface of the tablet by adding a coating step-to the production steps mentioned above.

Concrete examples of producing the tablet are as follows;

(1) Granulating Step

To a known granulating machine there are charged crystals of the drug substance of the invention, excipients, disintegrating agents and binders, and water is sprayed to the charged mixture, followed by granulating the mixture to obtain granules.

Otherwise, there may be charged crystals of the drug substance of the invention, excipients and disintegrating agents excluding binders, to a known granulating machine, and water in which binders are dissolved is sprayed to the charged mixture, followed by granulating the mixture to obtain granules.

In the former case, the granules at the end of spraying contains moisture (determined by the loss on drying method)

4

in an amount of 17 to 26% by weight while in the latter case, the granules at the end of spraying contains moisture in an amount of about 10 to 16% by weight. That is, it is possible in the latter case to produce granules with a lesser amount of water, enabling to shorten the production time. The loss on drying method is carried out by drying powder under heat by emission of infrared rays and determining the percentage (%) of the moisture in the powder based on the weight change caused by the evaporation of water.

10 In the latter case, there is a tendency that the content ratio of drug substance at each particle size group (the content of drug substance in granules classified by the particle size) becomes constant.

(2) Sieving Step

15 The obtained granules are sieved through a desired sieve to remove coarse particles, for example, particles of 710 μm or larger.

(3) Mixing Step

20 The sieved granules are mixed with disintegrating agents and lubricants to obtain lubricated granules to be tableted.

(4) Tableting Step

25 The lubricated granules are tableted by a conventionally known, rotary tableting machine to obtain plain tablets.

30 In this step, conditions for the tableting may be those known to persons in the art. A preferred tableting pressure, for example, is 1,300 kgf/cm² or more and 5,200 kgf/cm² or less.

(5) Coating Step

35 A coating solution is prepared by dissolving a coating agent in water. Subsequently, the plain tablets are coated with the coating solution by a known coating machine to obtain the tablets of the invention.

40 The crystal of the drug substance of the invention is not limited to a particular particle size. Preferred average particle size is in the range from 3 μm to 50 μm (measured by an image analysis). When the size is less than 3 μm , the particle tends to be dispersed at weighing, or care should be taken at weighing and at the time the starting material is charged into a manufacturing equipment. However, the solid preparations of the invention can be produced even if the average particle size is out of the range. When the average particle size is over 50 μm , the produced solid preparations vary in the dissolution profile.

45 According to the invention, there are provided solid preparations that have less variation in the dissolution profile by using a single crystal form (the crystal form of the drug substance of the invention) and a method for producing the same. When the particle size of the crystal of the drug substance is controlled to be in a predetermined range, it is possible to provide solid preparations having a uniform dissolution profile and a method for producing the same.

50 According to the invention, it is possible to provide solid preparations having an improved content uniformity by using a single crystal form (the crystal form of the drug substance of the invention) and a method for producing the same. When the particle size of the crystal of the drug substance is controlled to be in a predetermined range, it is possible to provide solid preparations having a still more improved content uniformity (i.e., small CV valued preparations) and a method for producing the same.

55 According to the invention, it is possible to provide stable solid preparations wherein no transformation of effective ingredients is occurred during the process of formulating to

US 7,361,676 B2

5

tablets, etc., by using a single crystal form (the crystal form of the drug substance of the invention) and a method for producing the same.

The drug substance of the invention is preferably administered 1 to 3 times a day in an amount of 0.8 to 50 mg/day.

The solid preparation and a method for producing the same can be used for producing an inhibitor of xanthine oxidase, uric acid reducing agent, gout therapeutic agent or hyperuricemia therapeutic agent and a method for production of these agents.

The gout or hyperuricemia can be treated by administering the solid preparations of the invention to patients.

That is, the invention provides a method for treating the gout or hyperuricemia, and a method for producing the therapeutic agent for treating the gout or hyperuricemia.

Further, the invention provides a method for administering a sole crystal form (crystal A) of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid in a form of a solid preparation.

The invention is explained by reference to working examples. It should naturally be understood that the invention is not limited by these examples.

EXAMPLES

The stability, dissolution rate, solid ¹³N-NMR and ¹³C-NMR of each crystal form of drug substances (crystals A, B, C, D, E and G) of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid were measured as reference examples.

The drug substances (crystals A, B, C, D, E and G) of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid can be produced, for example, by the methods shown in International Publication WO 92/09279 and WO 99/65885.

Reference Example 1

Physical Stability

Each of the drug substances (crystals A, B, C, D, E and G) of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid was tested in bottles with and without closure under the conditions of 40° C./75% RH. Any degradant was detected by a HPLC. Their transformation was detected by an X-ray powder diffraction pattern and by a thermal mass measurement method, and the 50% transform time was determined. The results are shown in Table 1. There was no degradant for all of the six crystal forms. Crystals A, C and G were stable even after storage for three months while transformation of crystals B, D and E was detected.

<50% Transform time>		
Analysis type	40° C./75% RH without closure	40° C./75% RH with closure
Crystal A XRD	(Not changed)	(Not changed)
Crystal B TG	14 hours	5 days
Crystal C XRD	(Not changed)	(Not changed)
Crystal D XRD	0.25 hours	17 days
Crystal E XRD	19 days	55 days
Crystal G XRD	(Not changed)	(Not changed)

6

For the above HPLC, Model 2690 produced by Waters was adopted, using an ODS column with a measured wave length of 217 nm at a predetermined temperature around 40° C.

5 For the above X-ray powder diffraction, Model XRD-6000 of Shimadzu Corp. was used.

For the above heat mass measurement, Model TGA7, Pyris1 produced by Perkin Elmer was used at a temperature rising speed of 40° C./min.

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Reference Example 2

Dissolution Rate

The dissolution rate was measured according to USP 24, <1087>Intrinsic Dissolution. Specifically, the measurement was carried out as follows:

50 mg each of crystals powdered lightly in an agate mortar was set between plates, and a pressure of 754 kgf/cm² was applied thereto for one minute to produce pellets. As the testing solution, 900 mL of the second fluid of the disintegration test of Japanese Pharmacopoeia was used and the test was carried out at 50 rpm using the dissolution apparatus produced by Vankel. Subsequently, the testing liquid was filtered through a filter and the resultant, used as the sample solution, was tested with respect to a standard solution by a spectrophotometry (wavelength of 317 nm). The results are shown in Table 2, in which the order of the dissolution rate of the six crystals is as follows: E>A>B>D>G>C.

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	Intrinsic rate (mg/cm ² /min)
Crystal A	0.1434
Crystal B	0.1242
Crystal C	0.0694
Crystal D	0.1092
Crystal E	0.1874
Crystal G	0.0967

Reference Example 3

Solid NMR Data of Crystal Forms

45 The analysis of the drug substance contained in the preparations is limited only to solid NMR. Therefore, Crystals A, B, C, D, E and G of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid was analyzed in advance by the solid NMR. The crystals show the following spectra: Solid ¹⁵N-NMR

50 Crystal A: Sharp peaks at 226 ppm, 228 ppm, 276 ppm and 282 ppm;

55 Crystal B: Broad peaks at 216 ppm, 222 ppm and 284 ppm;

55 Crystal C: Sharp single peaks at 210 ppm and 282 ppm;

Crystal D: Sharp single peaks at 229 ppm and 264 ppm;

Crystal E: Broad peaks at 223 ppm and 281 ppm;

60 Crystal G: Sharp single peaks at 216 ppm and 222 ppm, and a doublet peak at 283 ppm.

Solid ¹³C-NMR(specific peak at 20 ppm)

65 Crystal A: approximately equivalent doublet peaks;

Crystal B: non-equivalent doublet peaks;

Crystal C: approximately equivalent triplet peaks;

Crystal D: two single peaks;

Crystal E: Broad peaks;

Crystal G: non-equivalent triplet peaks.

US 7,361,676 B2

7

In the following examples, each of the crystal forms was determined using the spectrum data described above.

Example 1

82.05 g of crystal A of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid, 328.61 g of lactose (Pharmatose 200M, produced by DMV), 77.03 g of partly pregelatinized starch (PC-10, produced by Asahi Kasei Corp.), 12.31 g of hydroxypropyl cellulose (HPC-SL, produced by Nippon Soda Co.) were charged into a fluidized-bed granulator with agitator (New Marumerizer NQ-125, produced by Fuji Paudal) and were fluidized at a heater temperature of 60° C. with a air amount of 0.7 m³/min. Subsequently, ion exchanged water was sprayed thereto at a spraying speed of 16 g/min, and dried at 60° C. to obtain granules containing about 12% by weight of the drug substance. The produced granules were sieved through a vibrating screen for removing particles having a size of 710 µm or greater to obtain sieved granules. 1,200 g of the sieved granules were mixed with 24.6 g of cross carmellose sodium (Ac-Di-Sol, produced by Asahi Kasei Corp.) and 6.15 g of magnesium stearate (produced by Sakai Chemical Ind.) in a cross rotary mixer (CM-10-S, produced by Tsukasa Ind.) to obtain the lubricated granules. The lubricated granules was tableted with a rotary type tabletting machine (HT-P18, produced by Hata Tekkoshio, tablet size: 7 mmΦ, tabletting pressure: 2,500 kgf/cm³) The obtained preparations were analyzed by a solid ¹⁵N-NMR, with the result that there were sharp peaks at 226 ppm, 228 ppm, 276 ppm and 282 ppm. When the preparations were analyzed by a solid ¹³C-NMR, the peak at 20 ppm was an approximately equivalent doublet peak and, accordingly, it was confirmed that crystal form of the drug substance in the preparations is all crystal A.

Comparative Example 1

Tablets were prepared by a method same as that of Example 1 except that crystal C of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid was used. The obtained preparations were analyzed by a solid ¹⁵N-NMR, with the result that the peaks at 210 ppm and 282 ppm were broadened, an sharp peak was shown at 284 ppm and the peak at 20 ppm showed an broad peak when they were analyzed by a solid ¹³C-NMR. Accordingly, it was confirmed that crystals C and E were contained in the preparations.

Comparative Example 2

Tablets were prepared by a method same as that of Example 1 except that crystal B of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid was used. The obtained preparations were analyzed by a solid ¹⁵N-NMR, with the result that the peaks at 216 ppm and 222 ppm were broadened, and the peak at 20 ppm showed an broad peak when they were analyzed by a solid ¹³C-NMR. Accordingly, it was confirmed that crystals B, G and E were contained in the preparations.

Comparative Example 3

Tablets were prepared by a method same as that of Example 1 except that crystal D of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid was used. The obtained preparations were analyzed by a solid ¹⁵N-NMR, with the result that the peaks at 216 ppm, 222 ppm,

8

229 ppm and 264 ppm were broadened, and a broad peak was shown at 284 ppm. Further, the peak at 20 ppm showed a broad peak when they were analyzed by a solid ¹³C-NMR. Accordingly, it was confirmed that crystals D, G and E were contained in the preparations.

Comparative Example 4

Tablets were prepared by a method same as that of Example 1 except that crystal G of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid was used. The obtained preparations were analyzed by a solid ¹⁵N-NMR, with the result that the peaks at 216 ppm and 222 ppm were broadened, and a broad peak was shown at 284 ppm. Further, the peak at 20 ppm showed a broad peak when the preparations were analyzed by a solid ¹³C-NMR. Accordingly, it was confirmed that crystals G and E were contained in the preparations.

Example 2

The tablets prepared by the method shown in Example 1 were tested for six months under the conditions of 40° C./75% RH. Then the uniformity of content (the ratio of the amount of the drug substance contained in actual tablets to the amount charged) and the crystal form of the tablets just after produced and after six months storage were studied. The content in tablets just after produced was 99.72% and the CV value (coefficient of variation) showing the variation in content was 1.37%. The content after storage for six months was 99.5%, and the CV value showing the variation in content is 1.55%, which demonstrates a superior uniformity. The crystal form of the tablets was analyzed by a solid ¹⁵N-NMR, just as the case with immediately after produced. The result showed that sharp peaks were shown at 226 ppm, 228 ppm, 276 ppm and 282 ppm. Further, the results of the analysis by a solid ¹³C-NMR showed that the peak at 20 ppm was an approximately equivalent doublet peak and, accordingly, it was confirmed that the preparations contains crystal A.

Comparative Example 5

Tablets prepared in Comparative Examples 1 through 4 were tested for six months under the conditions of 40° C./75% RH, and the uniformity in content of the drug substance in tablets and the crystal form of the tablets just after produced and after six months were checked.

The content of the drug substance in tablets just after produced in Comparative Example 1 was 100.37% and the CV value (coefficient of variation) showing the variation in content was 1.11%. The content after storage for six months is 99.5% or greater, and the variation in content shown by a CV value showed an improved value of 1.68%. But it was confirmed that the preparations comprise crystals C and E according to the solid NMR. The analysis of preparations after storage showed that a part of crystal E was transformed to crystal G. For the preparations produced in Comparative Example 2, the content in tablets immediately after produced was 99.75% and the CV value showing the variation in content was 1.11%. The content after storage was 99.5% or greater and the variation expressed by a CV value showed an improved uniformity of 1.90%. But it was confirmed that the preparations comprise crystals B, G and E according to the solid NMR. Further, it was confirmed that the ratio of crystal E was reduced and that of crystal G was increased after storage For the preparations produced in Comparative

US 7,361,676 B2

9

Example 3, the content in tablets immediately after produced was 100.01% and the variation shown by a CV value was 1.39%. The content in tablets after storage maintained 99.5% or more and the CV value showed an improved uniformity of 1.54%. But it was confirmed that the preparations comprise crystals D, G and E according to the solid NMR. Further, it was confirmed that the ratio of crystal E was reduced and that of crystal G was increased after storage.

For the preparations produced in Comparative Example 4, the content in tablets immediately after produced was 93.5% and the variation shown by a CV value was 4.5%, which facts show that the content of the drug substance contained in tablets to the amount charged is very low and that there is a considerable variation. Therefore, the tablets did not reach the level of being brought to a market and, thus, no stability test has been carried out.

Example 3

The tablets prepared by the method shown in Example 1 were tested for six months under the conditions of 40° C./75% RH. Then the dissolution profiles of the tablets just after produced and after six months were compared. The dissolution test was carried out by a Paddle method using a McIlvaine buffer solution of pH 5.5 as a testing solution. Three lots (n=3), i.e., 9 test examples in total, were produced by a same method and were tested. The results are shown in Table 3. It was confirmed, as shown in Table 3, that there is little variation or difference in dissolution ratio between points and uniform dissolution profiles are maintained even after storage of six months.

TABLE 3

Dissolution time (min)	Immediately after produced		Six months after storage	
	Average dissolution ratio (%)	CV value (%)	Average dissolution ratio (%)	CV value (%)
15	69.8	2.8	71.6	3.1
60	90.1	2.8	91.7	2.9

Comparative Example 6

For the preparations produced in Comparative Examples 1 through 3 comparisons were made between the dissolution profiles of those immediately after produced and those having been tested for six months under the conditions of 40° C./75% RH. The dissolution test was carried out by a Paddle method using a McIlvaine buffer solution of pH 5.5 as a testing solution. Three lots (n=3), i.e., 9 test examples in total, were produced by a same method and were tested. The results are shown in Tables 4 through 6.

The preparations of Comparative Example 3 after storage showed a slower dissolution profile than those immediately after produced, as shown in Table 4. Further, there is some variation or difference in dissolution ratio between points for the preparations after storage. This is thought to be caused by that crystal E was transformed, by the storage, into crystal G having low solubility. The variation or difference in dissolution ratio between points are thought to be caused by that the ratio of crystals C and E is uneven between lots and that the transformed amount of crystal G from crystal E is not uniform.

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The preparations of Comparative Example 2 after storage showed a slower dissolution profile than those immediately after produced, as shown in Table 5. Further, there is some variation or difference in dissolution ratio between points for the preparations after storage. This is thought to be caused by that crystals B and E were transformed, by the storage, into crystal G having low solubility. The variation or difference in dissolution ratio between points are thought to be caused by that the ratio of crystals B and E is uneven between lots and that the transformed amount of crystal G from crystals B and E is not uniform.

The preparations of Comparative Example 3 after storage showed a slower dissolution profile than those immediately after produced, as shown in Table 6. Further, there is some variation or difference in dissolution ratio between points for the preparations after storage. This is thought to be caused by that crystals D and E were transformed, by the storage, into crystal G having low solubility. The variation or difference in dissolution ratio between points are thought to be caused by that the ratio of crystals D and E is uneven between lots and that the transformed amount of crystal G from crystals D and E is not uniform.

TABLE 4

Dissolution Profile of the Preparations Produced by Comparative Example 1

Dissolution time (min)	Immediately after produced		Six months after storage	
	Average dissolution ratio (%)	CV value (%)	Average dissolution ratio (%)	CV value (%)
15	54.8	18.5	46.2	19.8
60	75.1	15.7	62.1	16.4

TABLE 5

Dissolution Profile of the Preparations Produced by Comparative Example 2

Dissolution time (min)	Immediately after produced		Six months after storage	
	Average dissolution ratio (%)	CV value (%)	Average dissolution ratio (%)	CV value (%)
15	55.1	10.8	48.3	20.4
60	72.1	18.4	63.5	30.2

TABLE 6

Dissolution Profile of the Preparations Produced by Comparative Example 3

Dissolution time (min)	Immediately after produced		Six months after storage	
	Average dissolution ratio (%)	CV value (%)	Average dissolution ratio (%)	CV value (%)
15	53.3	18.1	47.3	19.4
60	60.4	10.9	56.1	22.0

US 7,361,676 B2

11

Example 4

Plain tablets were prepared by the method same as that of Example 1 except that particles (Particles 1~4) shown in Table 7, with crystal A and with four different kinds of average particle sizes, were used as 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid. The obtained plain tablets were coated with coating liquid comprising purified water, polyethylene glycol and hydroxypropylmethyl cellulose by a coating machine (High Coater HCT-30, Freund Ind.).

Dissolution tests were carried out for the four types of the obtained coated tablets by a Paddle method using a McIlvaine buffer solution with pH 5.5, as a testing liquid. The results are shown in Table 7.

TABLE 7

	Pulverizer	Pulverizing conditions	Pulverized particle size (μm) ¹⁾	
			Average particle diameter	95% cumulative diameter
Particle 1	Jet mill (Dalton, PJM-100SP)	Feeding speed: 5.0 kg/hr Pulverizing pressure: 0.65 MPa	3.5	5.6
Particle 2	Sample mill (Dalton, KII WG-1)	Screen 2.0 mmΦ 12,000 rpm	12.9	29.5
Particle 3	Impact mill (Dalton, DS-2)	Screen 1.0 mmΦ 6,120 rpm	26.2	74.7
Particle 4	Power mill (Dalton, P-3)	Screen 2 Hmm 4,000 rpm	48.6	140.8

¹⁾Results measured by an image analysis Measuring instruments (image analysis system, digital camera for microscope and biological microscope)

12

The invention claimed is:

1. A tablet comprising crystal A of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid with an X-ray powder diffraction pattern having specific peaks at a reflection angle 2θ, of 6.62°, 7.18°, 12.80°, 13.26°, 16.48°, 19.58°, 21.92°, 22.68°, 25.84°, 26.70°, 29.16° and 36.70°, an excipient, and a disintegrating agent, wherein the average particle diameter of the crystal A is from 12.9 μm to 26.2 μm.
2. The tablet according to claim 1, wherein the tablet is prepared by a wet granulating method.
3. The tablet according to claim 1 or 2, wherein said excipient is one or more selected from the group consisting of lactose and partly pregelatinized starch.
4. The tablet according to claim 1 or 2, further comprising hydroxypropyl cellulose as a binder.
5. The tablet according to claim 1 or 2, wherein the tablet is coated with polyethylene glycol.
6. A method for producing the tablet according to claim 2 comprising combining said crystal A of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid with an X-ray powder diffraction pattern having specific peaks at a reflection angle 2θ, of 6.62°, 7.18°, 12.80°, 13.26°, 16.48°, 19.58°, 21.92°, 22.68°, 25.84°, 26.70°, 29.16° and 36.70°, an excipient, and a disintegrating agent, wherein the average particle diameter of the crystal A is from 12.9 μm to 26.2 μm.
7. The method for producing a tablet according to claim 6, comprising a step of wet granulating.
8. The method for producing a tablet according to claim 6 or 7, wherein said excipient is one or more selected from the group consisting of lactose and partly pregelatinized starch.
9. The method for producing a tablet according to claim 6 or 7, wherein hydroxypropyl cellulose is added as a binder.
10. The method for producing a tablet according to claim 6 or 7, comprising a step of coating the tablet with polyethylene glycol.

* * * * *

EXHIBIT B

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(12) United States Patent
Gunawardhana et al.(10) Patent No.: US 8,372,872 B2
(45) Date of Patent: *Feb. 12, 2013

(54) METHODS FOR CONCOMITANT TREATMENT OF THEOPHYLLINE AND FEBUXOSTAT

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

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(57) ABSTRACT

Co-administration of febuxostat and theophylline to a hyperuricemic patient suffering from gout is disclosed.

1 Claim, 1 Drawing Sheet

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Page 7

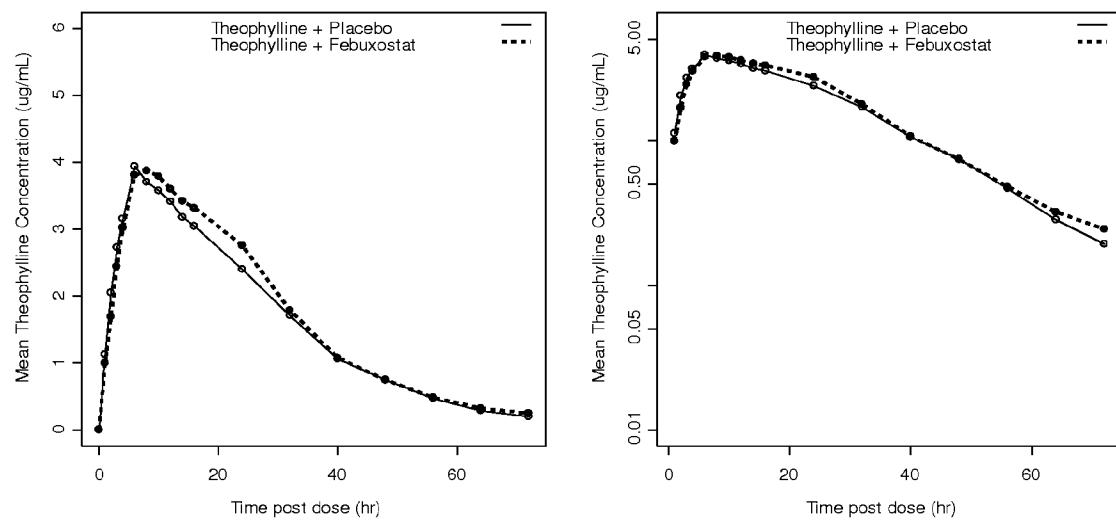
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U.S. Patent

Feb. 12, 2013

US 8,372,872 B2



US 8,372,872 B2

1**METHODS FOR CONCOMITANT TREATMENT OF THEOPHYLLINE AND FEBUXOSTAT****RELATED APPLICATION INFORMATION**

This is a continuation of U.S. patent application Ser. No. 13/227,828, filed on Sep. 8, 2011, which claims priority to U.S. Provisional Patent Application No. 61/381,482, filed on Sep. 10, 2010, the contents of all of which are herein incorporated by reference in their entirety.

FIELD

The present disclosure relates to novel methods for treating hyperuricemia in patients also requiring treatment with theophylline. Specifically, the invention is directed to a method of administering theophylline in conjunction with one or more xanthine oxidoreductase inhibitors, whereby the xanthine oxidoreductase inhibitors do not cause alterations in the plasma concentrations of theophylline.

BACKGROUND

A substantial number of patients are affected with diseases of the respiratory system, including asthma, acute bronchitis, chronic bronchitis, emphysema, neonatal apnea, and neonatal bradycardia. One of the primary treatments for respiratory diseases is the use of theophylline.

Theophylline is a useful medicine frequently used as an agent for treating symptoms of bronchial asthma. It is known in the art that effective blood concentrations range from about 10 to 20 µg/ml. However, if the concentration of theophylline in the blood exceeds 20 µg/ml, serious side effects sometimes appear with regard to the cardiovascular system and the central nervous system. Further, there is a large difference in blood levels among individuals. Various conditions (e.g., cardiac insufficiency, liver and kidney disease, etc.), age differences, smoking, etc. also have large effects. Additionally, theophylline has a short biological half-life of about 6 hours for adults. In order to maintain the effective blood level, four doses per day have been considered necessary. However, such frequent dosing is troublesome to patients, reduces patient compliance, and causes the state of the disease to become worse. In particular, attacks of bronchial asthma often occur at daybreak. It is not possible to sufficiently prevent such attacks with ingestion of theophylline just before going to bed, and therefore, repeat ingestion close to daybreak is necessary. Thus, in the past, continuous effort has been made to develop a sustained release type theophylline formulation. Several formulations are already available on the market.

Another disease that affects a substantial number of patients is gout. Gout affects 3 to 5 million individuals in the United States of America (USA) and is increasing in incidence and prevalence. Gout is a serious health condition characterized by flares of acute arthritis, chronic gouty arthropathy, tophi, and uric acid urolithiasis, and is associated with a broad range of comorbidities, including cardiovascular disease, chronic kidney disease, and metabolic syndrome. At the joint level, a gout flare is best characterized as an acute monoarthritis arthropathy process with proliferative bone reaction that can affect any joint and that can later develop into chronic polyarthritis. Gout attacks tend to occur mostly in the lower extremities and over time additional joints can be involved.

The underlying metabolic aberration in gout is hyperuricemia, which is a condition defined as an elevation in serum

2

urate (sUA) level ≥ 6.8 m/dL. Hyperuricemia develops into gout when urate crystals are formed from supersaturated body fluids and deposited in joints, tophi, and parenchymal organs due to a disorder in the urate metabolism. Uric acid is the end product of purine metabolism and is generated in the cascade of hypoxanthine \rightarrow xanthine \rightarrow uric acid.

Urate-lowering therapy (ULT) is used to treat hyperuricemia in subjects with gout. The goal of ULT is to reduce sUA to 6.0 mg/dL or less, below the concentration at which monosodium urate saturates extracellular fluid. Using ULT to reduce and maintain sUA levels <6.0 mg/dL ultimately improves the clinical symptoms of gout by reducing the frequency of gout flares, decreasing size and number of tophi, and improving quality of life. One alternative that may be used for the treatment of gout is the administration of xanthine oxidase inhibitors, such as allopurinol. Generally, allopurinol is considered one of the primary treatments of gout and has developed wide usage as a treatment for gout.

However, clinicians have few treatment options for hyperuricemic patients also suffering from respiratory diseases, such as chronic obstructive pulmonary disease, asthma, acute bronchitis, chronic bronchitis, emphysema, neonatal apnea, and neonatal bradycardia. One of the primary treatments for these respiratory diseases is the administration of theophylline, a bronchodilator. Although theophylline provides a treatment for the respiratory diseases described herein, the therapeutic range of theophylline blood concentrations is thought to be very narrow, ranging from about 10 to about 20 µg/ml. As such, if the theophylline dosing does not provide a minimum blood concentration of 10 µg/ml, the patient is not provided significant relief from the respiratory condition, and at blood concentrations greater than 20 µg/ml, the patient may be susceptible to adverse effects such as abdominal pain, headache, muscle cramps, tremors, tachycardia, and seizures. Therefore, clinicians must exercise caution in determining treatment options for patients requiring theophylline treatment, and must closely monitor the potential for drug interactions that may increase or decrease theophylline blood concentrations.

It is further known within the art that the administration of allopurinol interacts with the metabolism of theophylline, causing the theophylline to be metabolized slowly, and leading to increased blood concentrations. As discussed in the art, the area under the curve (AUC) for theophylline in patients co-administered allopurinol and theophylline has been reported to increase by up to 27%, the half-life increased by approximately 25%, and the clearance of theophylline may be decreased by 21% (Manfredi B A, et al., *Clin. Pharmacol. Ther.*, 1981; 29(2), pp. 224-229). Accordingly, clinicians are required to alter the theophylline dosing and/or the allopurinol dosing in hopes of establishing a therapeutic dose for both disease states, while avoiding unwanted adverse effects that may result from increased theophylline concentrations.

Thus, in view of these considerations, there exists within the art a need to develop a treatment option for hyperuricemic patients that also suffer from respiratory disorders, whereby the clinician can administer typical dosing of theophylline without adjusting for adverse drug interactions.

SUMMARY

The present disclosure is directed to methods for treating hyperuricemia in patients requiring treatment with theophylline. The methods of the current invention avoid the drug interactions typically associated with theophylline administration and concomitant treatment with xanthine oxidase inhibitors.

US 8,372,872 B2

3

In one embodiment, the present disclosure provides a method of treating hyperuricemia in a patient in need of treatment thereof, the method comprising the steps of: administering to the patient suffering from hyperuricemia and at least one secondary disease state, a therapeutically effective amount of at least one xanthine oxidoreductase inhibitor, wherein said subject is also receiving a concomitant administration of theophylline to treat the at least one secondary disease state; and further wherein (i) the administration of the at least one xanthine oxidoreductase inhibitor to said patient does not result in theophylline toxicity to said patient; and (ii) administration of the theophylline is in an amount ranging from about 90% to about 110% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor.

The secondary disease state may include asthma, acute bronchitis, chronic bronchitis, emphysema, neonatal apnea, neonatal bradycardia, and combinations thereof. As described in the method of this embodiment, the xanthine oxidoreductase inhibitor may include 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid, 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-(3-cyano-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylic acid, 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazolecarboxylic acid, 1-(3-cyano-4-(2,2-dimethylpropoxy)phenyl)-1H-pyrazole-4-carboxylic acid, 1-3-cyano-4-(2,2-dimethylpropoxy)phenyl]-1H-pyrazole-4-carboxylic acid, pyrazolo[1,5-a]-1,3,5-triazin-4-(1H)-one, 8-[3-methoxy-4-(phenylsulfinyl)phenyl]-sodium salt (\pm), 3-(2-methyl-4-pyridyl)-5-cyano-4-isobutoxyphenyl)-1,2,4-triazole and pharmaceutically acceptable salts thereof.

Moreover, the method of the current embodiment may include a theophylline dose ranging from about 95% to about 105%, and from about 99% to about 101% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor. The method of the current invention may also include patients suffering from a third disease state, including gout, hypertension, renal failure, nephrolithiasis, acute gouty arthritis, chronic gouty joint disease, tophaceous gout, uric acid urolithiasis, uric acid nephropathy, progressive renal disease, and combinations thereof. Further, the methods of the current embodiment include the treatment of hyperuricemia in patients that were previously receiving theophylline treatment prior to treatment with a xanthine oxidoreductase inhibitor.

In another embodiment, the current invention provides a method of treating hyperuricemia in a patient in need of treatment thereof, the method comprising the steps of: administering to the patient suffering from hyperuricemia and at least one second disease state, a therapeutically effective amount of at least one xanthine oxidoreductase inhibitor, wherein said subject will also be receiving a concomitant administration of theophylline to treat at least one second disease state, and further wherein (i) the administration of the at least one xanthine oxidoreductase inhibitor to said patient will not result in theophylline toxicity to said patient; and (ii) administration of the theophylline will be in an amount ranging from about 90% to about 110% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor.

The secondary disease state may include asthma, acute bronchitis, chronic bronchitis, emphysema, neonatal apnea, neonatal bradycardia, and combinations thereof. As

4

described in the method of this embodiment, the xanthine oxidoreductase inhibitor may include 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid, 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-(3-cyano-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylic acid, 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazolecarboxylic acid, 1-(3-cyano-4-(2,2-dimethylpropoxy)phenyl)-1H-pyrazole-4-carboxylic acid, 1-3-cyano-4-(2,2-dimethylpropoxy)phenyl]-1H-pyrazole-4-carboxylic acid, pyrazolo[1,5-a]-1,3,5-triazin-4-(1H)-one, 8-[3-methoxy-4-(phenylsulfinyl)phenyl]-sodium salt (\pm), 3-(2-methyl-4-pyridyl)-5-cyano-4-isobutoxyphenyl)-1,2,4-triazole and pharmaceutically acceptable salts thereof.

Moreover, the method of the current embodiment may include a theophylline dose ranging from about 95% to about 105%, and from about 99% to about 101% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor. The method of the current invention may also include patients suffering from a third disease state, including gout, hypertension, renal failure, nephrolithiasis, acute gouty arthritis, chronic gouty joint disease, tophaceous gout, uric acid urolithiasis, uric acid nephropathy, progressive renal disease, and combinations thereof. Further, the methods of the current embodiment include the treatment of hyperuricemia in patients that have not previously received theophylline treatment prior to treatment with a xanthine oxidoreductase inhibitor, and will begin treatment with both medications concurrently.

In yet another embodiment, the present disclosure provides a method of treating hyperuricemia in a patient suffering from gout and in need of treatment thereof, the method comprising the steps of: administering to the patient suffering from gout and hyperuricemia and at least one third disease state, a therapeutically effective amount of at least one xanthine oxidoreductase inhibitor, wherein said subject is also receiving a concomitant administration of theophylline to treat the at least one third disease state; and further wherein (i) the administration of the at least one xanthine oxidoreductase inhibitor to said patient does not result in theophylline toxicity to said patient; and (ii) administration of the theophylline is in an amount ranging from about 90% to about 110% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor.

The third disease state may include asthma, acute bronchitis, chronic bronchitis, emphysema, neonatal apnea, neonatal bradycardia, and combinations thereof. As described in the method of this embodiment, the xanthine oxidoreductase inhibitor may include 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid, 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-(3-cyano-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylic acid, 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazolecarboxylic acid, 1-(3-cyano-4-(2,2-dimethylpropoxy)phenyl)-1H-pyrazole-4-carboxylic acid, 1-3-cyano-4-(2,2-dimethylpropoxy)phenyl]-1H-pyrazole-4-carboxylic acid, pyrazolo[1,5-a]-1,3,5-triazin-4-(1H)-one, 8-[3-methoxy-4-(phenylsulfinyl)phenyl]-sodium salt (\pm), 3-(2-methyl-4-pyridyl)-5-cyano-4-isobutoxyphenyl)-1,2,4-triazole and pharmaceutically acceptable salts thereof.

Moreover, the method of the current embodiment may include a theophylline dose ranging from about 95% to about

US 8,372,872 B2

5

105%, and from about 99% to about 101% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor. The method of the current invention may also include patients suffering from a fourth disease state, including hypertension, renal failure, nephrolithiasis, acute gouty arthritis, chronic gouty joint disease, tophaceous gout, uric acid urolithiasis, uric acid nephropathy, progressive renal disease, and combinations thereof. Further, the methods of the current embodiment include the treatment of hyperuricemia in patients suffering from gout and that were previously receiving theophylline treatment prior to treatment with a xanthine oxidoreductase inhibitor.

In another embodiment, the current invention provides a method of treating hyperuricemia in a patient suffering from gout and in need of treatment thereof, the method comprising the steps of: administering to the patient suffering from gout and hyperuricemia and at least one third disease state, a therapeutically effective amount of at least one xanthine oxidoreductase inhibitor, wherein said subject will also be receiving a concomitant administration of theophylline to treat at least one third disease state, and further wherein (i) the administration of the at least one xanthine oxidoreductase inhibitor to said patient will not result in theophylline toxicity to said patient; and (ii) administration of the theophylline will be in an amount ranging from about 90% to about 110% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor.

The third disease state may include asthma, acute bronchitis, chronic bronchitis, emphysema, neonatal apnea, neonatal bradycardia, and combinations thereof. As described in the method of this embodiment, the xanthine oxidoreductase inhibitor may include 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid, 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2,2-dimethylpropoxy)phenyl]-1H-pyrazole-4-carboxylic acid, 1-(3-cyano-4-(2,2-dimethylpropoxy)phenyl)-1H-pyrazole-4-carboxylic acid, 1-(3-cyano-4-(2,2-dimethylpropoxy)phenyl)-1H-pyrazole-4-carboxylic acid, pyrazolo[1,5-a]-1,3,5-triazin-4-(1H)-one, 8-[3-methoxy-4-(phenylsulfinyl)phenyl]-sodium salt (\pm), 3-(2-methyl-4-pyridyl)-5-cyano-4-isobutoxyphenyl)-1,2,4-triazole and pharmaceutically acceptable salts thereof.

Moreover, the method of the current embodiment may include a theophylline dose ranging from about 95% to about 105%, and from about 99% to about 101% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor. The method of the current invention may also include patients suffering from a fourth disease state, including hypertension, renal failure, nephrolithiasis, acute gouty arthritis, chronic gouty joint disease, tophaceous gout, uric acid urolithiasis, uric acid nephropathy, progressive renal disease, and combinations thereof. Further, the methods of the current embodiment include the treatment of hyperuricemia in patients that have not previously received theophylline treatment prior to treatment with a xanthine oxidoreductase inhibitor, and will begin treatment with both medications concurrently.

In still yet another embodiment, the present disclosure provides a method of treating a patient in need of treatment thereof, the method comprising the steps of: administering to the patient suffering from at least one first disease state and at

6

least one secondary disease state, a therapeutically effective amount of at least one xanthine oxidoreductase inhibitor, wherein said subject is also receiving a concomitant administration of theophylline to treat the at least one secondary disease state; and further wherein (i) the administration of the at least one xanthine oxidoreductase inhibitor to said patient does not result in theophylline toxicity to said patient; and (ii) administration of the theophylline is in an amount ranging from about 90% to about 110% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor.

The first disease state may include gout, prostatitis, inflammatory bowel disease, QT interval prolongation, myocardial infarction, cardiac hypertrophy, hypertension, nephrolithiasis, renal impairment, chronic kidney disease, metabolic syndrome, diabetes, diabetic nephropathy, congestive heart failure and combinations thereof.

The secondary disease state may include asthma, acute bronchitis, chronic bronchitis, emphysema, neonatal apnea, neonatal bradycardia, and combinations thereof. As described in the method of this embodiment, the xanthine oxidoreductase inhibitor may include 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid, 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2,2-dimethylpropoxy)phenyl]-1H-pyrazole-4-carboxylic acid, 1-(3-cyano-4-(2,2-dimethylpropoxy)phenyl)-1H-pyrazole-4-carboxylic acid, 1-(3-cyano-4-(2,2-dimethylpropoxy)phenyl)-1H-pyrazole-4-carboxylic acid, pyrazolo[1,5-a]-1,3,5-triazin-4-(1H)-one, 8-[3-methoxy-4-(phenylsulfinyl)phenyl]-sodium salt (\pm), 3-(2-methyl-4-pyridyl)-5-cyano-4-isobutoxyphenyl)-1,2,4-triazole and pharmaceutically acceptable salts thereof.

Moreover, the method of the current embodiment may include a theophylline dose ranging from about 95% to about 105%, and from about 99% to about 101% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor. The method of the current invention may also include patients suffering from a third disease state, including gout, hypertension, renal failure, nephrolithiasis, acute gouty arthritis, chronic gouty joint disease, tophaceous gout, uric acid urolithiasis, uric acid nephropathy, progressive renal disease, and combinations thereof. Further, the methods of the current embodiment include the treatment of the first disease state in patients that were previously receiving theophylline treatment prior to treatment with a xanthine oxidoreductase inhibitor.

BRIEF DESCRIPTION OF THE FIGURE

FIG. 1 shows the mean theophylline plasma concentration-time profiles following an oral dose of 400 mg theophylline coadministered with 80 mg of 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid (also known as "febuxostat") or matching placebo as described in Example 1.

DETAILED DESCRIPTION OF THE DISCLOSURE

I. Definitions

Section headings as used in this section and the entire disclosure herein are not intended to be limiting.

US 8,372,872 B2

7

As used herein, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise. For the recitation of numeric ranges herein, each intervening number there between with the same degree of precision is explicitly contemplated. For example, for the range 6-9, the numbers 7 and 8 are contemplated in addition to 6 and 9, and for the range 6.0-7.0, the numbers 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9 and 7.0 are explicitly contemplated.

As used herein, the term “about” is used synonymously with the term “approximately.” Illustratively, the use of the term “about” indicates that values slightly outside the cited values, namely, plus or minus 10%. Such dosages are thus encompassed by the scope of the claims reciting the terms “about” and “approximately.”

As used herein, the term “AUC” refers to the area under the plasma concentration time curve of the active agent and which is calculated using the trapezoidal rule. The term “ AUC_t ” means the area under the plasma concentration time curve from time 0 to 120 hours after administration in units of $\text{ng}\cdot\text{h}/\text{mL}$ as determined using the trapezoidal rule. The term “ AUC_∞ ” means the area under the plasma concentration time curve from time 0 to infinite time. AUC_∞ is calculated as $AUC_t + LMT/(-\beta)$, where “LMT” is the last measurable plasma concentration and β is the terminal phase elimination rate constant. Unless otherwise noted herein, the reported value for the AUC is the central value of the AUC. The “central value” of the AUC is the mean $AUC \pm$ standard deviation.

The terms “administer”, “administering”, “administered” or “administration” refer to any manner of providing a drug (such as, a xanthine oxidoreductase inhibitor or a pharmaceutically acceptable salt thereof) to a subject or patient. Routes of administration can be accomplished through any means known by those skilled in the art. Such means include, but are not limited to, oral, buccal, intravenous, subcutaneous, intramuscular, transdermal, by inhalation and the like.

The term “active agent” as used herein refers to (1) a xanthine oxidoreductase inhibitor or a pharmaceutically acceptable salt thereof or (2) a xanthine oxidase inhibitor or a pharmaceutically acceptable salt thereof. The term “active agent” and “drug” are used interchangeably herein. The solid state form of the active agent used in preparing the dosage forms of the present disclosure is not critical. For example, active agent used in preparing the modified release dosage forms of the present disclosure can be amorphous or crystalline. The final dosage form contains at least a detectable amount of crystalline active agent. The crystalline nature of the active agent can be detected using powder X-ray diffraction analysis, by differential scanning calorimetry or any other techniques known in the art.

The term “ C_{max} ” refers to the maximum observed plasma concentration of a xanthine oxidoreductase inhibitor or salt thereof produced by the ingestion of the dosage forms of the present disclosure. Unless otherwise noted herein, the reported value for the C_{max} is the central value of the C_{max} . The “central value” of the C_{max} is the mean $C_{max} \pm$ standard deviation.

The term “dosage form” refers to any solid object, semi-solid, or liquid composition designed to contain a specific pre-determined amount (i.e., dose) of a certain active agent. Suitable dosage forms may be pharmaceutical drug delivery systems, including those for oral administration, buccal administration, rectal administration, topical or mucosal delivery or subcutaneous implants, or other implanted drug delivery systems and the like. In one aspect, the dosage forms of the present disclosure are considered to be solid, however,

8

they may contain liquid or semi-solid components. In another aspect, the dosage form is an orally administered system for delivering an active agent to the gastrointestinal tract of a subject. The dosage form of the present disclosure exhibit modified release of the active agent.

By an “effective amount” or a “therapeutically effective amount” of an active agent is meant a nontoxic but sufficient amount of the active agent to provide the desired effect. The amount of active agent that is “effective” will vary from subject to subject, depending on the age and general condition of the individual, the particular active agent or agents, and the like. Thus, it is not always possible to specify an exact “effective amount.” However, an appropriate “effective amount” in any individual case may be determined by one of ordinary skill in the art using routine experimentation. For example, the daily therapeutically effective or prophylactically effective amount of xanthine oxidoreductase inhibiting compounds administered to a patient in single or divided doses range from about 0.01 to about 750 milligram per kilogram of body weight per day (mg/kg/day). More specifically, a patient may be administered from about 5.0 mg to about 300 mg once daily, from about 20 mg to about 240 mg once daily and from about 40 mg to about 120 mg once daily of xanthine oxidoreductase inhibiting compounds. Of course, it will be understood by one skilled in the art that other dosage regimens may be utilized, such as dosing more than once per day, utilizing extended, controlled, or modified release dosage forms, and the like in order to achieve the desired result.

By “pharmaceutically acceptable,” such as in the recitation of a “pharmaceutically acceptable excipient,” or a “pharmaceutically acceptable additive,” is meant a material that is not biologically or otherwise undesirable, i.e., the material may be incorporated into a pharmaceutical composition administered to a patient without causing any undesirable biological effects.

The term “subject” refers to an animal. In one aspect, the animal is a mammal, including a human or non-human. The terms patient and subject may be used interchangeably herein.

The terms “treating” and “treatment” refer to reduction in severity and/or frequency of symptoms, elimination of symptoms and/or underlying cause, prevention of the occurrence of symptoms and/or their underlying cause, and improvement or remediation of damage. Thus, for example, “treating” a patient involves prevention of a particular disorder or adverse physiological event in a susceptible individual as well as treatment of a clinically symptomatic individual by inhibiting or causing regression of a disorder or disease.

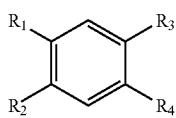
As used herein, the term “xanthine oxidoreductase” refers to at least one form of xanthine oxidoreductase enzyme, namely xanthine oxidase and/or xanthine dehydrogenase.

As used herein, the phrase “xanthine oxidoreductase inhibitor” refers to any compound that (1) is an inhibitor of a xanthine oxidoreductase, such as, but not limited to, xanthine oxidase; and (2) chemically, does not contain a purine ring in its structure (i.e. is a “non-purine” analogue). The phrase “xanthine oxidoreductase inhibitor” as defined herein also includes metabolites, polymorphs, solvates and prodrugs of such compounds, including metabolites, polymorphs, solvates and prodrugs of the exemplary compounds described as Formula I and Formula II below. Examples of xanthine oxidoreductase inhibitors include, but are not limited to, 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazole-carboxylic acid and compounds having the following Formula I or Formula II:

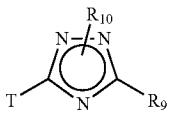
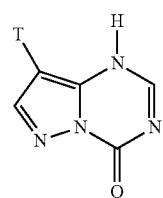
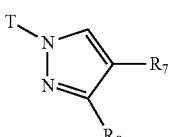
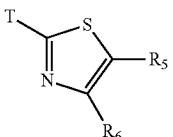
US 8,372,872 B2

9

Compounds of Formula I:



wherein R_1 and R_2 are each independently a hydrogen, a hydroxyl group, a COOH group, an unsubstituted or substituted C_1 - C_{10} alkyl group, an unsubstituted or substituted C_1 - C_{10} alkoxy, an unsubstituted or substituted hydroxy-alkoxy, a phenylsulfinyl group or a cyano ($-\text{CN}$) group;
wherein R_3 and R_4 are each independently a hydrogen or A, B, C or D as shown below:



wherein T connects or attaches A, B, C or D to the aromatic ring shown above at R_1 , R_2 , R_3 or R_4 .

wherein R_5 and R_6 are each independently a hydrogen, a hydroxyl group, a COOH group, an unsubstituted or substituted C_1 - C_{10} alkyl group, an unsubstituted or substituted C_1 - C_{10} alkoxy, an unsubstituted or substituted hydroxy-alkoxy, COO-Glucoronide or COO-Sulfate;

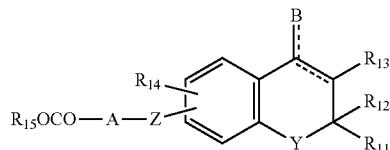
wherein R_7 and R_8 are each independently a hydrogen, a hydroxyl group, a COOH group, an unsubstituted or substituted C_1 - C_{10} alkyl group, an unsubstituted or substituted C_1 - C_{10} alkoxy, an unsubstituted or substituted hydroxy-alkoxy, COO-Glucoronide or COO-Sulfate;

wherein R_9 is an unsubstituted pyridyl group or a substituted pyridyl group; and

wherein R_{10} is a hydrogen or a lower alkyl group, a lower alkyl group substituted with a pivaloyloxy group and in each case, R_{10} bonds to one of the nitrogen atoms in the 1,2,4-triazole ring shown above in Formula I.

10

Compounds of Formula II:



wherein R_{11} and R_{12} are each independently a hydrogen, a substituted or unsubstituted lower alkyl group, a substituted or unsubstituted phenyl (the substituted phenyl in this Formula II refers to a phenyl substituted with a halogen or lower alkyl, and the like. Examples include, but are not limited to, p-tolyl and p-chlorophenyl), or R_{11} and R_{12} may together form a four- to eight-membered carbon ring together with the carbon atom to which they are attached;

wherein R_{13} is a hydrogen or a substituted or unsubstituted lower alkyl group;

wherein R_{14} is one or two radicals selected from a group consisting of a hydrogen, a halogen, a nitro group, a substituted or unsubstituted lower alkyl group, a substituted or unsubstituted phenyl (the substituted phenyl in this Formula II refers to a phenyl substituted with a halogen or lower alkyl group, and the like. Examples include, but are not limited to, p-tolyl and p-chlorophenyl), $-\text{OR}_{16}$ and $-\text{SO}_2\text{NR}_{17}\text{R}_{17'}$, wherein R_{16} is a hydrogen, a substituted or unsubstituted lower alkyl, a phenyl-substituted lower alkyl, a carboxymethyl or ester thereof, a hydroxyethyl or ether thereof, or an allyl; R_{17} and $R_{17'}$ are each independently a hydrogen or a substituted or unsubstituted lower alkyl group;

wherein R_{15} is a hydrogen or a pharmaceutically active ester-forming group;

wherein A is a straight or branched hydrocarbon radical having one to five carbon atoms;

wherein B is a halogen, an oxygen, or an ethylenedithio; wherein Y is an oxygen, a sulfur, a nitrogen or a substituted nitrogen;

wherein Z is an oxygen, a nitrogen or a substituted nitrogen; and
the dotted line refers to either a single bond, a double bond, or two single bonds (for example, when B is ethylenedithio, the dotted line shown in the ring structure can be two single bonds).

As used herein, the term “lower alkyl(s)” group refers to a C_1 - C_7 alkyl group, including, but not limited to, including methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, hexyl, heptal and the like.

As used herein, the term “lower alkoxy” refers to those groups formed by the bonding of a lower alkyl group to an oxygen atom, including, but not limited to, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentoxy, hexoxy, heptoxy and the like.

As used herein, the term “lower alkylthio” refers to those groups formed by the bonding of a lower alkyl to a sulfur atom.

As used herein, the term “halogen” refers to fluorine, chlorine, bromine and iodine.

As used herein, the term “substituted pyridyl” refers to a pyridyl group that can be substituted with a halogen, a cyano group, a lower alkyl, a lower alkoxy or a lower alkylthio group.

As used herein, the term “four- to eight-membered carbon ring” refers to cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like.

US 8,372,872 B2

11

As used herein, the phrase "pharmaceutically active ester-forming group" refers to a group which binds to a carboxyl group through an ester bond. Such ester-forming groups can be selected from carboxy-protecting groups commonly used for the preparation of pharmaceutically active substances, especially prodrugs. For the purpose of the present disclosure, said group should be selected from those capable of binding to compounds having Formula II wherein R₁₅ is hydrogen through an ester bond. Resultant esters are effective to increase the stability, solubility, and absorption in gastrointestinal tract of the corresponding non-esterified forms of said compounds having Formula II, and also prolong the effective blood-level of it. Additionally, the ester bond can be cleaved easily at the pH of body fluid or by enzymatic actions in vivo to provide a biologically active form of the compound having Formula II. Preferred pharmaceutically active ester-forming groups include, but are not limited to, 1-(oxygen substituted)-C₂ to C₁₅ alkyl groups, for example, a straight, branched, ringed, or partially ringed alkanoyloxyalkyl groups, such as acetoxyethyl, acetoxyethyl, propionyloxymethyl, pivaloyloxymethyl, pivaloyloxyethyl, cyclohexaneacetoxyethyl, cyclohexanecarbonyloxyacyclohexylmethyl, and the like, C₃ to C₁₅ alkoxy carbonyloxyalkyl groups, such as ethoxycarbonyloxyethyl, isopropoxycarbonyloxyethyl, isopropoxycarbonyloxypropyl, t-butoxycarbonyloxyethyl, isopentylloxycarbonyloxypropyl, cyclohexyloxycarbonyloxyethyl, cyclohexylmethoxycarbonyloxyethyl, bornyloxycarbonyloxyisopropyl, and the like, C₂ to C₈ alkoxyalkyls, such as methoxy methyl, methoxy ethyl, and the like, C₄ to C₈ 2-oxacycloalkyls such as tetrahydropyran, tetrahydrofuran, and the like, substituted C₈ to C₁₂ aralkyls, for example, phenacyl, phthalidyl, and the like, C₆ to C₁₂ aryl, for example, phenyl xylyl, indanyl, and the like, C₂ to C₁₂ alkenyl, for example, allyl, (2-oxo-1,3-dioxolyl)methyl, and the like, and [4,5-dihydro-4-oxo-1H-pyrazolo[3,4-d]pyrimidin-1-yl]methyl, and the like.

In R₁₆ in Formula II, the term "ester" as used in the phrase "the ester of carboxymethyl" refers to a lower alkyl ester, such as methyl or ethyl ester; and the term "ether" used in the phrase "the ether of hydroxyethyl" means an ether which is formed by substitution of the hydrogen atom of hydroxyl group in the hydroxyethyl group by aliphatic or aromatic alkyl group, such as benzyl.

The carboxy-protecting groups may be substituted in various ways. Examples of substituents include halogen atom, alkyl groups, alkoxy groups, alkylthio groups and carboxy groups.

As used herein, the term "straight or branched hydrocarbon radical" in the definition of A in Formula II above refers to methylene, ethylene, propylene, methylmethylen, or isopropylene.

As used herein, the substituent of the "substituted nitrogen" in the definition of Y and Z in Formula II above are hydrogen, lower alkyl, or acyl.

As used herein, the term "phenyl-substituted lower alkyl" refers to a lower alkyl group substituted with phenyl, such as benzyl, phenethyl or phenylpropyl.

As used herein, the term "prodrug" refers to a derivative of the compounds shown in the above-described Formula I and Formula II that have chemically or metabolically cleavable groups and become by solvolysis or under physiological conditions compounds that are pharmaceutically active in vivo. Esters of carboxylic acids are an example of prodrugs that can be used in the dosage forms of the present disclosure. Methyl ester prodrugs may be prepared by reaction of a compound having the above-described formula in a medium such as methanol with an acid or base esterification catalyst (e.g.,

12

NaOH, H₂SO₄). Ethyl ester prodrugs are prepared in similar fashion using ethanol in place of methanol.

Examples of compounds having the above Formula I are: 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid (also known as "febuxostat"), 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-(3-cyano-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylic acid, 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazolecarboxylic acid, 1-(3-cyano-4-(2,2-dimethylpropoxy)phenyl)-1H-pyrazole-4-carboxylic acid, 1-3-cyano-4-(2,2-dimethylpropoxy)phenyl]-1H-pyrazole-4-carboxylic acid, pyrazolo[1,5-a]-1,3,5-triazin-4-(1H)-one, 8-[3-methoxy-4-(phenylsulfinyl)phenyl]-sodium salt (±) or 3-(2-methyl-4-pyridyl)-5-cyano-4-isobutoxyphenyl)-1,2,4-triazole.

Preferred compounds having the above Formula I are: 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid, 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-(3-cyano-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylic acid, 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazolecarboxylic acid. These preferred compounds have also been found not have an effect at a therapeutically effective amount in a subject on the activity of any of the following enzymes involved in purine and pyrimidine metabolism: guanine deaminase, hypoxanthine-guanine phosphoribosyltransferase, purine nucleotide phosphorylase, orotate phosphoribosyltransferase or orotidine-5-monophosphate decarboxylase (i.e., meaning that it is "selective" for none of these enzymes which are involved in purine and pyrimidine metabolism). Assays for determining the activity for each of the above-described enzymes is described in Yasuhiro Takano, et al., *Life Sciences*, 76:1835-1847 (2005). These preferred compounds have also been referred to in the literature as nonpurine, selective inhibitors of xanthine oxidase (NP/SIXO).

Examples of compounds having the above Formula II are described in U.S. Pat. No. 5,268,386 and EP 0 415 566 A1, and are incorporated, in their entirety, herein.

With the exception of pyrazolo[1,5-a]-1,3,5-triazin-4-(1H)-one, 8-[3-methoxy-4-(phenylsulfinyl)phenyl]-sodium salt (±), methods for making xanthine oxidoreductase inhibiting compounds of Formulas I and II for use in the methods of the present disclosure are known in the art and are described, for example, in U.S. Pat. Nos. 5,268,386, 5,614,520, 6,225,474, 7,074,816 and EP 0 415 566 A1 and in the publications Ishibuchi, S. et al., *Bioorg. Med. Chem. Lett.*, 11:879-882 (2001) and which are each herein incorporated by reference. Other xanthine oxidoreductase inhibiting compounds can be found using xanthine oxidoreductase and xanthine in assays to determine if such candidate compounds inhibit conversion of xanthine into uric acid. Such assays are well known in the art.

Pyrazolo[1,5-a]-1,3,5-triazin-4-(1H)-one, 8-[3-methoxy-4-(phenylsulfinyl)phenyl]-sodium salt (±) is available from Otsuka Pharmaceutical Co. Ltd. (Tokyo, Japan) and is described in the following publications: Uematsu T., et al., "Pharmacokinetic and Pharmacodynamic Properties of a Novel Xanthine Oxidase Inhibitor, BOF-4272, in Healthy Volunteers, *J. Pharmacology and Experimental Therapeutics*, 270:453-459 (August 1994), Sato, S., A Novel Xanthine Deydrogenase Inhibitor (BOF-4272). *In Purine and Pyrimidine Metabolism in Man*, Vol. VII, Part A, ed. By P. A. Harkness, pp. 135-138, Plenum Press, New York. Pyrazolo[1,5-a]-

US 8,372,872 B2

13

1,3,5-triazin-4-(1H)-one, 8-[3-methoxy-4-(phenylsulfinyl)phenyl]-sodium salt (\pm) can be made using routine techniques known in the art.

II. Methods of Treatment

The present disclosure relates to methods of treating hyperuricemia in patients that also require treatment with theophylline, without having to adjust the theophylline dose to account for the hyperuricemia treatment. Specifically, the present disclosure provides in one aspect, a method of treating hyperuricemia in a patient in need of treatment thereof, the method comprising the step of: administering to a patient suffering from hyperuricemia and at least one secondary disease state, a therapeutically effective amount of at least one xanthine oxidoreductase inhibitor, wherein said subject is also receiving a concomitant administration of theophylline to treat the at least one second disease state, and further wherein (i) the administration of the at least one xanthine oxidoreductase inhibitor to said patient does not result in theophylline toxicity to said patient; and (ii) administration of the theophylline is in an amount ranging from about 90% to about 110% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor. More specifically, administration of the theophylline can be in an amount ranging from about 91% to about 109%, about 91% to about 108%, about 91% to about 107%, about 91% to about 106%, about 91% to about 105%, about 91% to about 104%, about 91% to about 103%, about 91% to about 102%, about 91% to about 101%, about 92% to about 109%, about 92% to about 108%, about 92% to about 107%, about 92% to about 106%, about 92% to about 105%, about 92% to about 104%, about 92% to about 103%, about 92% to about 102%, about 92% to about 101%, about 93% to about 109%, about 93% to about 108%, about 93% to about 107%, about 93% to about 106%, about 93% to about 105%, about 93% to about 104%, about 93% to about 103%, about 93% to about 102%, about 93% to about 101%, about 94% to about 109%, about 94% to about 108%, about 94% to about 107%, about 94% to about 106%, about 94% to about 105%, about 94% to about 104%, about 94% to about 103%, about 94% to about 102%, about 94% to about 101%, about 95% to about 109%, about 95% to about 108%, about 95% to about 107%, about 95% to about 106%, about 95% to about 105%, about 95% to about 104%, about 95% to about 103%, about 95% to about 102%, about 95% to about 101%, about 96% to about 109%, about 96% to about 108%, about 96% to about 107%, about 96% to about 106%, about 96% to about 105%, about 96% to about 104%, about 96% to about 103%, about 96% to about 102%, about 96% to about 101%, about 97% to about 109%, about 97% to about 108%, about 97% to about 107%, about 97% to about 106%, about 97% to about 105%, about 97% to about 104%, about 97% to about 103%, about 97% to about 102%, about 97% to about 101%, about 98% to about 109%, about 98% to about 108%, about 98% to about 107%, about 98% to about 106%, about 98% to about 105%, about 98% to about 104%, about 98% to about 103%, about 98% to about 102% or about 99% to about 101% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor.

In another aspect, the present disclosure provides a method of treating hyperuricemia in a patient in need of treatment

14

thereof, the method comprising the step of: administering to a patient suffering from hyperuricemia and at least one secondary disease state, a therapeutically effective amount of at least one xanthine oxidoreductase inhibitor, wherein said subject will also be receiving a concomitant administration of theophylline ("will also be receiving" meaning such as, concurrently with the xanthine oxidoreductase inhibitor, or subsequent to the initiation of treatment with the xanthine oxidoreductase inhibitor) to treat the at least one second disease state, and further wherein (i) the administration of the at least one xanthine oxidoreductase inhibitor to said patient does not result in theophylline toxicity to said patient; and (ii) administration of the theophylline is in an amount ranging from about 90% to about 110% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor. More specifically, administration of the theophylline can be in an amount ranging from about 91% to about 109%, about 91% to about 108%, about 91% to about 107%, about 91% to about 106%, about 91% to about 105%, about 91% to about 104%, about 91% to about 103%, about 91% to about 102%, about 91% to about 101%, about 92% to about 109%, about 92% to about 108%, about 92% to about 107%, about 92% to about 106%, about 92% to about 105%, about 92% to about 104%, about 92% to about 103%, about 92% to about 102%, about 92% to about 101%, about 93% to about 109%, about 93% to about 108%, about 93% to about 107%, about 93% to about 106%, about 93% to about 105%, about 93% to about 104%, about 93% to about 103%, about 93% to about 102%, about 93% to about 101%, about 94% to about 109%, about 94% to about 108%, about 94% to about 107%, about 94% to about 106%, about 94% to about 105%, about 94% to about 104%, about 94% to about 103%, about 94% to about 102%, about 94% to about 101%, about 95% to about 109%, about 95% to about 108%, about 95% to about 107%, about 95% to about 106%, about 95% to about 105%, about 95% to about 104%, about 95% to about 103%, about 95% to about 102%, about 95% to about 101%, about 96% to about 109%, about 96% to about 108%, about 96% to about 107%, about 96% to about 106%, about 96% to about 105%, about 96% to about 104%, about 96% to about 103%, about 96% to about 102%, about 96% to about 101%, about 97% to about 109%, about 97% to about 108%, about 97% to about 107%, about 97% to about 106%, about 97% to about 105%, about 97% to about 104%, about 97% to about 103%, about 97% to about 102%, about 97% to about 101%, about 98% to about 109%, about 98% to about 108%, about 98% to about 107%, about 98% to about 106%, about 98% to about 105%, about 98% to about 104%, about 98% to about 103%, about 98% to about 102%, about 98% to about 101%, about 99% to about 109%, about 99% to about 108%, about 99% to about 107%, about 99% to about 106%, about 99% to about 105%, about 99% to about 104%, about 99% to about 103%, about 99% to about 102% or about 99% to about 101% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor.

The method of the current invention comprises the co-administration of a xanthine oxidoreductase inhibitor and theophylline. The term xanthine oxidoreductase includes multiple therapeutic compounds, which have been described previously, and which are incorporated in their entirety herein. Generally, xanthine oxidoreductase inhibitors are compounds that inhibit the activity of xanthine oxidase, an enzyme involved in purine metabolism. In humans, inhibition of xanthine oxidase reduces the production of uric acid, which leads to secondary disease states such as gout, and other related diseases. Xanthine oxidoreductase inhibitors

US 8,372,872 B2

15

typically are classified as one of two types: purine analogues and non-purine analogues. The xanthine oxidoreductase inhibitors of the current invention include non-purine analogues, and, as noted previously, lack a purine ring in its chemical structure. In one embodiment, the xanthine oxidoreductase inhibitor includes, but is not limited to 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid (also known as "febuxostat"), 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-(3-cyano-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylic acid, 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazolecarboxylic acid, 1-(3-cyano-4-(2,2-dimethylpropoxy)phenyl)-1H-pyrazole-4-carboxylic acid, 1-3-cyano-4-(2,2-dimethylpropoxy)phenyl]-1H-pyrazole-4-carboxylic acid, pyrazolo[1,5-a]-1,3,5-triazin-4-(1H)-one, 8-[3-methoxy-4-(phenylsulfonyl)phenyl]-sodium salt (\pm) or 3-(2-methyl-4-pyridyl)-5-cyano-4-isobutoxyphenyl)-1,2,4-triazole. In another embodiment, the xanthine oxidoreductase inhibitor includes 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid, 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, and pharmaceutically acceptable salts thereof. In a further embodiment, the xanthine oxidoreductase inhibitor is 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid and pharmaceutically acceptable salts thereof.

The phrase "pharmaceutically acceptable salt(s)", as used herein, means those salts of compounds of the invention that are safe and effective for administration to a patient and that do not adversely affect the therapeutic qualities of the compound. Pharmaceutically acceptable salts include salts of acidic or basic groups present in compounds of the invention. Pharmaceutically acceptable acid addition salts include, but are not limited to, hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzensulfonate, p-toluenesulfonate and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Certain compounds of the invention can form pharmaceutically acceptable salts with various amino acids. Suitable base salts include, but are not limited to, aluminum, calcium, lithium, magnesium, potassium, sodium, zinc, and diethanolamine salts. For a review on pharmaceutically acceptable salts see Berge et al., *J. Pharm. Sci.*, 1977; 66:1-19, incorporated herein by reference, in its entirety.

One of skill in the art will also understand that the xanthine oxidoreductase inhibitors incorporated into the methods of the current invention may also incorporate pharmaceutically acceptable excipients. The dosage forms of the present disclosure will typically include pharmaceutically acceptable excipients. As is well known to those skilled in the art, pharmaceutical excipients are routinely incorporated into solid dosage forms to alter the physical and chemical characteristics of the dosage form. This is done to ease the manufacturing process as well as to improve the performance of the dosage form. Common excipients include, but are not limited to diluents, bulking agents, lubricants, binders, preservatives, antioxidants, and combinations thereof.

As used herein, the term "hyperuricemia" denotes a disease state in which the patient has as an elevation in serum urate (sUA) levels greater than or equal to 6.0 mg/dL in women and

16

men. Many factors contribute to hyperuricemia, including: genetics, insulin resistance, hypertension, renal insufficiency, obesity, diet, use of diuretics, and consumption of alcoholic beverages. Causes of hyperuricemia can be classified into three functional types: increased production of uric acid, decreased excretion of uric acid, and mixed type, incorporating both of the previous etiologies. Increased production etiologies result from high levels of purine in the diet and increased purine metabolism. Decreased excretion etiologies result from kidney disease, certain drugs, and competition for excretion between uric acid and other molecules. Mixed causes include high levels of alcohol and/or fructose in the diet, and starvation. Hyperuricemia typically develops into gout when urate crystals are formed from supersaturated body fluids and deposited in joints, tophi, and parenchymal organs due to a disorder in the urate metabolism. Uric acid is the end product of purine metabolism and is generated in the cascade of hypoxanthine \rightarrow xanthine \rightarrow uric acid.

In addition to suffering from hyperuricemia and at least one second disease state, the patients being treated according to the methods of the present disclosure may also be suffering from at least one third (or more) additional disease states. These third or more additional disease states include, but are not limited to, gout, hypertension, chronic stable angina, renal failure, nephrolithiasis, acute gouty arthritis, chronic gouty joint disease, tophaceous gout, uric acid urolithiasis, uric acid nephropathy, progressive renal disease, and combinations thereof. Alternatively, the patients being treated according to the methods of the present invention may be suffering from both gout and hyperuricemia. In such instances, the patient will also be suffering from at least one third disease state. The patient is or will be concomitantly administered theophylline to treat the at least third disease state. The at least one third disease state includes, but is not limited to asthma, acute bronchitis, chronic bronchitis, emphysema, neonatal apnea, neonatal bradycardia and combinations thereof. In addition, the patient may also be suffering from at least one fourth (or more) additional disease states. These fourth or more additional disease states include, but are not limited to, hypertension, chronic stable angina, renal failure, nephrolithiasis, acute gouty arthritis, chronic gouty joint disease, tophaceous gout, uric acid urolithiasis, uric acid nephropathy, progressive renal disease, and combinations thereof.

The methods of the current disclosure are directed to treating patients with secondary disease states that are indicated for, or require theophylline treatment. Theophylline is a methylxanthine compound used in the treatment of respiratory diseases resulting from airway constriction. Theophylline elicits a physiological response by two primary mechanisms, including competitive nonselective phosphodiesterase inhibitor, which raises intracellular cAMP, activates PKA, inhibits TNF-alpha and inhibits leukotriene synthesis, and reduces inflammation and innate immunity; and nonselective adenosine receptor antagonism, antagonizing A1, A2, and A3 receptors almost equally, which explains many of its cardiac effects and some of its anti-asthmatic effects. One skilled in the art will appreciate that the theophylline compound, as described herein is also known by its chemical name, 1,3-dimethyl-7H-purine-2,6-dione, its CAS Number, 58-55-9, and a multitude of brand name theophylline pharmaceutical products, incorporating theophylline as at least one of the active pharmaceutical ingredients. The theophylline component of the current methods also encompasses immediate release formulations, in addition to modified release formulations, including extended release, controlled release, and delayed release theophylline dosage forms. Dosage forms of

US 8,372,872 B2

17

theophylline may include tablets, capsules, sprinkle caps, liquid formulations, such as solutions and suspensions, and parenteral dosage forms including intravenous, intramuscular, intraarterial, intracerebral, intradermal, intrathecal, and intracerebral dosage forms, and subcutaneous dosage forms.

The methods of the current disclosure allow for theophylline to continue to be administered according to the manufacturer's suggested dosing of the compound. As used herein, the phrase "manufacturer's suggested dosing" signifies the dosing disclosed in the package insert of the theophylline dosage form and available in a variety of pharmaceutical treatment references. The methods of the current disclosure encompass the recommended dosing for all dosage forms, and include the treatment of all patients, for all disease states in which theophylline treatment may be effective. For example, a manufacturer's suggested dosing for oral theophylline may be 4-6 mg/kg. Thus, as described previously herein, in the present disclosure, administration of the theophylline is in an amount ranging from about 90% to about 110% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor. If the manufacturer's suggested dosing is 4-6 mg/kg, about 90% to about 110% would be from about 3.6 to about 6.6 mg/kg.

The methods of the current disclosure are directed to treating hyperuricemia in patients having a secondary disease state that is indicated for, or is being treated with theophylline. The secondary disease states may include chronic obstructive pulmonary disease (COPD), chronic obstructive lung disease (COLD), chronic obstructive airway disease (COAD), chronic airflow limitation (CAL) and chronic obstructive respiratory disease (CORD), asthma, acute bronchitis, chronic bronchitis, emphysema, neonatal apnea, neonatal bradycardia, and combinations thereof. It is also contemplated that the patient requiring treatment for hyperuricemia may suffer from at least one additional disease state. Generally, the at least one additional disease state may be secondary to the patient's hyperuricemia, or may derive from an etiology unrelated to the hyperuricemia. Examples of the at least one additional disease state include, but are not limited to, gout, hypertension, renal failure, nephrolithiasis, acute gouty arthritis, chronic gouty arthritis, tophaceous gout, uric acid urolithiasis, uric acid nephropathy, progressive renal disease, and combinations thereof.

The methods of the current disclosure are based on the surprising findings that certain xanthine oxidoreductase inhibitors may be administered concomitantly with theophylline without adversely affecting blood serum levels and theophylline, and, consequently, avoiding the typical adjustment in dosing due to hyperuricemia treatment. Theophylline is metabolized by cytochrome P-450 (hereinafter "CYP 450") to 1-methylxanthine, 3-methylxanthine, and 1,3-methyluric acid. Further, metabolism of 1-methylxanthine to 1-methyluric acid is mediated by xanthine oxidase. The xanthine oxidoreductase inhibitors described herein are not expected to have any inhibitory effect on CYP 450 involved in the metabolism of theophylline; however, because the xanthine oxidoreductase inhibitors are non-purine selective inhibitors of xanthine oxidase, it is generally expected that the compounds affect the xanthine oxidase mediate metabolism of theophylline and will decrease the clearance of theophylline, leading to increased theophylline serum levels. As stated previously, theophylline has a narrow therapeutic window, and even small increases in blood serum levels of the compound may result in serious adverse effects for the patient. However, the inventors surprisingly found that the administration of the xanthine oxidoreductase inhibitors described

18

herein do not adversely affect theophylline serum levels, and that adjustment of theophylline treatment dosages is not required. Additional details pertaining to the pharmacokinetic parameters of the coadministration of a xanthine oxidoreductase inhibitor and theophylline are described in the Examples.

Prior to the discovery of the present invention, in previous studies using the xanthine oxidoreductase inhibitor febuxostat, subjects taking concomitant therapy with certain medications, including theophylline, could be enrolled in the study only if the certain excluded medication was discontinued for a certain length of time. For example, as shown in Table 1 below, febuxostat study F-GT06-153 specifically provided that subjects taking theophylline could not be enrolled in the study, unless the theophylline was discontinued at least 30 days prior to the day 1 randomization visit.

TABLE 1

Inclusion Criteria for Febuxostat Study F-GT06-153

"5.2.4 Prohibited Concomitant Therapy

Subjects may not take any medication (other than study drug) for the purpose of lowering sUA levels. Subjects who have taken any of the excluded medications listed below, prior to the study, can be enrolled into the study if the excluded medication is discontinued at least 30 days prior to Day 1/Randomization Visit.

The following medications are not to be administered 30 days prior or during the study:

Any other urate-lowering drug, other than study drug;
Use of NSAIDs and COX-2 inhibitors other than protocol required prophylaxis therapy
(short-term use of NSAIDs and COX-2 inhibitors for treatment of gout flares is allowed);
Salicylates (chronic use of aspirin ≤ 325 mg/day is allowed);
Thiazide diuretics;
Losartan;
Azathioprine;
Mercaptopurine;
Theophylline;
IV Colchicine;
Cyclosporine;
Cyclophosphamide;
Pyrazinamide;
Sulfamethoxazole/trimethoprim;
Use of corticosteroids (chronic prednisone ≤ 10 mg/day or its equivalent and short-term use of higher doses of prednisone for treatment of gout flares is allowed);
Changes in hormone replacement therapy or oral contraceptive therapy within 3 months of the Day 1/Randomization Visit or during the course of the study."

As is evident from Table 1 above, the coadministration of theophylline and urate-lowering therapies is a significant clinical concern, and one that must be considered prior to initiation of urate-lowering therapies.

While hyperuricemia is one of the primary disease states treated by the xanthine oxidoreductase inhibitors discussed herein, one of skill in the art will appreciate that the methods of the current disclosure are equally applicable to other disease states that are typically treated by administration of one or more xanthine oxidoreductase inhibitors. These other disease states include, but are not limited to, gout, prostatitis, inflammatory bowel disease, QT interval prolongation, myocardial infarction, cardiac hypertrophy, hypertension, nephrolithiasis, renal impairment, chronic kidney disease, metabolic syndrome (also referred to as "Syndrome X" and includes, at least one of abdominal obesity, atherogenic dyslipidemia, insulin resistance, glucose intolerance, a prothrombotic state or a proinflammatory state), diabetes, diabetic nephropathy, congestive heart failure and combinations thereof (these conditions are sometimes collectively referred to herein as "at least one first disease state"). Accordingly, the

US 8,372,872 B2

19

current methods encompass treating a patient having one of the aforementioned at least one first disease state and also having a second disease state requiring theophylline treatment, through the administration of a xanthine oxidoreductase inhibitor without significant adjustment of the manufacturer's suggested dosing, and without inducing theophylline toxicity. Moreover, the current methods further encompass treating a patient having one of the aforementioned at least one first disease state, at least one second disease state requiring the theophylline treatment and at least one third disease state. In addition to suffering from hyperuricemia and at least one second disease state, the patients being treated according to the methods of the present disclosure may also be suffering from at least one third (or more) additional disease states. These third or more additional disease states include, but are not limited to, gout, hypertension, chronic stable angina, renal failure, nephrolithiasis, acute gouty arthritis, chronic gouty joint disease, tophaceous gout, uric acid urolithiasis, uric acid nephropathy, progressive renal disease, and combinations thereof.

By way of example, and not of limitation, examples of the present disclosure will now be given.

EXAMPLE 1

Effects of Multiple Febuxostat Doses on the Pharmacokinetics of Theophylline Administration

An experiment was performed to determine the effects of multiple doses of a xanthine oxidoreductase inhibitor, 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid, also known as "febuxostat", on theophylline doses. The experiment was a phase I, double-blind, randomized, 2-period crossover study, in which 24 patients (12 male and 12 female) were enrolled in the study. Specifically, the total duration of the study was approximately 8 weeks (60 days), consisting of a Screening Period (Days-28 to -2), Check-in (Day-1) for Period 1, 7-day Treatment, a Washout Period (minimum of 7 days), Check-in for Period 2, 7-day Treatment, Study Exit or Early Termination, and a Follow-up phone call 10±2 days after the last dose of study medication. Subjects received both Regimens A and B in randomly assigned order. These regimens consisted of 7 daily doses of double-blind febuxostat 80 mg (A: two encapsulated febuxostat 40 mg tablets or B: matching placebo) and one dose (on Day 5 of each period) open-label theophylline 400 mg tablet.

On Days 1 to 7 of each period, subjects received febuxostat 80 mg or matching placebo at approximately 0900 hours after a minimum 10-hour fast, and followed 1 hour later by a standardized breakfast. On Day 5 of each period, subjects received a single oral dose of Uniphyll® (theophylline, anhydrous) 400 mg tablet along with the daily dose of febuxostat or matching placebo; food was first allowed 4 hours postdose. Water was available as desired, except for 1 hour before through 1 hour after study drug administration. Only 240 mL of water was allowed during dosing. Subjects were discharged in the morning of Day 8 of each Period (1 and 2), after plasma and urine pharmacokinetic sample collections and all study procedures were completed. For Day-1 of Period 2, subjects returned to the clinic after a minimum of 7 day washout period. For all subjects that completed both Periods 1 and 2 (or discontinued the study prematurely at an Early Termination visit, i.e., withdrew from study), a follow-up phone call was made 10±2 days after the last dose of study medication or Early Termination (ET). The effect of multiple oral doses of febuxostat on the pharmacokinetics of a single oral dose of theophylline were evaluated through measurement of plasma and urine concentration levels of theophylline at designated time points. Safety, tolerability, and theophyll-

20

line toxicity were assessed throughout the study by monitoring adverse effects, clinical laboratory tests, vital signs, ECGs, and physical examination findings.

Theophylline plasma concentrations were determined from 7 mL blood samples obtained according to the schedules in Table 1 below. Trough febuxostat plasma concentrations were determined from 6 mL blood samples obtained according to the schedules in Table 2.

TABLE 2

Period 1 and 2: Blood Collection Schedules for Determination of Plasma Concentrations of Theophylline and Febuxostat		
	Blood Sample Collection for Pharmacokinetics	
	Theophylline	Febuxostat
15	Predose (up to 30 minutes prior to dosing [0 hour]) and at 1, 2, 3, 4, 6, 8, 10, 12, and 14 hours postdose	Predose (up to 30 minutes prior to dosing [0 hour])
20	16, 24, and 32 hours post Periods 1 and 2 Day 5 dosing Day 7 of 40, 48, and 56 hours post Periods 1 and 2 Day 5 dosing Day 8 of 64 and 72 hours post Periods 1 and 2 Day 5 dosing	Predose (up to 30 minutes prior to dosing [0 hour]) None None

Additionally, to ensure that the drug plasma levels were not altered by secondary conditions and medications, this experiment required subjects to abstain from the use of certain medications and other agents prior to and during the testing periods. The excluded medications and agents are summarized in Table 3 (prescription and nonprescription), including specifications on applicable time points through completion of all study activities.

TABLE 3

Excluded Medications and Agents			
6 weeks prior to Check-in (Day-1)	28 days prior to Check-in (Day-1)	14 days prior to Check-in (Day-1)	48 hours prior to Check-in (Day-1)
Nicotine-containing products	Prescription medications	Foods or beverages containing grapefruit or Seville oranges	Alcohol-containing products
Hormonal contraception (oral, patch, implant, vaginal ring, or injectable)	Over-the-counter medications, vitamins, herbal, or dietary supplements	Food or beverages containing caffeine or xanthine related substances	
Hormone replacement therapy	Hepatic or renal clearance altering agents (erythromycin, cimetidine, barbituates, phenothiazines, etc)	Charbroiled foods	
Febuxostat or Allopurinol			

Note:
excluded medications are from timepoints through completion of all study activities.

Subjects were instructed not to take any medications or non-prescription drugs, vitamins, herbal supplements, or dietary supplements within 28 days prior to Check-in (Day-1).

The subjects of the current experiment were administered the appropriate dosage regimens and the pharmacokinetic data were evaluated. Mean plasma theophylline concentration vs. time profiles (linear and log-linear formats) for the two treatment regimens are depicted in FIG. 1. Additionally, individual and summary statistics of noncompartmental phar-

US 8,372,872 B2

21

macokinetic parameter estimates for theophylline following coadministration with febuxostat or placebo are presented in Table 4 below.

22

As illustrated in Table 5 above, the mean amount of parent drug (i.e., theophylline) excreted in the urine over a 72 hour interval were comparable between regimen arms and consis-

TABLE 4

Summary of Theophylline Pharmacokinetic Parameter Estimates Following an Oral Dose of 400 mg Theophylline Coadministered With 80 mg Febuxostat or Matching Placebo							
	Tmax (hr)	Cmax (μ g/mL)	AUC(0-tlqc) (μ g · hr/mL)	AUC(0-inf)(a) (μ g · hr/mL)	T _{1/2} (a) (hr)	CL/F(a) (mL/h)	Vz/F(a) (mL)
Theophylline + Febuxostat (Regimen A)							
N	23	23	23	18	18	18	18
Mean	8.43(b)	4.39	122	114	9.69(c)	4430	56900
SD	4.62	1.74	55.7	53.4	2.32	2370	20400
CV %	55	40	45	47	24	53	36
Theophylline + Placebo (Regimen B)							
N	23	23	23	18	18	18	18
Mean	7.05(b)	4.14	115	107	9.69(c)	4430	58200
SD	2.88	1.19	50.3	49.9	2.07	1930	17200
CV %	41	29	44	46	21	44	30

Regimen A: Febuxostat 80 mg (two 40 mg encapsulated tablets) QD for 7 consecutive days and a single oral dose of theophylline, anhydrous 400 mg tablet on Day 5.

Regimen B: Matching placebo for febuxostat 80 mg (two 40 mg encapsulated tablets) QD for 7 consecutive days and a single oral dose of theophylline, anhydrous 400 mg tablet on Day 5.

(a)The terminal phase of the pharmacokinetic profile of theophylline could not be adequately characterized in the remaining subjects.

(b)Median Tmax values for Regimens A and B were 6.02 and 6.00 hr, respectively.

(c)Harmonic mean T_{1/2} values for Regimens A and B were 9.13 and 9.28 hr, respectively.

As illustrated in Table 4 above, theophylline was absorbed with a mean T_{max} value of 7 to 9 hours (median=6 hours) and eliminated with a mean terminal half-life of 9.69 hours following oral administration of 400 mg theophylline with placebo or febuxostat. Mean theophylline C_{max} values were 4.14 and 4.39 μ g/mL for subjects coadministered with placebo and febuxostat, respectively. Mean theophylline AUC(0-tlqc) values were 115 μ g·hr/mL and 122 μ g·hr/mL for subjects coadministered with placebo and febuxostat, respectively. Likewise, mean AUC(0-inf) values were also comparable between regimens. The intersubject variability (% CV) of C_{max} and AUC(0-tlqc) values of theophylline ranged from 29% to 40% and 44% to 45%, respectively. The estimated mean $T_{1/2}$, CL/F, and V_z/F values for theophylline were generally similar between the 2 treatment regimens.

tent with the literature. See Melethil S et al., *Res Commun Chem Pathol Pharmacol.*, 1982; 35(2):341-4. The mean amounts of 1,3-dimethyluric acid and 3-methylxanthine were also similar between the 2 regimens. In contrast, 1-methyluric acid decreased and 1-methylxanthine increased in subjects administered theophylline with febuxostat compared with those subjects administered theophylline with placebo.

A statistical analysis of the data was also performed. The effects of sequence, period, and regimen on theophylline T_{max} , ln(C_{max}), ln(AUC[0-tlqc]), and ln(AUC[0-inf]) following coadministration of febuxostat or placebo were assessed. None of the aforementioned effects were statistically significant on the pharmacokinetic parameters ($P>0.05$) observed in the experiment. Further, the bioavailability of theophylline coadministered with febuxostat (Regimen A) relative to that of theophylline with placebo (Regimen B) was assessed via

TABLE 5

Summary of Total Amount of Theophylline and Its Metabolites Excreted in Urine Over 72 Hours Following an Oral Dose of 400 mg Theophylline Coadministered With 80 mg Febuxostat or Matching Placebo					
	Theophylline (mg)	1,3-Dimethyluric acid (mg)	1-Methyluric acid (mg)	1-Methylxanthine (mg)	3-Methylxanthine (mg)
Theophylline + Febuxostat (Regimen A)					
N	23	23	23	23	23
Mean	35.0	105.2	3.1	40.1	26.9
SD	18.1	23.3	4.0	7.6	9.5
CV %	52	22	127	19	35
Theophylline + Placebo (Regimen B)					
N	23	23	23	23	23
Mean	35.0	114.8	56.2	0.1	30.9
SD	16.8	32.2	17.4	0.4	11.6
CV %	48	28	31	337	38

Regimen A: Febuxostat 80 mg (two 40 mg encapsulated tablets) QD for 7 consecutive days and a single oral dose of theophylline, anhydrous 400 mg tablet on Day 5.

Regimen B: Matching placebo for febuxostat 80 mg (two 40 mg encapsulated tablets) QD for 7 consecutive days and a single oral dose of theophylline, anhydrous 400 mg tablet on Day 5.

US 8,372,872 B2

23

point estimates and 90% confidence intervals for the ratios of the central values for C_{max} , AUC(0-tlqc), and AUC(0-inf), and is summarized in Table 6.

TABLE 6

Relative Bioavailability of Febuxostat Following Administration of a Single Oral Dose of 80 mg Febuxostat		
Parameter	Point Estimate	90% Confidence Interval
Regimen A vs Regimen B		
Cmax	1.03	(0.917, 1.149)
AUC(0-tlqc)	1.04	(0.927, 1.156)
AUC(0-inf)	1.05	(0.924, 1.189)

Regimen A: Febuxostat 80 mg (two 40 mg encapsulated tablets) QD for 7 consecutive days and a single oral dose of theophylline, anhydrous 400 mg tablet on Day 5.
 Regimen B: Matching Placebo for febuxostat 80 mg (two 40 mg encapsulated tablets) QD for 7 consecutive days and a single oral dose of theophylline, anhydrous 400 mg tablet on Day 5.

Note:

The point estimates and confidence intervals were obtained from the exponentiated results of analysis of the natural logarithm transformed data.

From the statistical analyses of the pharmacokinetic data, the point estimates for theophylline C_{max} , AUC(0-tlqc), and AUC

24

(0-inf) were close to 100%, and the 90% confidence intervals for the ratios were within the bioequivalence limit of 0.80 to 1.25.

The results of this experiment showed that the maximum observed theophylline concentration (C_{max}) and exposure to theophylline (AUC) were comparable between treatment with febuxostat and treatment with placebo. Therefore, no adjustment of the theophylline dose was needed when coadministered with febuxostat.

What is claimed is:

1. A method of co-administering febuxostat and theophylline to a hyperuricemic patient suffering from gout, the method comprising the steps of:

administering to the hyperuricemic patient suffering from gout a therapeutically effective amount of febuxostat in a dose of 80 mg; and

administering to the patient a therapeutically effective amount of theophylline subsequent to the administration of the febuxostat without adjusting the amount of theophylline administered for adverse drug interactions.

* * * * *

EXHIBIT C

(12) **United States Patent**
Gunawardhana et al.(10) **Patent No.:** US 9,107,912 B2
(45) **Date of Patent:** *Aug. 18, 2015

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(58) **Field of Classification Search**

CPC . *A61K 31/426*; *A61K 31/415*; *A61K 31/522*; *A61K 45/06*

USPC 514/365, 263.34

See application file for complete search history.

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Primary Examiner — Jennifer M Kim**(74) Attorney, Agent, or Firm — Lisa V. Mueller; Michael Best & Friedrich LLP**(57) **ABSTRACT**

The present disclosure relates to a method of treating hyperuricemia in a patient that also suffers from a second disease state requiring treatment with theophylline, wherein the patient receives concomitant treatment with a xanthine oxidoreductase inhibitor and theophylline without resulting in theophylline toxicity to the patient and without substantial adjustments to the manufacturer's recommended dosage of theophylline.

US 9,107,912 B2

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Page 5

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US 9,107,912 B2

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US 9,107,912 B2

Page 10

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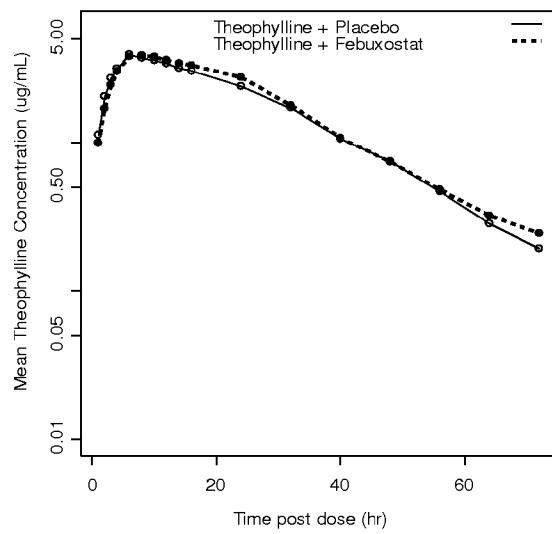
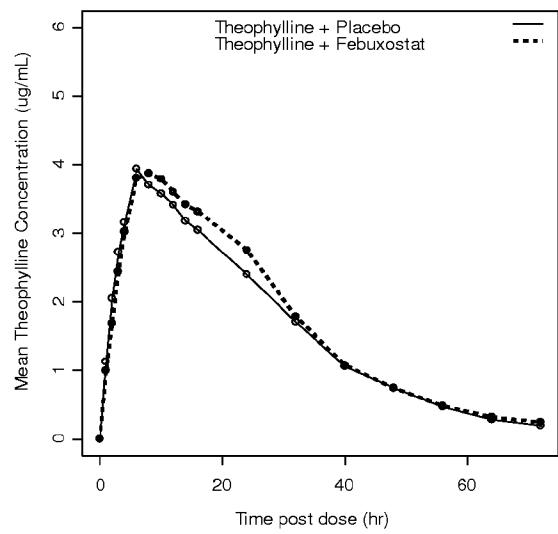
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U.S. Patent

Aug. 18, 2015

US 9,107,912 B2



US 9,107,912 B2

1

**METHODS FOR CONCOMITANT
TREATMENT OF THEOPHYLLINE AND
FEBUXOSTAT**

RELATED APPLICATION INFORMATION

This application claims priority to U.S. Provisional Patent Application No. 61/381,482 filed on Sep. 10, 2010, the contents of which are herein incorporated by reference in their entirety.

FIELD

The present disclosure relates to novel methods for treating hyperuricemia in patients also requiring treatment with theophylline. Specifically, the invention is directed to a method of administering theophylline in conjunction with one or more xanthine oxidoreductase inhibitors, whereby the xanthine oxidoreductase inhibitors do not cause alterations in the plasma concentrations of theophylline.

BACKGROUND

A substantial number of patients are affected with diseases of the respiratory system, including asthma, acute bronchitis, chronic bronchitis, emphysema, neonatal apnea, and neonatal bradycardia. One of the primary treatments for respiratory diseases is the use of theophylline.

Theophylline is a useful medicine frequently used as an agent for treating symptoms of bronchial asthma. It is known in the art that effective blood concentrations range from about 10 to 20 µg/ml. However, if the concentration of theophylline in the blood exceeds 20 µg/ml, serious side effects sometimes appear with regard to the cardiovascular system and the central nervous system. Further, there is a large difference in blood levels among individuals. Various conditions (e.g., cardiac insufficiency, liver and kidney disease, etc.), age differences, smoking, etc. also have large effects. Additionally, theophylline has a short biological half-life of about 6 hours for adults. In order to maintain the effective blood level, four doses per day have been considered necessary. However, such frequent dosing is troublesome to patients, reduces patient compliance, and causes the state of the disease to become worse. In particular, attacks of bronchial asthma often occur at daybreak. It is not possible to sufficiently prevent such attacks with ingestion of theophylline just before going to bed, and therefore, repeat ingestion close to daybreak is necessary. Thus, in the past, continuous effort has been made to develop a sustained release type theophylline formulation. Several formulations are already available on the market.

Another disease that affects a substantial number of patients is gout. Gout affects 3 to 5 million individuals in the United States of America (USA) and is increasing in incidence and prevalence. Gout is a serious health condition characterized by flares of acute arthritis, chronic gouty arthropathy, tophi, and uric acid urolithiasis, and is associated with a broad range of comorbidities, including cardiovascular disease, chronic kidney disease, and metabolic syndrome. At the joint level, a gout flare is best characterized as an acute monoarthritis arthropathy process with proliferative bone reaction that can affect any joint and that can later develop into chronic polyarthritis. Gout attacks tend to occur mostly in the lower extremities and over time additional joints can be involved.

The underlying metabolic aberration in gout is hyperuricemia, which is a condition defined as an elevation in serum urate (sUA) level ≥6.8 mg/dL. Hyperuricemia develops into

2

gout when urate crystals are formed from supersaturated body fluids and deposited in joints, tophi, and parenchymal organs due to a disorder in the urate metabolism. Uric acid is the end product of purine metabolism and is generated in the cascade of hypoxanthine→xanthine→uric acid.

Urate-lowering therapy (ULT) is used to treat hyperuricemia in subjects with gout. The goal of ULT is to reduce sUA to 6.0 mg/dL or less, below the concentration at which monosodium urate saturates extracellular fluid. Using ULT to reduce and maintain sUA levels <6.0 mg/dL ultimately improves the clinical symptoms of gout by reducing the frequency of gout flares, decreasing size and number of tophi, and improving quality of life. One alternative that may be used for the treatment of gout is the administration of xanthine oxidase inhibitors, such as allopurinol. Generally, allopurinol is considered one of the primary treatments of gout and has developed wide usage as a treatment for gout.

However, clinicians have few treatment options for hyperuricemic patients also suffering from respiratory diseases, such as chronic obstructive pulmonary disease, asthma, acute bronchitis, chronic bronchitis, emphysema, neonatal apnea, and neonatal bradycardia. One of the primary treatments for these respiratory diseases is the administration of theophylline, a bronchodilator. Although theophylline provides a treatment for the respiratory diseases described herein, the therapeutic range of theophylline blood concentrations is thought to be very narrow, ranging from about 10 to about 20 µg/ml. As such, if the theophylline dosing does not provide a minimum blood concentration of 10 µg/ml, the patient is not provided significant relief from the respiratory condition, and at blood concentrations greater than 20 µg/ml, the patient may be susceptible to adverse effects such as abdominal pain, headache, muscle cramps, tremors, tachycardia, and seizures. Therefore, clinicians must exercise caution in determining treatment options for patients requiring theophylline treatment, and must closely monitor the potential for drug interactions that may increase or decrease theophylline blood concentrations.

It is further known within the art that the administration of allopurinol interacts with the metabolism of theophylline, causing the theophylline to be metabolized slowly, and leading to increased blood concentrations. As discussed in the art, the area under the curve (AUC) for theophylline in patients co-administered allopurinol and theophylline has been reported to increase by up to 27%, the half-life increased by approximately 25%, and the clearance of theophylline may be decreased by 21% (Manfredi B A, et al., *Clin. Pharmacol. Ther.*, 1981; 29(2), pp. 224-229). Accordingly, clinicians are required to alter the theophylline dosing and/or the allopurinol dosing in hopes of establishing a therapeutic dose for both disease states, while avoiding unwanted adverse effects that may result from increased theophylline concentrations.

Thus, in view of these considerations, there exists within the art a need to develop a treatment option for hyperuricemic patients that also suffer from respiratory disorders, whereby the clinician can administer typical dosing of theophylline without adjusting for adverse drug interactions.

SUMMARY

The present disclosure is directed to methods for treating hyperuricemia in patients requiring treatment with theophylline. The methods of the current invention avoid the drug interactions typically associated with theophylline administration and concomitant treatment with xanthine oxidase inhibitors.

US 9,107,912 B2

3

In one embodiment, the present disclosure provides a method of treating hyperuricemia in a patient in need of treatment thereof, the method comprising the steps of: administering to the patient suffering from hyperuricemia and at least one secondary disease state, a therapeutically effective amount of at least one xanthine oxidoreductase inhibitor, wherein said subject is also receiving a concomitant administration of theophylline to treat the at least one secondary disease state; and further wherein (i) the administration of the at least one xanthine oxidoreductase inhibitor to said patient does not result in theophylline toxicity to said patient; and (ii) administration of the theophylline is in an amount ranging from about 90% to about 110% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor.

The secondary disease state may include asthma, acute bronchitis, chronic bronchitis, emphysema, neonatal apnea, neonatal bradycardia, and combinations thereof. As described in the method of this embodiment, the xanthine oxidoreductase inhibitor may include 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid, 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-(3-cyano-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylic acid, 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazolecarboxylic acid, 1-(3-cyano-4-(2,2-dimethylpropoxy)phenyl)-1H-pyrazole-4-carboxylic acid, 1-3-cyano-4-(2,2-dimethylpropoxy)phenyl]-1H-pyrazole-4-carboxylic acid, pyrazolo[1,5-a]-1,3,5-triazin-4-(1H)-one, 8-[3-methoxy-4-(phenylsulfinyl)phenyl]-sodium salt (\pm), 3-(2-methyl-4-pyridyl)-5-cyano-4-isobutoxyphenyl)-1,2,4-triazole and pharmaceutically acceptable salts thereof.

Moreover, the method of the current embodiment may include a theophylline dose ranging from about 95% to about 105%, and from about 99% to about 101% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor. The method of the current invention may also include patients suffering from a third disease state, including gout, hypertension, renal failure, nephrolithiasis, acute gouty arthritis, chronic gouty joint disease, tophaceous gout, uric acid urolithiasis, uric acid nephropathy, progressive renal disease, and combinations thereof. Further, the methods of the current embodiment include the treatment of hyperuricemia in patients that were previously receiving theophylline treatment prior to treatment with a xanthine oxidoreductase inhibitor.

In another embodiment, the current invention provides a method of treating hyperuricemia in a patient in need of treatment thereof, the method comprising the steps of: administering to the patient suffering from hyperuricemia and at least one second disease state, a therapeutically effective amount of at least one xanthine oxidoreductase inhibitor, wherein said subject will also be receiving a concomitant administration of theophylline to treat at least one second disease state, and further wherein (i) the administration of the at least one xanthine oxidoreductase inhibitor to said patient will not result in theophylline toxicity to said patient; and (ii) administration of the theophylline will be in an amount ranging from about 90% to about 110% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor.

The secondary disease state may include asthma, acute bronchitis, chronic bronchitis, emphysema, neonatal apnea, neonatal bradycardia, and combinations thereof. As

4

described in the method of this embodiment, the xanthine oxidoreductase inhibitor may include 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid, 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-(3-cyano-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylic acid, 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazolecarboxylic acid, 1-(3-cyano-4-(2,2-dimethylpropoxy)phenyl)-1H-pyrazole-4-carboxylic acid, 1-3-cyano-4-(2,2-dimethylpropoxy)phenyl]-1H-pyrazole-4-carboxylic acid, pyrazolo[1,5-a]-1,3,5-triazin-4-(1H)-one, 8-[3-methoxy-4-(phenylsulfinyl)phenyl]-sodium salt (\pm), 3-(2-methyl-4-pyridyl)-5-cyano-4-isobutoxyphenyl)-1,2,4-triazole and pharmaceutically acceptable salts thereof.

Moreover, the method of the current embodiment may include a theophylline dose ranging from about 95% to about 105%, and from about 99% to about 101% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor. The method of the current invention may also include patients suffering from a third disease state, including gout, hypertension, renal failure, nephrolithiasis, acute gouty arthritis, chronic gouty joint disease, tophaceous gout, uric acid urolithiasis, uric acid nephropathy, progressive renal disease, and combinations thereof. Further, the methods of the current embodiment include the treatment of hyperuricemia in patients that have not previously received theophylline treatment prior to treatment with a xanthine oxidoreductase inhibitor, and will begin treatment with both medications concurrently.

In yet another embodiment, the present disclosure provides a method of treating hyperuricemia in a patient suffering from gout and in need of treatment thereof, the method comprising the steps of: administering to the patient suffering from gout and hyperuricemia and at least one third disease state, a therapeutically effective amount of at least one xanthine oxidoreductase inhibitor, wherein said subject is also receiving a concomitant administration of theophylline to treat the at least one third disease state; and further wherein (i) the administration of the at least one xanthine oxidoreductase inhibitor to said patient does not result in theophylline toxicity to said patient; and (ii) administration of the theophylline is in an amount ranging from about 90% to about 110% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor.

The third disease state may include asthma, acute bronchitis, chronic bronchitis, emphysema, neonatal apnea, neonatal bradycardia, and combinations thereof. As described in the method of this embodiment, the xanthine oxidoreductase inhibitor may include 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid, 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-(3-cyano-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylic acid, 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazolecarboxylic acid, 1-(3-cyano-4-(2,2-dimethylpropoxy)phenyl)-1H-pyrazole-4-carboxylic acid, 1-3-cyano-4-(2,2-dimethylpropoxy)phenyl]-1H-pyrazole-4-carboxylic acid, pyrazolo[1,5-a]-1,3,5-triazin-4-(1H)-one, 8-[3-methoxy-4-(phenylsulfinyl)phenyl]-sodium salt (\pm), 3-(2-methyl-4-pyridyl)-5-cyano-4-isobutoxyphenyl)-1,2,4-triazole and pharmaceutically acceptable salts thereof.

Moreover, the method of the current embodiment may include a theophylline dose ranging from about 95% to about

US 9,107,912 B2

5

105%, and from about 99% to about 101% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor. The method of the current invention may also include patients suffering from a fourth disease state, including hypertension, renal failure, nephrolithiasis, acute gouty arthritis, chronic gouty joint disease, tophaceous gout, uric acid urolithiasis, uric acid nephropathy, progressive renal disease, and combinations thereof. Further, the methods of the current embodiment include the treatment of hyperuricemia in patients suffering from gout and that were previously receiving theophylline treatment prior to treatment with a xanthine oxidoreductase inhibitor.

In another embodiment, the current invention provides a method of treating hyperuricemia in a patient suffering from gout and in need of treatment thereof, the method comprising the steps of: administering to the patient suffering from gout and hyperuricemia and at least one third disease state, a therapeutically effective amount of at least one xanthine oxidoreductase inhibitor, wherein said subject will also be receiving a concomitant administration of theophylline to treat at least one third disease state, and further wherein (i) the administration of the at least one xanthine oxidoreductase inhibitor to said patient will not result in theophylline toxicity to said patient; and (ii) administration of the theophylline will be in an amount ranging from about 90% to about 110% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor.

The third disease state may include asthma, acute bronchitis, chronic bronchitis, emphysema, neonatal apnea, neonatal bradycardia, and combinations thereof. As described in the method of this embodiment, the xanthine oxidoreductase inhibitor may include 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid, 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2,2-dimethylpropoxy)phenyl]-1H-pyrazole-4-carboxylic acid, 1-(3-cyano-4-(2,2-dimethylpropoxy)phenyl)-1H-pyrazole-4-carboxylic acid, 1-(3-cyano-4-(2,2-dimethylpropoxy)phenyl)-1H-pyrazole-4-carboxylic acid, pyrazolo[1,5-a]-1,3,5-triazin-4-(1H)-one, 8-[3-methoxy-4-(phenylsulfinyl)phenyl]-sodium salt (\pm), 3-(2-methyl-4-pyridyl)-5-cyano-4-isobutoxyphenyl)-1,2,4-triazole and pharmaceutically acceptable salts thereof.

Moreover, the method of the current embodiment may include a theophylline dose ranging from about 95% to about 105%, and from about 99% to about 101% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor. The method of the current invention may also include patients suffering from a fourth disease state, including hypertension, renal failure, nephrolithiasis, acute gouty arthritis, chronic gouty joint disease, tophaceous gout, uric acid urolithiasis, uric acid nephropathy, progressive renal disease, and combinations thereof. Further, the methods of the current embodiment include the treatment of hyperuricemia in patients that have not previously received theophylline treatment prior to treatment with a xanthine oxidoreductase inhibitor, and will begin treatment with both medications concurrently.

In still yet another embodiment, the present disclosure provides a method of treating a patient in need of treatment thereof, the method comprising the steps of: administering to the patient suffering from at least one first disease state and at

6

least one secondary disease state, a therapeutically effective amount of at least one xanthine oxidoreductase inhibitor, wherein said subject is also receiving a concomitant administration of theophylline to treat the at least one secondary disease state; and further wherein (i) the administration of the at least one xanthine oxidoreductase inhibitor to said patient does not result in theophylline toxicity to said patient; and (ii) administration of the theophylline is in an amount ranging from about 90% to about 110% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor.

The first disease state may include gout, prostatitis, inflammatory bowel disease, QT interval prolongation, myocardial infarction, cardiac hypertrophy, hypertension, nephrolithiasis, renal impairment, chronic kidney disease, metabolic syndrome, diabetes, diabetic nephropathy, congestive heart failure and combinations thereof.

The secondary disease state may include asthma, acute bronchitis, chronic bronchitis, emphysema, neonatal apnea, neonatal bradycardia, and combinations thereof. As described in the method of this embodiment, the xanthine oxidoreductase inhibitor may include 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid, 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2,2-dimethylpropoxy)phenyl]-1H-pyrazole-4-carboxylic acid, 1-(3-cyano-4-(2,2-dimethylpropoxy)phenyl)-1H-pyrazole-4-carboxylic acid, 1-(3-cyano-4-(2,2-dimethylpropoxy)phenyl)-1H-pyrazole-4-carboxylic acid, pyrazolo[1,5-a]-1,3,5-triazin-4-(1H)-one, 8-[3-methoxy-4-(phenylsulfinyl)phenyl]-sodium salt (\pm), 3-(2-methyl-4-pyridyl)-5-cyano-4-isobutoxyphenyl)-1,2,4-triazole and pharmaceutically acceptable salts thereof.

Moreover, the method of the current embodiment may include a theophylline dose ranging from about 95% to about 105%, and from about 99% to about 101% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor. The method of the current invention may also include patients suffering from a third disease state, including gout, hypertension, renal failure, nephrolithiasis, acute gouty arthritis, chronic gouty joint disease, tophaceous gout, uric acid urolithiasis, uric acid nephropathy, progressive renal disease, and combinations thereof. Further, the methods of the current embodiment include the treatment of the first disease state in patients that were previously receiving theophylline treatment prior to treatment with a xanthine oxidoreductase inhibitor.

BRIEF DESCRIPTION OF THE FIGURE

FIG. 1 shows the mean theophylline plasma concentration-time profiles following an oral dose of 400 mg theophylline coadministered with 80 mg of 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid (also known as "febuxostat") or matching placebo as described in Example 1.

DETAILED DESCRIPTION OF THE DISCLOSURE

I. Definitions

Section headings as used in this section and the entire disclosure herein are not intended to be limiting.

US 9,107,912 B2

7

As used herein, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise. For the recitation of numeric ranges herein, each intervening number there between with the same degree of precision is explicitly contemplated. For example, for the range 6-9, the numbers 7 and 8 are contemplated in addition to 6 and 9, and for the range 6.0-7.0, the numbers 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9 and 7.0 are explicitly contemplated.

As used herein, the term “about” is used synonymously with the term “approximately.” Illustratively, the use of the term “about” indicates that values slightly outside the cited values, namely, plus or minus 10%. Such dosages are thus encompassed by the scope of the claims reciting the terms “about” and “approximately.”

As used herein, the term “AUC” refers to the area under the plasma concentration time curve of the active agent and which is calculated using the trapezoidal rule. The term “ AUC_t ” means the area under the plasma concentration time curve from time 0 to 120 hours after administration in units of $\text{ng}\cdot\text{h}/\text{mL}$ as determined using the trapezoidal rule. The term “ AUC_∞ ” means the area under the plasma concentration time curve from time 0 to infinite time. AUC_∞ is calculated as $AUC_t + LMT/(-\beta)$, where “LMT” is the last measurable plasma concentration and β is the terminal phase elimination rate constant. Unless otherwise noted herein, the reported value for the AUC is the central value of the AUC. The “central value” of the AUC is the mean $AUC \pm$ standard deviation.

The terms “administer”, “administering”, “administered” or “administration” refer to any manner of providing a drug (such as, a xanthine oxidoreductase inhibitor or a pharmaceutically acceptable salt thereof) to a subject or patient. Routes of administration can be accomplished through any means known by those skilled in the art. Such means include, but are not limited to, oral, buccal, intravenous, subcutaneous, intramuscular, transdermal, by inhalation and the like.

The term “active agent” as used herein refers to (1) a xanthine oxidoreductase inhibitor or a pharmaceutically acceptable salt thereof or (2) a xanthine oxidase inhibitor or a pharmaceutically acceptable salt thereof. The term “active agent” and “drug” are used interchangeably herein. The solid state form of the active agent used in preparing the dosage forms of the present disclosure is not critical. For example, active agent used in preparing the modified release dosage forms of the present disclosure can be amorphous or crystalline. The final dosage form contains at least a detectable amount of crystalline active agent. The crystalline nature of the active agent can be detected using powder X-ray diffraction analysis, by differential scanning calorimetry or any other techniques known in the art.

The term “ C_{max} ” refers to the maximum observed plasma concentration of a xanthine oxidoreductase inhibitor or salt thereof produced by the ingestion of the dosage forms of the present disclosure. Unless otherwise noted herein, the reported value for the C_{max} is the central value of the C_{max} . The “central value” of the C_{max} is the mean $C_{max} \pm$ standard deviation.

The term “dosage form” refers to any solid object, semi-solid, or liquid composition designed to contain a specific pre-determined amount (i.e., dose) of a certain active agent. Suitable dosage forms may be pharmaceutical drug delivery systems, including those for oral administration, buccal administration, rectal administration, topical or mucosal delivery or subcutaneous implants, or other implanted drug delivery systems and the like. In one aspect, the dosage forms of the present disclosure are considered to be solid, however,

8

they may contain liquid or semi-solid components. In another aspect, the dosage form is an orally administered system for delivering an active agent to the gastrointestinal tract of a subject. The dosage form of the present disclosure exhibit modified release of the active agent.

By an “effective amount” or a “therapeutically effective amount” of an active agent is meant a nontoxic but sufficient amount of the active agent to provide the desired effect. The amount of active agent that is “effective” will vary from subject to subject, depending on the age and general condition of the individual, the particular active agent or agents, and the like. Thus, it is not always possible to specify an exact “effective amount.” However, an appropriate “effective amount” in any individual case may be determined by one of ordinary skill in the art using routine experimentation. For example, the daily therapeutically effective or prophylactically effective amount of xanthine oxidoreductase inhibiting compounds administered to a patient in single or divided doses range from about 0.01 to about 750 milligram per kilogram of body weight per day (mg/kg/day). More specifically, a patient may be administered from about 5.0 mg to about 300 mg once daily, from about 20 mg to about 240 mg once daily and from about 40 mg to about 120 mg once daily of xanthine oxidoreductase inhibiting compounds. Of course, it will be understood by one skilled in the art that other dosage regimens may be utilized, such as dosing more than once per day, utilizing extended, controlled, or modified release dosage forms, and the like in order to achieve the desired result.

By “pharmaceutically acceptable,” such as in the recitation of a “pharmaceutically acceptable excipient,” or a “pharmaceutically acceptable additive,” is meant a material that is not biologically or otherwise undesirable, i.e., the material may be incorporated into a pharmaceutical composition administered to a patient without causing any undesirable biological effects.

The term “subject” refers to an animal. In one aspect, the animal is a mammal, including a human or non-human. The terms patient and subject may be used interchangeably herein.

The terms “treating” and “treatment” refer to reduction in severity and/or frequency of symptoms, elimination of symptoms and/or underlying cause, prevention of the occurrence of symptoms and/or their underlying cause, and improvement or remediation of damage. Thus, for example, “treating” a patient involves prevention of a particular disorder or adverse physiological event in a susceptible individual as well as treatment of a clinically symptomatic individual by inhibiting or causing regression of a disorder or disease.

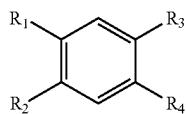
As used herein, the term “xanthine oxidoreductase” refers to at least one form of xanthine oxidoreductase enzyme, namely xanthine oxidase and/or xanthine dehydrogenase.

As used herein, the phrase “xanthine oxidoreductase inhibitor” refers to any compound that (1) is an inhibitor of a xanthine oxidoreductase, such as, but not limited to, xanthine oxidase; and (2) chemically, does not contain a purine ring in its structure (i.e. is a “non-purine” analogue). The phrase “xanthine oxidoreductase inhibitor” as defined herein also includes metabolites, polymorphs, solvates and prodrugs of such compounds, including metabolites, polymorphs, solvates and prodrugs of the exemplary compounds described as Formula I and Formula II below. Examples of xanthine oxidoreductase inhibitors include, but are not limited to, 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazole-carboxylic acid and compounds having the following Formula I or Formula II:

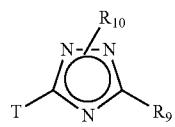
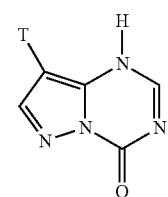
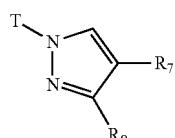
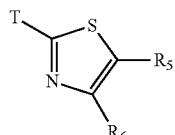
US 9,107,912 B2

9

Compounds of Formula I:



wherein R₁ and R₂ are each independently a hydrogen, a hydroxyl group, a COOH group, an unsubstituted or substituted C₁-C₁₀ alkyl group, an unsubstituted or substituted C₁-C₁₀ alkoxy, an unsubstituted or substituted hydroxy-alkoxy, a phenylsulfinyl group or a cyano (—CN) group; wherein R₃ and R₄ are each independently a hydrogen or A, B, C or D as shown below:



wherein T connects or attaches A, B, C or D to the aromatic ring shown above at R₁, R₂, R₃ or R₄.

wherein R₅ and R₆ are each independently a hydrogen, a hydroxyl group, a COOH group, an unsubstituted or substituted C₁-C₁₀ alkyl group, an unsubstituted or substituted C₁-C₁₀ alkoxy, an unsubstituted or substituted hydroxy-alkoxy, COO-Glucoronide or COO-Sulfate;

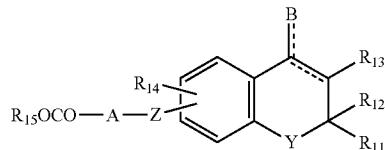
wherein R₇ and R₈ are each independently a hydrogen, a hydroxyl group, a COOH group, an unsubstituted or substituted C₁-C₁₀ alkyl group, an unsubstituted or substituted C₁-C₁₀ alkoxy, an unsubstituted or substituted hydroxy-alkoxy, COO-Glucoronide or COO-Sulfate;

wherein R₉ is an unsubstituted pyridyl group or a substituted pyridyl group; and

wherein R₁₀ is a hydrogen or a lower alkyl group, a lower alkyl group substituted with a pivaloyloxy group and in each case, R₁₀ bonds to one of the nitrogen atoms in the 1,2,4-triazole ring shown above in Formula I.

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Compounds of Formula II:



wherein R₁₁ and R₁₂ are each independently a hydrogen, a substituted or unsubstituted lower alkyl group, a substituted or unsubstituted phenyl (the substituted phenyl in this Formula II refers to a phenyl substituted with a halogen or lower alkyl, and the like. Examples include, but are not limited to, p-tolyl and p-chlorophenyl), or R₁₁ and R₁₂ may together form a four- to eight-membered carbon ring together with the carbon atom to which they are attached;

wherein R₁₃ is a hydrogen or a substituted or unsubstituted lower alkyl group;

wherein R₁₄ is one or two radicals selected from a group consisting of a hydrogen, a halogen, a nitro group, a substituted or unsubstituted lower alkyl group, a substituted or unsubstituted phenyl (the substituted phenyl in this Formula II refers to a phenyl substituted with a halogen or lower alkyl group, and the like. Examples include, but are not limited to, p-tolyl and p-chlorophenyl), —OR₁₆ and —SO₂NR₁₇R₁₈, wherein R₁₆ is a hydrogen, a substituted or unsubstituted lower alkyl, a phenyl-substituted lower alkyl, a carboxymethyl or ester thereof, a hydroxyethyl or ether thereof, or an allyl; R₁₇ and R₁₈ are each independently a hydrogen or a substituted or unsubstituted lower alkyl group;

wherein R₁₅ is a hydrogen or a pharmaceutically active ester-forming group;

wherein A is a straight or branched hydrocarbon radical having one to five carbon atoms;

wherein B is a halogen, an oxygen, or an ethylenedithio; wherein Y is an oxygen, a sulfur, a nitrogen or a substituted nitrogen;

wherein Z is an oxygen, a nitrogen or a substituted nitrogen; and the dotted line refers to either a single bond, a double bond, or two single bonds (for example, when B is ethylenedithio, the dotted line shown in the ring structure can be two single bonds).

As used herein, the term “lower alkyl(s)” group refers to a C₁-C₇ alkyl group, including, but not limited to, including methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, hexyl, heptal and the like.

As used herein, the term “lower alkoxy” refers to those groups formed by the bonding of a lower alkyl group to an oxygen atom, including, but not limited to, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentoxy, hexoxy, heptoxy and the like.

As used herein, the term “lower alkylthio group” refers to those groups formed by the bonding of a lower alkyl to a sulfur atom.

As used herein, the term “halogen” refers to fluorine, chlorine, bromine and iodine.

As used herein, the term “substituted pyridyl” refers to a pyridyl group that can be substituted with a halogen, a cyano group, a lower alkyl, a lower alkoxy or a lower alkylthio group.

As used herein, the term “four- to eight-membered carbon ring” refers to cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like.

US 9,107,912 B2

11

As used herein, the phrase "pharmaceutically active ester-forming group" refers to a group which binds to a carboxyl group through an ester bond. Such ester-forming groups can be selected from carboxy-protecting groups commonly used for the preparation of pharmaceutically active substances, especially prodrugs. For the purpose of the present disclosure, said group should be selected from those capable of binding to compounds having Formula II wherein R₁₅ is hydrogen through an ester bond. Resultant esters are effective to increase the stability, solubility, and absorption in gastrointestinal tract of the corresponding non-esterified forms of said compounds having Formula II, and also prolong the effective blood-level of it. Additionally, the ester bond can be cleaved easily at the pH of body fluid or by enzymatic actions in vivo to provide a biologically active form of the compound having Formula II. Preferred pharmaceutically active ester-forming groups include, but are not limited to, 1-(oxygen substituted)-C₂ to C₁₅ alkyl groups, for example, a straight, branched, ringed, or partially ringed alkanoyloxyalkyl groups, such as acetoxyethyl, acetoxyethyl, propionyloxymethyl, pivaloyloxymethyl, pivaloyloxyethyl, cyclohexaneacetoxyethyl, cyclohexanecarbonyloxycyclohexylmethyl, and the like, C₃ to C₁₅ alkoxy carbonyloxyalkyl groups, such as ethoxycarbonyloxyethyl, isopropoxycarbonyloxyethyl, isopropoxycarbonyloxypropyl, t-butoxycarbonyloxyethyl, isopentylloxycarbonyloxypropyl, cyclohexyloxycarbonyloxyethyl, cyclohexylmethoxycarbonyloxyethyl, bornyloxycarbonyloxyisopropyl, and the like, C₂ to C₈ alkoxyalkyls, such as methoxy methyl, methoxy ethyl, and the like, C₄ to C₈ 2-oxacycloalkyls such as tetrahydropyranyl, tetrahydrofuranyl, and the like, substituted C₈ to C₁₂ aralkyls, for example, phenacyl, phthalidyl, and the like, C₆ to C₁₂ aryl, for example, phenyl xylol, indanyl, and the like, C₂ to C₁₂ alkenyl, for example, allyl, (2-oxo-1,3-dioxolyl)methyl, and the like, and [4,5-dihydro-4-oxo-1H-pyrazolo[3,4-d]pyrimidin-1-yl]methyl, and the like.

In R₁₆ in Formula II, the term "ester" as used in the phrase "the ester of carboxymethyl" refers to a lower alkyl ester, such as methyl or ethyl ester; and the term "ether" used in the phrase "the ether of hydroxyethyl" means an ether which is formed by substitution of the hydrogen atom of hydroxyl group in the hydroxyethyl group by aliphatic or aromatic alkyl group, such as benzyl.

The carboxy-protecting groups may be substituted in various ways. Examples of substituents include halogen atom, alkyl groups, alkoxy groups, alkylthio groups and carboxy groups.

As used herein, the term "straight or branched hydrocarbon radical" in the definition of A in Formula II above refers to methylene, ethylene, propylene, methylmethylen, or isopropylene.

As used herein, the substituent of the "substituted nitrogen" in the definition of Y and Z in Formula II above are hydrogen, lower alkyl, or acyl.

As used herein, the term "phenyl-substituted lower alkyl" refers to a lower alkyl group substituted with phenyl, such as benzyl, phenethyl or phenylpropyl. As used herein, the term "prodrug" refers to a derivative of the compounds shown in the above-described Formula I and Formula II that have chemically or metabolically cleavable groups and become by solvolysis or under physiological conditions compounds that are pharmaceutically active in vivo. Esters of carboxylic acids are an example of prodrugs that can be used in the dosage forms of the present disclosure. Methyl ester prodrugs may be prepared by reaction of a compound having the above-described formula in a medium such as methanol with an acid or

12

base esterification catalyst (e.g., NaOH, H₂SO₄). Ethyl ester prodrugs are prepared in similar fashion using ethanol in place of methanol.

Examples of compounds having the above Formula I are:

- 5 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid (also known as "febuxostat"), 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-(3-cyano-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylic acid, 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazolecarboxylic acid, 1-(3-cyano-4-(2,2-dimethylpropoxy)phenyl)-1H-pyrazole-4-carboxylic acid, 1-3-cyano-4-(2,2-dimethylpropoxy)phenyl]-1H-pyrazole-4-carboxylic acid, pyrazolo[1,5-a]-1,3,5-triazin-4-(1H)-one, 8-[3-methoxy-4-(phenylsulfinyl)phenyl]-sodium salt (±) or 3-(2-methyl-4-pyridyl)-5-cyano-4-isobutoxyphenyl)-1,2,4-triazole.
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Preferred compounds having the above Formula I are:

- 20 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid, 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-(3-cyano-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylic acid, 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazolecarboxylic acid. These preferred compounds have also been found not have an effect at a therapeutically effective amount in a subject on the activity of any of the following enzymes involved in purine and pyrimidine metabolism: guanine deaminase, hypoxanthine-guanine phosphoribosyltransferase, purine nucleotide phosphorylase, orotate phosphoribosyltransferase or orotidine-5-monophosphate decarboxylase (i.e., meaning that it is "selective" for none of these enzymes which are involved in purine and pyrimidine metabolism). Assays for determining the activity for each of the above-described enzymes is described in Yasuhiro Takano, et al., *Life Sciences*, 76:1835-1847 (2005). These preferred compounds have also been referred to in the literature as nonpurine, selective inhibitors of xanthine oxidase (NP/SIXO).
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Examples of compounds having the above Formula II are described in U.S. Pat. No. 5,268,386 and EP 0 415 566 A1, and are incorporated, in their entirety, herein.

With the exception of pyrazolo[1,5-a]-1,3,5-triazin-4-(1H)-one, 8-[3-methoxy-4-(phenylsulfinyl)phenyl]-sodium salt (±), methods for making xanthine oxidoreductase inhibiting compounds of Formulas I and II for use in the methods of the present disclosure are known in the art and are described, for example, in U.S. Pat. Nos. 5,268,386, 5,614,520, 6,225,474, 7,074,816 and EP 0 415 566 A1 and in the publications Ishibuchi, S. et al., *Bioorg. Med. Chem. Lett.*, 11:879-882 (2001) and which are each herein incorporated by reference. Other xanthine oxidoreductase inhibiting compounds can be found using xanthine oxidoreductase and xanthine in assays to determine if such candidate compounds inhibit conversion of xanthine into uric acid. Such assays are well known in the art.

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- Pyrazolo[1,5-a]-1,3,5-triazin-4-(1H)-one, 8-[3-methoxy-4-(phenylsulfinyl)phenyl]-sodium salt (±) is available from Otsuka Pharmaceutical Co. Ltd. (Tokyo, Japan) and is described in the following publications: Uematsu T., et al., "Pharmacokinetic and Pharmacodynamic Properties of a Novel Xanthine Oxidase Inhibitor, BOF-4272, in Healthy Volunteers, *J. Pharmacology and Experimental Therapeutics*, 270:453-459 (August 1994), Sato, S., A Novel Xanthine Deydrogenase Inhibitor (BOF-4272). *In Purine and Pyrimidine Metabolism in Man*, Vol. VII, Part A, ed. By P. A. Hark-

US 9,107,912 B2

13

ness, pp. 135-138, Plenum Press, New York. Pyrazolo[1,5-a]-1,3,5-triazin-4-(1H)-one, 8-[3-methoxy-4-(phenylsulfinyl)phenyl]-sodium salt (\pm) can be made using routine techniques known in the art.

II. Methods of Treatment

The present disclosure relates to methods of treating hyperuricemia in patients that also require treatment with theophylline, without having to adjust the theophylline dose to account for the hyperuricemia treatment. Specifically, the present disclosure provides in one aspect, a method of treating hyperuricemia in a patient in need of treatment thereof, the method comprising the step of: administering to a patient suffering from hyperuricemia and at least one secondary disease state, a therapeutically effective amount of at least one xanthine oxidoreductase inhibitor, wherein said subject is also receiving a concomitant administration of theophylline to treat the at least one second disease state, and further wherein (i) the administration of the at least one xanthine oxidoreductase inhibitor to said patient does not result in theophylline toxicity to said patient; and (ii) administration of the theophylline is in an amount ranging from about 90% to about 110% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor. More specifically, administration of the theophylline can be in an amount ranging from about 91% to about 109%, about 91% to about 108%, about 91% to about 107%, about 91% to about 106%, about 91% to about 105%, about 91% to about 104%, about 91% to about 103%, about 91% to about 102%, about 91% to about 101%, about 92% to about 109%, about 92% to about 108%, about 92% to about 107%, about 92% to about 106%, about 92% to about 105%, about 92% to about 104%, about 92% to about 103%, about 92% to about 102%, about 92% to about 101%, about 93% to about 109%, about 93% to about 108%, about 93% to about 107%, about 93% to about 106%, about 93% to about 105%, about 93% to about 104%, about 93% to about 103%, about 93% to about 102%, about 93% to about 101%, about 94% to about 109%, about 94% to about 108%, about 94% to about 107%, about 94% to about 106%, about 94% to about 105%, about 94% to about 104%, about 94% to about 103%, about 94% to about 102%, about 94% to about 101%, about 95% to about 109%, about 95% to about 108%, about 95% to about 107%, about 95% to about 106%, about 95% to about 105%, about 95% to about 104%, about 95% to about 103%, about 95% to about 102%, about 95% to about 101%, about 96% to about 109%, about 96% to about 108%, about 96% to about 107%, about 96% to about 106%, about 96% to about 105%, about 96% to about 104%, about 96% to about 103%, about 96% to about 102%, about 96% to about 101%, about 97% to about 109%, about 97% to about 108%, about 97% to about 107%, about 97% to about 106%, about 97% to about 105%, about 97% to about 104%, about 97% to about 103%, about 97% to about 102%, about 97% to about 101%, about 98% to about 109%, about 98% to about 108%, about 98% to about 107%, about 98% to about 106%, about 98% to about 105%, about 98% to about 104%, about 98% to about 103%, about 98% to about 102%, about 98% to about 101%, about 99% to about 109%, about 99% to about 108%, about 99% to about 107%, about 99% to about 106%, about 99% to about 105%, about 99% to about 104%, about 99% to about 103%, about 99% to about 102% or about 99% to about 101% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor.

14

In another aspect, the present disclosure provides a method of treating hyperuricemia in a patient in need of treatment thereof, the method comprising the step of: administering to a patient suffering from hyperuricemia and at least one secondary disease state, a therapeutically effective amount of at least one xanthine oxidoreductase inhibitor, wherein said subject will also be receiving a concomitant administration of theophylline ("will also be receiving" meaning such as, concurrently with the xanthine oxidoreductase inhibitor, or subsequent to the initiation of treatment with the xanthine oxidoreductase inhibitor) to treat the at least one second disease state, and further wherein (i) the administration of the at least one xanthine oxidoreductase inhibitor to said patient does not result in theophylline toxicity to said patient; and (ii) administration of the theophylline is in an amount ranging from about 90% to about 110% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor. More specifically, administration of the theophylline can be in an amount ranging from about 91% to about 109%, about 91% to about 108%, about 91% to about 107%, about 91% to about 106%, about 91% to about 105%, about 91% to about 104%, about 91% to about 103%, about 91% to about 102%, about 91% to about 101%, about 92% to about 109%, about 92% to about 108%, about 92% to about 107%, about 92% to about 106%, about 92% to about 105%, about 92% to about 104%, about 92% to about 103%, about 92% to about 102%, about 92% to about 101%, about 93% to about 109%, about 93% to about 108%, about 93% to about 107%, about 93% to about 106%, about 93% to about 105%, about 93% to about 104%, about 93% to about 103%, about 93% to about 102%, about 93% to about 101%, about 94% to about 109%, about 94% to about 108%, about 94% to about 107%, about 94% to about 106%, about 94% to about 105%, about 94% to about 104%, about 94% to about 103%, about 94% to about 102%, about 94% to about 101%, about 95% to about 109%, about 95% to about 108%, about 95% to about 107%, about 95% to about 106%, about 95% to about 105%, about 95% to about 104%, about 95% to about 103%, about 95% to about 102%, about 95% to about 101%, about 96% to about 109%, about 96% to about 108%, about 96% to about 107%, about 96% to about 106%, about 96% to about 105%, about 96% to about 104%, about 96% to about 103%, about 96% to about 102%, about 96% to about 101%, about 97% to about 109%, about 97% to about 108%, about 97% to about 107%, about 97% to about 106%, about 97% to about 105%, about 97% to about 104%, about 97% to about 103%, about 97% to about 102%, about 97% to about 101%, about 98% to about 109%, about 98% to about 108%, about 98% to about 107%, about 98% to about 106%, about 98% to about 105%, about 98% to about 104%, about 98% to about 103%, about 98% to about 102%, about 98% to about 101%, about 99% to about 109%, about 99% to about 108%, about 99% to about 107%, about 99% to about 106%, about 99% to about 105%, about 99% to about 104%, about 99% to about 103%, about 99% to about 102% or about 99% to about 101% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor.

The method of the current invention comprises the co-administration of a xanthine oxidoreductase inhibitor and theophylline. The term xanthine oxidoreductase includes multiple therapeutic compounds, which have been described previously, and which are incorporated in their entirety herein. Generally, xanthine oxidoreductase inhibitors are compounds that inhibit the activity of xanthine oxidase, an enzyme involved in purine metabolism. In humans, inhibition of xanthine oxidase reduces the production of uric acid,

US 9,107,912 B2

15

which leads to secondary disease states such as gout, and other related diseases. Xanthine oxidoreductase inhibitors typically are classified as one of two types: purine analogues and non-purine analogues. The xanthine oxidoreductase inhibitors of the current invention include non-purine analogues, and, as noted previously, lack a purine ring in its chemical structure. In one embodiment, the xanthine oxidoreductase inhibitor includes, but is not limited to 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid (also known as "febuxostat"), 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-(3-cyano-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylic acid, 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazolecarboxylic acid, 1-(3-cyano-4-(2,2-dimethylpropoxy)phenyl)-1H-pyrazole-4-carboxylic acid, 1-3-cyano-4-(2,2-dimethylpropoxy)phenyl]-1H-pyrazole-4-carboxylic acid, pyrazolo[1,5-a]1,3,5-triazin-4-(1H)-one, 8-[3-methoxy-4-(phenylsulfonyl)phenyl]-sodium salt (\pm) or 3-(2-methyl-4-pyridyl)-5-cyano-4-isobutoxypyhenyl)-1,2,4-triazole. In another embodiment, the xanthine oxidoreductase inhibitor includes 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid, 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, and pharmaceutically acceptable salts thereof. In a further embodiment, the xanthine oxidoreductase inhibitor is 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid and pharmaceutically acceptable salts thereof.

The phrase "pharmaceutically acceptable salt(s)", as used herein, means those salts of compounds of the invention that are safe and effective for administration to a patient and that do not adversely affect the therapeutic qualities of the compound. Pharmaceutically acceptable salts include salts of acidic or basic groups present in compounds of the invention. Pharmaceutically acceptable acid addition salts include, but are not limited to, hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzensulfonate, p-toluenesulfonate and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Certain compounds of the invention can form pharmaceutically acceptable salts with various amino acids. Suitable base salts include, but are not limited to, aluminum, calcium, lithium, magnesium, potassium, sodium, zinc, and diethanolamine salts. For a review on pharmaceutically acceptable salts see Berge et al., *J. Pharm. Sci.*, 1977; 66:1-19, incorporated herein by reference, in its entirety.

One of skill in the art will also understand that the xanthine oxidoreductase inhibitors incorporated into the methods of the current invention may also incorporate pharmaceutically acceptable excipients. The dosage forms of the present disclosure will typically include pharmaceutically acceptable excipients. As is well known to those skilled in the art, pharmaceutical excipients are routinely incorporated into solid dosage forms to alter the physical and chemical characteristics of the dosage form. This is done to ease the manufacturing process as well as to improve the performance of the dosage form. Common excipients include, but are not limited to diluents, bulking agents, lubricants, binders, preservatives, antioxidants, and combinations thereof.

16

As used herein, the term "hyperuricemia" denotes a disease state in which the patient has as an elevation in serum urate (sUA) levels greater than or equal to 6.0 mg/dL in women and men. Many factors contribute to hyperuricemia, including: genetics, insulin resistance, hypertension, renal insufficiency, obesity, diet, use of diuretics, and consumption of alcoholic beverages. Causes of hyperuricemia can be classified into three functional types: increased production of uric acid, decreased excretion of uric acid, and mixed type, incorporating both of the previous etiologies. Increased production etiologies result from high levels of purine in the diet and increased purine metabolism. Decreased excretion etiologies result from kidney disease, certain drugs, and competition for excretion between uric acid and other molecules. Mixed causes include high levels of alcohol and/or fructose in the diet, and starvation. Hyperuricemia typically develops into gout when urate crystals are formed from supersaturated body fluids and deposited in joints, tophi, and parenchymal organs due to a disorder in the urate metabolism. Uric acid is the end product of purine metabolism and is generated in the cascade of hypoxanthine \rightarrow xanthine \rightarrow uric acid.

In addition to suffering from hyperuricemia and at least one second disease state, the patients being treated according to the methods of the present disclosure may also be suffering from at least one third (or more) additional disease states. These third or more additional disease states include, but are not limited to, gout, hypertension, chronic stable angina, renal failure, nephrolithiasis, acute gouty arthritis, chronic gouty joint disease, tophaceous gout, uric acid urolithiasis, uric acid nephropathy, progressive renal disease, and combinations thereof. Alternatively, the patients being treated according to the methods of the present invention may be suffering from both gout and hyperuricemia. In such instances, the patient will also be suffering from at least one third disease state. The patient is or will be concomitantly administered theophylline to treat the at least third disease state. The at least one third disease state includes, but is not limited to asthma, acute bronchitis, chronic bronchitis, emphysema, neonatal apnea, neonatal bradycardia and combinations thereof. In addition, the patient may also be suffering from at least one fourth (or more) additional disease states. These fourth or more additional disease states include, but are not limited to, hypertension, chronic stable angina, renal failure, nephrolithiasis, acute gouty arthritis, chronic gouty joint disease, tophaceous gout, uric acid urolithiasis, uric acid nephropathy, progressive renal disease, and combinations thereof.

The methods of the current disclosure are directed to treating patients with secondary disease states that are indicated for, or require theophylline treatment. Theophylline is a methylxanthine compound used in the treatment of respiratory diseases resulting from airway constriction. Theophylline elicits a physiological response by two primary mechanisms, including competitive nonselective phosphodiesterase inhibitor, which raises intracellular cAMP, activates PKA, inhibits TNF-alpha and inhibits leukotriene synthesis, and reduces inflammation and innate immunity; and nonselective adenosine receptor antagonism, antagonizing A1, A2, and A3 receptors almost equally, which explains many of its cardiac effects and some of its anti-asthmatic effects. One skilled in the art will appreciate that the theophylline compound, as described herein is also known by its chemical name, 1,3-dimethyl-7H-purine-2,6-dione, its CAS Number, 58-55-9, and a multitude of brand name theophylline pharmaceutical products, incorporating theophylline as at least one of the active pharmaceutical ingredients. The theophylline component of the current methods also encompasses immediate

US 9,107,912 B2

17

release formulations, in addition to modified release formulations, including extended release, controlled release, and delayed release theophylline dosage forms. Dosage forms of theophylline may include tablets, capsules, sprinkle caps, liquid formulations, such as solutions and suspensions, and parenteral dosage forms including intravenous, intramuscular, intraarterial, intracerebral, intradermal, intrathecal, and intracerebral dosage forms, and subcutaneous dosage forms.

The methods of the current disclosure allow for theophylline to continue to be administered according to the manufacturer's suggested dosing of the compound. As used herein, the phrase "manufacturer's suggested dosing" signifies the dosing disclosed in the package insert of the theophylline dosage form and available in a variety of pharmaceutical treatment references. The methods of the current disclosure encompass the recommended dosing for all dosage forms, and include the treatment of all patients, for all disease states in which theophylline treatment may be effective. For example, a manufacturer's suggested dosing for oral theophylline may be 4-6 mg/kg. Thus, as described previously herein, in the present disclosure, administration of the theophylline is in an amount ranging from about 90% to about 110% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor. If the manufacturer's suggested dosing is 4-6 mg/kg, about 90% to about 110% would be from about 3.6 to about 6.6 mg/kg.

The methods of the current disclosure are directed to treating hyperuricemia in patients having a secondary disease state that is indicated for, or is being treated with theophylline. The secondary disease states may include chronic obstructive pulmonary disease (COPD), chronic obstructive lung disease (COLD), chronic obstructive airway disease (COAD), chronic airflow limitation (CAL) and chronic obstructive respiratory disease (CORD), asthma, acute bronchitis, chronic bronchitis, emphysema, neonatal apnea, neonatal bradycardia, and combinations thereof. It is also contemplated that the patient requiring treatment for hyperuricemia may suffer from at least one additional disease state. Generally, the at least one additional disease state may be secondary to the patient's hyperuricemia, or may derive from an etiology unrelated to the hyperuricemia. Examples of the at least one additional disease state include, but are not limited to, gout, hypertension, renal failure, nephrolithiasis, acute gouty arthritis, chronic gouty arthritis, tophaceous gout, uric acid urolithiasis, uric acid nephropathy, progressive renal disease, and combinations thereof.

The methods of the current disclosure are based on the surprising findings that certain xanthine oxidoreductase inhibitors may be administered concomitantly with theophylline without adversely affecting blood serum levels and theophylline, and, consequently, avoiding the typical adjustment in dosing due to hyperuricemia treatment. Theophylline is metabolized by cytochrome P-450 (hereinafter "CYP 450") to 1-methylxanthine, 3-methylxanthine, and 1,3-methyluric acid. Further, metabolism of 1-methylxanthine to 1-methyluric acid is mediated by xanthine oxidase. The xanthine oxidoreductase inhibitors described herein are not expected to have any inhibitory effect on CYP 450 involved in the metabolism of theophylline; however, because the xanthine oxidoreductase inhibitors are non-purine selective inhibitors of xanthine oxidase, it is generally expected that the compounds affect the xanthine oxidase mediated metabolism of theophylline and will decrease the clearance of theophylline, leading to increased theophylline serum levels. As stated previously, theophylline has a narrow therapeutic window, and even small increases in blood serum levels of the com-

18

pound may result in serious adverse effects for the patient. However, the inventors surprisingly found that the administration of the xanthine oxidoreductase inhibitors described herein do not adversely affect theophylline serum levels, and that adjustment of theophylline treatment dosages is not required. Additional details pertaining to the pharmacokinetic parameters of the coadministration of a xanthine oxidoreductase inhibitor and theophylline are described in the Examples.

Prior to the discovery of the present invention, in previous studies using the xanthine oxidoreductase inhibitor febuxostat, subjects taking concomitant therapy with certain medications, including theophylline, could be enrolled in the study only if the certain excluded medication was discontinued for a certain length of time. For example, as shown in Table 1 below, febuxostat study F-GT06-153 specifically provided that subjects taking theophylline could not be enrolled in the study, unless the theophylline was discontinued at least 30 days prior to the day 1 randomization visit.

TABLE 1

Inclusion Criteria for Febuxostat Study F-GT06-153

"5.2.4 Prohibited Concomitant Therapy
Subjects may not take any medication (other than study drug) for the purpose of lowering sUA levels. Subjects who have taken any of the excluded medications listed below, prior to the study, can be enrolled into the study if the excluded medication is discontinued at least 30 days prior to Day 1/Randomization Visit.
The following medications are not to be administered 30 days prior or during the study:
Any other urate-lowering drug, other than study drug;
Use of NSAIDs and COX-2 inhibitors other than protocol required prophylaxis therapy
(short-term use of NSAIDs and COX-2 inhibitors for treatment of gout flares is allowed);
Salicylates (chronic use of aspirin ≤325 mg/day is allowed);
Thiazide diuretics;
Losartan;
Azathioprine;
Mercaptopurine;
Theophylline;
IV Colchicine;
Cyclosporine;
Cyclophosphamide;
Pyrazinamide;
Sulfamethoxazole/trimethoprim;
Use of corticosteroids (chronic prednisone ≤10 mg/day or its equivalent and short-term use of higher doses of prednisone for treatment of gout flares is allowed);
Changes in hormone replacement therapy or oral contraceptive therapy within 3 months of the Day 1/Randomization Visit or during the course of the study."

As is evident from Table 1 above, the coadministration of theophylline and urate-lowering therapies is a significant clinical concern, and one that must be considered prior to initiation of urate-lowering therapies.

While hyperuricemia is one of the primary disease states treated by the xanthine oxidoreductase inhibitors discussed herein, one of skill in the art will appreciate that the methods of the current disclosure are equally applicable to other disease states that are typically treated by administration of one or more xanthine oxidoreductase inhibitors. These other disease states include, but are not limited to, gout, prostatitis, inflammatory bowel disease, QT interval prolongation, myocardial infarction, cardiac hypertrophy, hypertension, nephrolithiasis, renal impairment, chronic kidney disease, metabolic syndrome (also referred to as "Syndrome X" and includes, at least one of abdominal obesity, atherogenic dyslipidemia, insulin resistance, glucose intolerance, a prothrombotic state or a proinflammatory state), diabetes, dia-

US 9,107,912 B2

19

betic nephropathy, congestive heart failure and combinations thereof (these conditions are sometimes collectively referred to herein as “at least one first disease state”). Accordingly, the current methods encompass treating a patient having one of the aforementioned at least one first disease state and also having a second disease state requiring theophylline treatment, through the administration of a xanthine oxidoreductase inhibitor without significant adjustment of the manufacturer’s suggested dosing, and without inducing theophylline toxicity. Moreover, the current methods further encompass treating a patient having one of the aforementioned at least one first disease state, at least one second disease state requiring the theophylline treatment and at least one third disease state. In addition to suffering from hyperuricemia and at least one second disease state, the patients being treated according to the methods of the present disclosure may also be suffering from at least one third (or more) additional disease states. These third or more additional disease states include, but are not limited to, gout, hypertension, chronic stable angina, renal failure, nephrolithiasis, acute gouty arthritis, chronic gouty joint disease, tophaceous gout, uric acid urolithiasis, uric acid nephropathy, progressive renal disease, and combinations thereof.

By way of example, and not of limitation, examples of the present disclosure will now be given.

Example 1

Effects of Multiple Febuxostat Doses on the Pharmacokinetics of Theophylline Administration

An experiment was performed to determine the effects of multiple doses of a xanthine oxidoreductase inhibitor, 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid, also known as “febuxostat”, on theophylline doses. The experiment was a phase I, double-blind, randomized, 2-period crossover study, in which 24 patients (12 male and 12 female) were enrolled in the study. Specifically, the total duration of the study was approximately 8 weeks (60 days), consisting of a Screening Period (Days -28 to -2), Check-in (Day -1) for Period 1, 7-day Treatment, a Washout Period (minimum of 7 days), Check-in for Period 2, 7-day Treatment, Study Exit or Early Termination, and a Follow-up phone call 10±2 days after the last dose of study medication. Subjects received both Regimens A and B in randomly assigned order. These regimens consisted of 7 daily doses of double-blind febuxostat 80 mg (A: two encapsulated febuxostat 40 mg tablets or B: matching placebo) and one dose (on Day 5 of each period) open-label theophylline 400 mg tablet.

On Days 1 to 7 of each period, subjects received febuxostat 80 mg or matching placebo at approximately 0900 hours after a minimum 10-hour fast, and followed 1 hour later by a standardized breakfast. On Day 5 of each period, subjects received a single oral dose of Uniphyll® (theophylline, anhy-

20

drous) 400 mg tablet along with the daily dose of febuxostat or matching placebo; food was first allowed 4 hours postdose. Water was available as desired, except for 1 hour before through 1 hour after study drug administration. Only 240 mL of water was allowed during dosing. Subjects were discharged in the morning of Day 8 of each Period (1 and 2), after plasma and urine pharmacokinetic sample collections and all study procedures were completed. For Day -1 of Period 2, subjects returned to the clinic after a minimum of 7 day washout period. For all subjects that completed both Periods 1 and 2 (or discontinued the study prematurely at an Early Termination visit, i.e., withdrew from study), a follow-up phone call was made 10±2 days after the last dose of study medication or Early Termination (ET). The effect of multiple oral doses of febuxostat on the pharmacokinetics of a single oral dose of theophylline were evaluated through measurement of plasma and urine concentration levels of theophylline at designated time points. Safety, tolerability, and theophylline toxicity were assessed throughout the study by monitoring adverse effects, clinical laboratory tests, vital signs, ECGs, and physical examination findings.

Theophylline plasma concentrations were determined from 7 mL blood samples obtained according to the schedules in Table 1 below. Trough febuxostat plasma concentrations were determined from 6 mL blood samples obtained according to the schedules in Table 2.

TABLE 2

Period 1 and 2: Blood Collection Schedules for Determination of Plasma Concentrations of Theophylline and Febuxostat		
	Blood Sample Collection for Pharmacokinetics	
	Theophylline	Febuxostat
Day 5 of Periods 1 and 2	Predose (up to 30 minutes prior to dosing [0 hour]) and at 1, 2, 3, 4, 6, 8, 10, 12, and 14 hours postdose	Predose (up to 30 minutes prior to dosing [0 hour])
Day 6 of Periods 1 and 2	16, 24, and 32 hours post Day 5 dosing	Predose (up to 30 minutes prior to dosing [0 hour])
Day 7 of Periods 1 and 2	40, 48, and 56 hours post Day 5 dosing	None
Day 8 of Periods 1 and 2	64 and 72 hours post Day 5 dosing	None

Additionally, to ensure that the drug plasma levels were not altered by secondary conditions and medications, this experiment required subjects to abstain from the use of certain medications and other agents prior to and during the testing periods. The excluded medications and agents are summarized in Table 3 (prescription and nonprescription), including specifications on applicable time points through completion of all study activities.

TABLE 3

Excluded Medications and Agents			
6 weeks prior to Check-in (Day -1)	28 days prior to Check-in (Day -1)	14 days prior to Check-in (Day -1)	48 hours prior to Check-in (Day -1)
Nicotine-containing products	Prescription medications	Foods or beverages containing grapefruit or Seville oranges	Alcohol-containing products
Hormonal contraception (oral, patch, implant, vaginal ring, or injectable)	Over-the-counter medications, vitamins, herbal, or dietary supplements	Food or beverages containing caffeine or xanthine related substances	

US 9,107,912 B2

21

22

TABLE 3-continued

Excluded Medications and Agents			
6 weeks prior to Check-in (Day -1)	28 days prior to Check-in (Day -1)	14 days prior to Check-in (Day -1)	48 hours prior to Check-in (Day -1)
Hormone replacement therapy	Hepatic or renal clearance altering agents (erythromycin, cimetidine, barbiturates, phenothiazines, etc)	Charbroiled foods	
Febuxostat or Allopurinol			

Note:
excluded medications are from timepoints through completion of all study activities.

15

Subjects were instructed not to take any medications or non-prescription drugs, vitamins, herbal supplements, or dietary supplements within 28 days prior to Check-in (Day -1).

The subjects of the current experiment were administered the appropriate dosage regimens and the pharmacokinetic data were evaluated. Mean plasma theophylline concentration vs. time profiles (linear and log-linear formats) for the two treatment regimens are depicted in FIG. 1. Additionally, individual and summary statistics of noncompartmental pharmacokinetic parameter estimates for theophylline following coadministration with febuxostat or placebo are presented in Table 4 below.

eliminated with a mean terminal half-life of 9.69 hours following oral administration of 400 mg theophylline with placebo or febuxostat. Mean theophylline C_{max} values were 4.14 and 4.39 $\mu\text{g}/\text{mL}$ for subjects coadministered with placebo and febuxostat, respectively. Mean theophylline AUC(0-tlqc) values were 115 $\mu\text{g}\cdot\text{hr}/\text{mL}$ and 122 $\mu\text{g}\cdot\text{hr}/\text{mL}$ for subjects coadministered with placebo and febuxostat, respectively. Likewise, mean AUC(0-inf) values were also comparable between regimens. The intersubject variability (% CV) of C_{max} and AUC(0-tlqc) values of theophylline ranged from 29% to 40% and 44% to 45%, respectively. The estimated mean $T_{1/2}$,

TABLE 4

Summary of Theophylline Pharmacokinetic Parameter Estimates Following an Oral Dose of 400 mg Theophylline Coadministered With 80 mg Febuxostat or Matching Placebo						
	T _{max} (hr)	C _{max} ($\mu\text{g}/\text{mL}$)	AUC(0-tlqc) ($\mu\text{g} \cdot \text{hr}/\text{mL}$)	AUC(0-inf)(a) ($\mu\text{g} \cdot \text{hr}/\text{mL}$)	T _{1/2} (a) (hr)	CL/F(a) (mL/h)
Theophylline + Febuxostat (Regimen A)						
N	23	23	23	18	18	18
Mean	8.43(b)	4.39	122	114	9.69(c)	4430
SD	4.62	1.74	55.7	53.4	2.32	2370
CV %	55	40	45	47	24	53
Theophylline + Placebo (Regimen B)						
N	23	23	23	18	18	18
Mean	7.05(b)	4.14	115	107	9.69(c)	4430
SD	2.88	1.19	50.3	49.9	2.07	1930
CV %	41	29	44	46	21	44
						30

Regimen A: Febuxostat 80 mg (two 40 mg encapsulated tablets) QD for 7 consecutive days and a single oral dose of theophylline, anhydrous 400 mg tablet on Day 5.
Regimen B: Matching placebo for febuxostat 80 mg (two 40 mg encapsulated tablets) QD for 7 consecutive days and a single oral dose of theophylline, anhydrous 400 mg tablet on Day 5.

(a)The terminal phase of the pharmacokinetic profile of theophylline could not be adequately characterized in the remaining subjects.

(b)Median T_{max} values for Regimens A and B were 6.02 and 6.00 hr, respectively.

(c)Harmonic mean T_{1/2} values for Regimens A and B were 9.13 and 9.28 hr, respectively.

As illustrated in Table 4 above, theophylline was absorbed with a mean T_{max} value of 7 to 9 hours (median=6 hours) and

CL/F, and V_z/F values for theophylline were generally similar between the 2 treatment regimens.

TABLE 5

Summary of Total Amount of Theophylline and Its Metabolites Excreted in Urine Over 72 Hours Following an Oral Dose of 400 mg Theophylline Coadministered With 80 mg Febuxostat or Matching Placebo				
	Theophylline (mg)	1,3-Dimethyluric acid (mg)	1-Methyluric acid (mg)	1-Methylxanthine (mg)
Theophylline + Febuxostat (Regimen A)				
N	23	23	23	23
Mean	35.0	105.2	3.1	40.1
				26.9

US 9,107,912 B2

23

TABLE 5-continued

Summary of Total Amount of Theophylline and Its Metabolites Excreted in Urine Over 72 Hours Following an Oral Dose of 400 mg Theophylline Coadministered With 80 mg Febuxostat or Matching Placebo					
	Theophylline (mg)	1,3-Dimethyluric acid (mg)	1-Methyluric acid (mg)	1-Methylxanthine (mg)	3-Methylxanthine (mg)
SD	18.1	23.3	4.0	7.6	9.5
CV %	52	22	127	19	35
Theophylline + Placebo (Regimen B)					
N	23	23	23	23	23
Mean	35.0	114.8	56.2	0.1	30.9
SD	16.8	32.2	17.4	0.4	11.6
CV %	48	28	31	337	38

Regimen A: Febuxostat 80 mg (two 40 mg encapsulated tablets) QD for 7 consecutive days and a single oral dose of theophylline, anhydrous 400 mg tablet on Day 5.

Regimen B: Matching placebo for febuxostat 80 mg (two 40 mg encapsulated tablets) QD for 7 consecutive days and a single oral dose of theophylline, anhydrous 400 mg tablet on Day 5.

As illustrated in Table 5 above, the mean amount of parent drug (i.e., theophylline) excreted in the urine over a 72 hour interval were comparable between regimen arms and consistent with the literature. See Melethil S et al., *Res Commun Chem Pathol Pharmacol.*, 1982; 35(2):341-4. The mean amounts of 1,3-dimethyluric acid and 3-methylxanthine were also similar between the 2 regimens. In contrast, 1-methyluric acid decreased and 1-methylxanthine increased in subjects administered theophylline with febuxostat compared with those subjects administered theophylline with placebo.

A statistical analysis of the data was also performed. The effects of sequence, period, and regimen on theophylline T_{max} , $\ln(C_{max})$, $\ln(AUC[0-tlqc])$, and $\ln(AUC[0-inf])$ following coadministration of febuxostat or placebo were assessed. None of the aforementioned effects were statistically significant on the pharmacokinetic parameters ($P>0.05$) observed in the experiment. Further, the bioavailability of theophylline coadministered with febuxostat (Regimen A) relative to that of theophylline with placebo (Regimen B) was assessed via point estimates and 90% confidence intervals for the ratios of the central values for C_{max} , $AUC(0-tlqc)$, and $AUC(0-inf)$, and is summarized in Table 6.

TABLE 6

Relative Bioavailability of Febuxostat Following Administration of a Single Oral Dose of 80 mg Febuxostat		
Parameter	Point Estimate	90% Confidence Interval
Regimen A vs Regimen B		
Cmax	1.03	(0.917, 1.149)
AUC(0-tlqc)	1.04	(0.927, 1.156)
AUC(0-inf)	1.05	(0.924, 1.189)

Regimen A: Febuxostat 80 mg (two 40 mg encapsulated tablets) QD for 7 consecutive days and a single oral dose of theophylline, anhydrous 400 mg tablet on Day 5.

Regimen B: Matching Placebo for febuxostat 80 mg (two 40 mg encapsulated tablets) QD for 7 consecutive days and a single oral dose of theophylline, anhydrous 400 mg tablet on Day 5.

Note:

The point estimates and confidence intervals were obtained from the exponentiated results of analysis of the natural logarithm transformed data.

From the statistical analyses of the pharmacokinetic data, the point estimates for theophylline C_{max} , $AUC(0-tlqc)$, and $AUC(0-inf)$ were close to 100%, and the 90% confidence intervals for the ratios were within the bioequivalence limit of 0.80 to 1.25.

24

The results of this experiment showed that the maximum observed theophylline concentration (C_{max}) and exposure to theophylline (AUC) were comparable between treatment with febuxostat and treatment with placebo. Therefore, no adjustment of the theophylline dose was needed when coadministered with febuxostat.

What is claimed is:

1. A method of treating hyperuricemia in a patient in need of treatment thereof, the method comprising the steps of: administering to a patient suffering from hyperuricemia and at least one second disease state, a therapeutically effective amount of 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid or a pharmaceutically acceptable salt thereof, wherein the subject is also receiving concomitant administration of theophylline to treat the at least one second disease state, and further wherein (i) the administration of 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid or a pharmaceutically acceptable salt thereof, to the patient does not result in theophylline toxicity to the patient; and (ii) administration of the theophylline is in an amount ranging from about 90% to about 110% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor.
2. The method of claim 1, wherein the second disease state is asthma.
3. The method of claim 1, wherein the patient is further suffering from at least one third disease state, wherein the third disease is gout.
4. The method of claim 1, wherein the theophylline dosage amount ranges from about 95% to about 105% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor.
5. The method of claim 1, wherein the theophylline dosage amount ranges from about 99% to about 101% of a manufacturer's recommended theophylline dosage amount in the absence of administration of at least one xanthine oxidoreductase inhibitor.
6. The method of claim 1, wherein the patient suffering from hyperuricemia and the at least one second disease state is previously administered theophylline prior to initiation of treatment with 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid.

* * * * *

EXHIBIT D

HIGHLIGHTS OF PRESCRIBING INFORMATION

These HIGHLIGHTS do not include all the information needed to use ULORIC safely and effectively. See full prescribing information for ULORIC.

ULORIC (febuxostat) tablet for oral use

Initial U.S. Approval: 2009

INDICATIONS AND USAGE

ULORIC is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in patients with gout. (1)

ULORIC is not recommended for the treatment of asymptomatic hyperuricemia. (1)

DOSAGE AND ADMINISTRATION

- ULORIC is recommended at 40 mg or 80 mg once daily. The recommended starting dose of ULORIC is 40 mg once daily. For patients who do not achieve a serum uric acid (sUA) less than 6 mg per dL after 2 weeks with 40 mg, ULORIC 80 mg is recommended. (2.1)
- ULORIC can be administered without regard to food or antacid use. (2.1)
- No dose adjustment is necessary when administering ULORIC to patients with mild to moderate renal or hepatic impairment. (2.2)

DOSAGE FORMS AND STRENGTHS

Tablet: 40 mg, 80 mg. (3)

CONTRAINDICATIONS

ULORIC is contraindicated in patients being treated with azathioprine, mercaptopurine, or theophylline. (4)

WARNINGS AND PRECAUTIONS

- Gout Flare:** An increase in gout flares is frequently observed during initiation of anti-hyperuricemic agents, including ULORIC. If a gout flare occurs during treatment, ULORIC need not be discontinued. Prophylactic therapy (i.e., non-steroidal anti-inflammatory drug (NSAID) or colchicine upon initiation of treatment) may be beneficial for up to six months. (2.4, 5.1)

FULL PRESCRIBING INFORMATION: CONTENTS***1 INDICATIONS AND USAGE****2 DOSAGE AND ADMINISTRATION**

- Recommended Dose
- Special Populations
- Uric Acid Level
- Gout Flares

3 DOSAGE FORMS AND STRENGTHS**4 CONTRAINDICATIONS****5 WARNINGS AND PRECAUTIONS**

- Gout Flare
- Cardiovascular Events
- Liver Enzyme Elevations

6 ADVERSE REACTIONS

- Clinical Trials Experience

7 DRUG INTERACTIONS

- Xanthine Oxidase Substrate Drugs
- Cytotoxic Chemotherapy Drugs
- In Vivo Drug Interaction Studies

8 USE IN SPECIFIC POPULATIONS

- Pregnancy
- Nursing Mothers
- Pediatric Use

- Cardiovascular Events:** A higher rate of cardiovascular thromboembolic events was observed in patients treated with ULORIC than allopurinol in clinical trials. Monitor for signs and symptoms of MI and stroke. (5.2)
- Liver Enzyme Elevation:** Transaminase elevations have been observed in ULORIC-treated patients. Monitor liver function tests periodically. (5.3)

ADVERSE REACTIONS

Adverse reactions occurring in at least 1% of ULORIC-treated patients, and, at least 0.5% greater than placebo, are liver function abnormalities, nausea, arthralgia, and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1.877.825.3327 or FDA at 1.800.FDA.1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Concomitant administration of ULORIC with XO substrate drugs, azathioprine, mercaptopurine, or theophylline could increase plasma concentrations of these drugs resulting in severe toxicity. (7)

USE IN SPECIFIC POPULATIONS

- There is insufficient data in patients with severe renal impairment. No studies have been conducted in patients with severe hepatic impairment. Caution should be exercised in these patients. (8.6, 8.7)
- No studies have been conducted in patients with secondary hyperuricemia (including patients being treated for Lesch-Nyhan syndrome or malignant disease, or in organ transplant recipients); therefore, ULORIC is not recommended for use in these patients. (8.8)

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

Revised: February 2009

8.5 Geriatric Use**8.6 Renal Impairment****8.7 Hepatic Impairment****8.8 Secondary Hyperuricemia****10 OVERDOSAGE****11 DESCRIPTION****12 CLINICAL PHARMACOLOGY****12.1 Mechanism of Action****12.2 Pharmacodynamics****12.3 Pharmacokinetics****13 NONCLINICAL TOXICOLOGY****13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility****13.2 Animal Toxicology****14 CLINICAL STUDIES****14.1 Management of Hyperuricemia in Gout****16 HOW SUPPLIED/STORAGE AND HANDLING****17 PATIENT COUNSELING INFORMATION****17.1 General Information****17.2 FDA-Approved Patient Labeling**

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ULORIC® is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in patients with gout.

ULORIC is not recommended for the treatment of asymptomatic hyperuricemia.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

For treatment of hyperuricemia in patients with gout, ULORIC is recommended at 40 mg or 80 mg once daily.

The recommended starting dose of ULORIC is 40 mg once daily. For patients who do not achieve a serum uric acid (sUA) less than 6 mg per dL after 2 weeks with 40 mg, ULORIC 80 mg is recommended.

ULORIC can be taken without regard to food or antacid use [see *Clinical Pharmacology (12.3)*].

2.2 Special Populations

No dose adjustment is necessary when administering ULORIC in patients with mild to moderate renal impairment [see *Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)*]. The recommended starting dose of ULORIC is 40 mg once daily. For patients who do not achieve a sUA less than 6 mg per dL after 2 weeks with 40 mg, ULORIC 80 mg is recommended.

No dose adjustment is necessary in patients with mild to moderate hepatic impairment [see *Use in Specific Populations (8.7)* and *Clinical Pharmacology (12.3)*].

2.3 Uric Acid Level

Testing for the target serum uric acid level of less than 6 mg per dL may be performed as early as 2 weeks after initiating ULORIC therapy.

2.4 Gout Flares

Gout flares may occur after initiation of ULORIC due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. Flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended upon initiation of ULORIC. Prophylactic therapy may be beneficial for up to six months [see *Clinical Studies (14.1)*].

If a gout flare occurs during ULORIC treatment, ULORIC need not be discontinued. The gout flare should be managed concurrently, as appropriate for the individual patient [see *Warnings and Precautions (5.1)*].

3 DOSAGE FORMS AND STRENGTHS

- 40 mg tablets, light green to green, round shaped, debossed with “TAP” and “40”
- 80 mg tablets, light green to green, teardrop shaped, debossed with “TAP” and “80”

4 CONTRAINDICATIONS

ULORIC is contraindicated in patients being treated with azathioprine, mercaptopurine, or theophylline [see *Drug Interactions (7)*].

5 WARNINGS AND PRECAUTIONS

5.1 Gout Flare

After initiation of ULORIC, an increase in gout flares is frequently observed. This increase is due to reduction in serum uric acid levels resulting in mobilization of urate from tissue deposits.

In order to prevent gout flares when ULORIC is initiated, concurrent prophylactic treatment with an NSAID or colchicine is recommended [see *Dosage and Administration* (2.4)].

5.2 Cardiovascular Events

In the randomized controlled studies, there was a higher rate of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) in patients treated with ULORIC [0.74 per 100 P-Y (95% CI 0.36-1.37)] than allopurinol [0.60 per 100 P-Y (95% CI 0.16-1.53)] [see *Adverse Reactions* (6.1)]. A causal relationship with ULORIC has not been established. Monitor for signs and symptoms of myocardial infarction (MI) and stroke.

5.3 Liver Enzyme Elevations

During randomized controlled studies, transaminase elevations greater than 3 times the upper limit of normal (ULN) were observed (AST: 2%, 2%, and ALT: 3%, 2% in ULORIC and allopurinol-treated patients, respectively). No dose-effect relationship for these transaminase elevations was noted. Laboratory assessment of liver function is recommended at, for example, 2 and 4 months following initiation of ULORIC and periodically thereafter.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

A total of 2757 subjects with hyperuricemia and gout were treated with ULORIC 40 mg or 80 mg daily in clinical studies. For ULORIC 40 mg, 559 patients were treated for \geq 6 months. For ULORIC 80 mg, 1377 subjects were treated for \geq 6 months, 674 patients were treated for \geq 1 year and 515 patients were treated for \geq 2 years.

Most Common Adverse Reactions

In three randomized, controlled clinical studies (Studies 1, 2 and 3), which were 6 to 12 months in duration, the following adverse reactions were reported by the treating physician as related to study drug. Table 1 summarizes adverse reactions reported at a rate of at least 1% in ULORIC treatment groups and at least 0.5% greater than placebo.

Table 1: Adverse Reactions Occurring in ≥ 1% of ULORIC-Treated Patients and at Least 0.5% Greater than Seen in Patients Receiving Placebo in Controlled Studies

Adverse Reactions	Placebo	ULORIC		allopurinol*
	(N=134)	40 mg daily (N=757)	80 mg daily (N=1279)	(N=1277)
Liver Function Abnormalities	0.7%	6.6%	4.6%	4.2%
Nausea	0.7%	1.1%	1.3%	0.8%
Arthralgia	0%	1.1%	0.7%	0.7%
Rash	0.7%	0.5%	1.6%	1.6%

* Of the subjects who received allopurinol, 10 received 100 mg, 145 received 200 mg, and 1122 received 300 mg, based on level of renal impairment.

The most common adverse reaction leading to discontinuation from therapy was liver function abnormalities in 1.8% of ULORIC 40 mg, 1.2% of ULORIC 80 mg, and in 0.9% of allopurinol-treated subjects.

In addition to the adverse reactions presented in Table 1, dizziness was reported in more than 1% of ULORIC-treated subjects although not at a rate more than 0.5% greater than placebo.

Less Common Adverse Reactions

In phase 2 and 3 clinical studies the following adverse reactions occurred in less than 1% of subjects and in more than one subject treated with doses ranging from 40 mg to 240 mg of ULORIC. This list also includes adverse reactions (less than 1% of subjects) associated with organ systems from Warnings and Precautions.

Blood and Lymphatic System Disorders: anemia, idiopathic thrombocytopenic purpura, leukocytosis/leukopenia, neutropenia, pancytopenia, splenomegaly, thrombocytopenia.

Cardiac Disorders: angina pectoris, atrial fibrillation/flutter, cardiac murmur, ECG abnormal, palpitations, sinus bradycardia, tachycardia.

Ear and Labyrinth Disorders: deafness, tinnitus, vertigo.

Eye Disorders: vision blurred.

Gastrointestinal Disorders: abdominal distention, abdominal pain, constipation, dry mouth, dyspepsia, flatulence, frequent stools, gastritis, gastroesophageal reflux disease, gastrointestinal discomfort, gingival pain, haematemesis, hyperchlorhydria, hematochezia, mouth ulceration, pancreatitis, peptic ulcer, vomiting.

General Disorders and Administration Site Conditions: asthenia, chest pain/discomfort, edema, fatigue, feeling abnormal, gait disturbance, influenza-like symptoms, mass, pain, thirst.

Hepatobiliary Disorders: cholelithiasis/cholecystitis, hepatic steatosis, hepatitis, hepatomegaly.

Immune System Disorder: hypersensitivity.

Infections and Infestations: herpes zoster.

Procedural Complications: contusion.

Metabolism and Nutrition Disorders: anorexia, appetite decreased/increased, dehydration, diabetes mellitus, hypercholesterolemia, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypokalemia, weight decreased/increased.

Musculoskeletal and Connective Tissue Disorders: arthritis, joint stiffness, joint swelling, muscle spasms/twitching/tightness/weakness, musculoskeletal pain/stiffness, myalgia.

Nervous System Disorders: altered taste, balance disorder, cerebrovascular accident, Guillain-Barré syndrome, headache, hemiparesis, hypoesthesia, hyposmia, lacunar infarction, lethargy, mental impairment, migraine, paresthesia, somnolence, transient ischemic attack, tremor.

Psychiatric Disorders: agitation, anxiety, depression, insomnia, irritability, libido decreased, nervousness, panic attack, personality change.

Renal and Urinary Disorders: hematuria, nephrolithiasis, pollakiuria, proteinuria, renal failure, renal insufficiency, urgency, incontinence.

Reproductive System and Breast Changes: breast pain, erectile dysfunction, gynecomastia.

Respiratory, Thoracic and Mediastinal Disorders: bronchitis, cough, dyspnea, epistaxis, nasal dryness, paranasal sinus hypersecretion, pharyngeal edema, respiratory tract congestion, sneezing, throat irritation, upper respiratory tract infection.

Skin and Subcutaneous Tissue Disorders: alopecia, angio-edema, dermatitis, dermographism, ecchymosis, eczema, hair color changes, hair growth abnormal, hyperhidrosis, peeling skin, petechiae, photosensitivity, pruritus, purpura, skin discoloration/alteration/pigmentation, skin lesion, skin odor abnormal, urticaria.

Vascular Disorders: flushing, hot flush, hypertension, hypotension.

Laboratory Parameters: activated partial thromboplastin time prolonged, creatine increased, bicarbonate decreased, sodium increased, EEG abnormal, glucose increased, cholesterol increased, triglycerides increased, amylase increased, potassium increased, TSH increased, platelet count decreased, hematocrit decreased, hemoglobin decreased, MCV increased, RBC decreased, creatinine increased, blood urea increased, BUN/creatinine ratio increased, creatine phosphokinase (CPK) increased, alkaline phosphatase increased, LDH increased, PSA increased, urine output increased/decreased, lymphocyte count decreased, neutrophil count decreased, WBC increased/decreased, coagulation test abnormal, low density lipoprotein (LDL) increased, prothrombin time prolonged, urinary casts, urine positive for white blood cells and protein.

Cardiovascular Safety

Cardiovascular events and deaths were adjudicated to one of the pre-defined endpoints from the Anti-Platelet Trialists' Collaborations (APTC) (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) in the randomized controlled and long-term extension studies. In the Phase 3 randomized controlled studies, the incidences of adjudicated APTC events per 100 patient-years of exposure were: Placebo 0 (95% CI 0.00-6.16), ULORIC 40 mg 0 (95% CI 0.00-1.08), ULORIC 80 mg 1.09 (95% CI 0.44-2.24), and allopurinol 0.60 (95% CI 0.16-1.53).

In the long-term extension studies, the incidences of adjudicated APTC events were: ULORIC 80 mg 0.97 (95% CI 0.57-1.56), and allopurinol 0.58 (95% CI 0.02-3.24).

Overall, a higher rate of APTC events was observed in ULORIC than in allopurinol-treated patients. A causal relationship with ULORIC has not been established. Monitor for signs and symptoms of MI and stroke.

7 DRUG INTERACTIONS

7.1 Xanthine Oxidase Substrate Drugs

ULORIC is an XO inhibitor. Drug interaction studies of ULORIC with drugs that are metabolized by XO (e.g., theophylline, mercaptopurine, azathioprine) have not been conducted. Inhibition of XO by ULORIC may cause increased plasma concentrations of these drugs leading to toxicity [see *Clinical Pharmacology* (12.3)]. ULORIC is contraindicated in patients being treated with azathioprine, mercaptopurine, or theophylline [see *Contraindications* (4)].

7.2 Cytotoxic Chemotherapy Drugs

Drug interaction studies of ULORIC with cytotoxic chemotherapy have not been conducted. No data are available regarding the safety of ULORIC during cytotoxic chemotherapy.

7.3 In Vivo Drug Interaction Studies

Based on drug interaction studies in healthy subjects, ULORIC does not have clinically significant interactions with colchicine, naproxen, indomethacin, hydrochlorothiazide, warfarin or desipramine [see *Clinical Pharmacology* (12.3)]. Therefore, ULORIC may be used concomitantly with these medications.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. ULORIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Febuxostat was not teratogenic in rats and rabbits at oral doses up to 48 mg per kg (40 and 51 times the human plasma exposure at 80 mg per day for equal body surface area, respectively) during organogenesis. However, increased neonatal mortality and a reduction in the neonatal body weight gain were observed when pregnant rats were treated with oral doses up to 48 mg per kg (40 times the human plasma exposure at 80 mg per day) during organogenesis and through lactation period.

8.3 Nursing Mothers

Febuxostat is excreted in the milk of rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ULORIC is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients under 18 years of age have not been established.

8.5 Geriatric Use

No dose adjustment is necessary in elderly patients. Of the total number of subjects in clinical studies of ULORIC, 16 percent were 65 and over, while 4 percent were 75 and over. Comparing subjects in different age groups, no clinically significant differences in safety or effectiveness were observed but greater sensitivity of some older individuals cannot be ruled out. The C_{max} and AUC_{24} of febuxostat following multiple oral doses of ULORIC in geriatric subjects (≥ 65 years) were similar to those in younger subjects (18-40 years) [see *Clinical Pharmacology* (12.3)].

8.6 Renal Impairment

No dose adjustment is necessary in patients with mild or moderate renal impairment (Cl_{cr} 30-89 mL per min). The recommended starting dose of ULORIC is 40 mg once daily. For patients who do not achieve a sUA less than 6 mg per dL after 2 weeks with 40 mg, ULORIC 80 mg is recommended.

There are insufficient data in patients with severe renal impairment (Cl_{cr} less than 30 mL per min); therefore, caution should be exercised in these patients [see *Clinical Pharmacology* (12.3)].

8.7 Hepatic Impairment

No dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh Class A or B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C); therefore, caution should be exercised in these patients [see *Clinical Pharmacology* (12.3)].

8.8 Secondary Hyperuricemia

No studies have been conducted in patients with secondary hyperuricemia (including organ transplant recipients); ULORIC is not recommended for use in patients whom the rate of urate formation is greatly increased (e.g., malignant disease and its treatment, Lesch-Nyhan syndrome). The concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract.

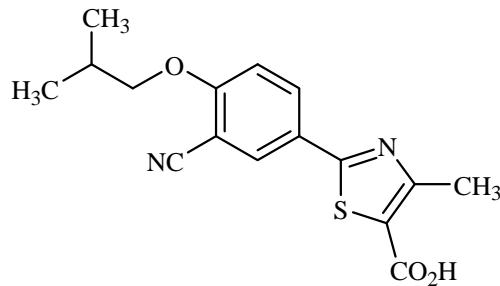
10 OVERDOSAGE

ULORIC was studied in healthy subjects in doses up to 300 mg daily for seven days without evidence of dose-limiting toxicities. No overdose of ULORIC was reported in clinical studies. Patients should be managed by symptomatic and supportive care should there be an overdose.

11 DESCRIPTION

ULORIC (febuxostat) is a xanthine oxidase inhibitor. The active ingredient in ULORIC is 2-[3-cyano-4-(2-methylpropoxy) phenyl]-4-methylthiazole-5-carboxylic acid, with a molecular weight of 316.38. The empirical formula is $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_3\text{S}$.

The chemical structure is:



Febuxostat is a non-hygroscopic, white crystalline powder that is freely soluble in dimethylformamide; soluble in dimethylsulfoxide; sparingly soluble in ethanol; slightly soluble in methanol and acetonitrile; and practically insoluble in water. The melting range is 205°C to 208°C.

ULORIC tablets for oral use contain the active ingredient, febuxostat, and are available in two dosage strengths, 40 mg and 80 mg. Inactive ingredients include lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, sodium croscarmellose, silicon dioxide and magnesium stearate. ULORIC tablets are coated with Opadry II, green.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ULORIC, a xanthine oxidase inhibitor, achieves its therapeutic effect by decreasing serum uric acid. ULORIC is not expected to inhibit other enzymes involved in purine and pyrimidine synthesis and metabolism at therapeutic concentrations.

12.2 Pharmacodynamics

Effect on Uric Acid and Xanthine Concentrations: In healthy subjects, ULORIC resulted in a dose dependent decrease in 24-hour mean serum uric acid concentrations, and an increase in 24-hour mean serum xanthine concentrations. In addition, there was a decrease in the total daily urinary uric acid excretion. Also, there was an increase in total daily urinary xanthine excretion. Percent reduction in 24-hour mean serum uric acid concentrations was between 40% to 55% at the exposure levels of 40 mg and 80 mg daily doses.

Effect on Cardiac Repolarization: The effect of ULORIC on cardiac repolarization as assessed by the QTc interval was evaluated in normal healthy subjects and in patients with gout. ULORIC in doses up to 300 mg daily, at steady state, did not demonstrate an effect on the QTc interval.

12.3 Pharmacokinetics

In healthy subjects, maximum plasma concentrations (C_{max}) and AUC of febuxostat increased in a dose proportional manner following single and multiple doses of 10 mg to 120 mg. There is no accumulation when therapeutic doses are administered every 24 hours. Febuxostat has an apparent mean terminal elimination half-life ($t_{1/2}$) of approximately 5 to 8 hours. Febuxostat pharmacokinetic parameters for patients with hyperuricemia and gout estimated by population pharmacokinetic analyses were similar to those estimated in healthy subjects.

Absorption: The absorption of radiolabeled febuxostat following oral dose administration was estimated to be at least 49% (based on total radioactivity recovered in urine). Maximum plasma concentrations of febuxostat occurred between 1 to 1.5 hours post-dose. After multiple oral 40 mg and 80 mg once daily doses, C_{max} is approximately 1.6 ± 0.6 mcg per mL (N=30), and 2.6 ± 1.7 mcg per mL (N=227), respectively. Absolute bioavailability of the febuxostat tablet has not been studied.

Following multiple 80 mg once daily doses with a high fat meal, there was a 49% decrease in C_{max} and an 18% decrease in AUC, respectively. However, no clinically significant change in the percent decrease in serum uric acid concentration was observed (58% fed vs. 51% fasting). Thus, ULORIC may be taken without regard to food.

Concomitant ingestion of an antacid containing magnesium hydroxide and aluminum hydroxide with an 80 mg single dose of ULORIC has been shown to delay absorption of febuxostat (approximately 1 hour) and to cause a 31% decrease in C_{max} and a 15% decrease in AUC_∞. As AUC rather than C_{max} was related to drug effect, change observed in AUC was not considered clinically significant. Therefore, ULORIC may be taken without regard to antacid use.

Distribution: The mean apparent steady state volume of distribution (V_{ss}/F) of febuxostat was approximately 50 L (CV ~40%). The plasma protein binding of febuxostat is approximately 99.2%, (primarily to albumin), and is constant over the concentration range achieved with 40 mg and 80 mg doses.

Metabolism: Febuxostat is extensively metabolized by both conjugation via uridine diphosphate glucuronosyltransferase (UGT) enzymes including UGT1A1, UGT1A3, UGT1A9, and UGT2B7 and oxidation via cytochrome P450 (CYP) enzymes including CYP1A2, 2C8 and 2C9 and non-P450 enzymes. The relative contribution of each enzyme isoform in the metabolism of febuxostat is not clear. The oxidation of the isobutyl side chain leads to the formation of four pharmacologically active hydroxy metabolites, all of which occur in plasma of humans at a much lower extent than febuxostat.

In urine and feces, acyl glucuronide metabolites of febuxostat (~35% of the dose), and oxidative metabolites, 67M-1 (~10% of the dose), 67M-2 (~11% of the dose), and 67M-4, a secondary metabolite from 67M-1, (~14% of the dose) appeared to be the major metabolites of febuxostat *in vivo*.

Elimination: Febuxostat is eliminated by both hepatic and renal pathways. Following an 80 mg oral dose of ¹⁴C-labeled febuxostat, approximately 49% of the dose was recovered in the urine as unchanged febuxostat (3%), the acyl glucuronide of the drug (30%), its known oxidative metabolites and their conjugates (13%), and other unknown metabolites (3%). In addition to the urinary excretion, approximately 45% of the dose was recovered in the feces as the unchanged febuxostat (12%), the acyl glucuronide of the drug (1%), its known oxidative metabolites and their conjugates (25%), and other unknown metabolites (7%).

The apparent mean terminal elimination half-life ($t_{1/2}$) of febuxostat was approximately 5 to 8 hours.

Special Populations

Pediatric Use: The pharmacokinetics of ULORIC in patients under the age of 18 years have not been studied.

Geriatric Use: The C_{max} and AUC of febuxostat and its metabolites following multiple oral doses of ULORIC in geriatric subjects (≥ 65 years) were similar to those in younger subjects (18-40 years). In addition, the percent decrease in serum uric acid concentration was similar between elderly and younger subjects. No dose adjustment is necessary in geriatric patients [see *Use in Specific Populations* (8.5)].

Renal Impairment: Following multiple 80 mg doses of ULORIC in healthy subjects with mild (Cl_{cr} 50-80 mL per min), moderate (Cl_{cr} 30-49 mL per min) or severe renal impairment (Cl_{cr} 10-29 mL per min), the C_{max} of febuxostat did not change relative to subjects with normal renal function (Cl_{cr} greater than 80 mL per min). AUC and half-life of febuxostat increased in subjects with renal impairment in comparison to subjects with normal renal function, but values were similar among three renal impairment groups. Mean febuxostat AUC values were up to 1.8 times higher in subjects with renal impairment compared to those with normal renal function. Mean C_{max} and AUC values for 3 active metabolites increased up to 2- and 4-fold, respectively. However, the percent decrease in serum uric acid concentration for subjects with renal impairment was comparable to those with normal renal function (58% in normal renal function group and 55% in the severe renal function group).

No dose adjustment is necessary in patients with mild to moderate renal impairment [see *Dosage and Administration* (2) and *Use in Specific Populations* (8.6)]. The recommended starting dose of ULORIC is 40 mg once daily. For patients who do not achieve a sUA less than 6 mg per dL after 2 weeks with 40 mg, ULORIC 80 mg is recommended. There is insufficient data in patients with severe renal impairment; caution should be exercised in those patients [see *Use in Specific Populations* (8.6)].

ULORIC has not been studied in end stage renal impairment patients who are on dialysis.

Hepatic Impairment: Following multiple 80 mg doses of ULORIC in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, an average of 20-30% increase was observed for both C_{max} and AUC_{24} (total and unbound) in hepatic impairment groups compared to subjects with normal hepatic function. In addition, the percent decrease in serum uric acid concentration was comparable between different hepatic groups (62% in healthy group, 49% in mild hepatic impairment group, and 48% in moderate hepatic impairment group). No dose adjustment is necessary in patients with mild or moderate hepatic impairment. No studies have been conducted in subjects with severe hepatic impairment (Child-Pugh Class C); caution should be exercised in those patients [see *Use in Specific Populations* (8.7)].

Gender: Following multiple oral doses of ULORIC, the C_{max} and AUC_{24} of febuxostat were 30% and 14% higher in females than in males, respectively. However, weight-corrected C_{max} and AUC were similar between the genders. In addition, the percent decrease in serum uric acid concentrations was similar between genders. No dose adjustment is necessary based on gender.

Race: No specific pharmacokinetic study was conducted to investigate the effects of race.

Drug-Drug Interactions

Effect of ULORIC on Other Drugs

Xanthine Oxidase Substrate Drugs-Azathioprine, Mercaptopurine, and Theophylline: Febuxostat is an XO inhibitor. Drug interaction studies of ULORIC with drugs that are metabolized by XO (e.g., theophylline, mercaptopurine, azathioprine) have not been conducted. Inhibition of XO by ULORIC may cause increased plasma concentrations of these drugs leading to toxicity. ULORIC is contraindicated in patients being treated with azathioprine, mercaptopurine, and theophylline [see *Contraindications (4)* and *Drug Interactions (7)*].

Azathioprine and mercaptopurine undergo metabolism via three major metabolic pathways, one of which is mediated by XO. Although ULORIC drug interaction studies with azathioprine and mercaptopurine have not been conducted, concomitant administration of allopurinol [a xanthine oxidase inhibitor] with azathioprine or mercaptopurine has been reported to substantially increase plasma concentrations of these drugs. Because ULORIC is a xanthine oxidase inhibitor, it could inhibit the XO-mediated metabolism of azathioprine and mercaptopurine leading to increased plasma concentrations of azathioprine or mercaptopurine that could result in severe toxicity.

Theophylline is a CYP1A2 and XO substrate. Although no ULORIC drug interaction study with theophylline has been conducted, concomitant administration of theophylline with allopurinol, a xanthine oxidase inhibitor at doses ≥ 600 mg per day, has been reported to increase theophylline plasma concentrations. Because ULORIC is a xanthine oxidase inhibitor and theophylline is a low therapeutic index drug, ULORIC could inhibit the XO-mediated metabolism of theophylline leading to increased plasma concentrations of theophylline that could induce severe theophylline toxicity.

P450 Substrate Drugs: *In vitro* studies have shown that febuxostat does not inhibit P450 enzymes CYP1A2, 2C9, 2C19, 2D6, or 3A4 and it also does not induce CYP1A2, 2B6, 2C9, 2C19, or 3A4 at clinically relevant concentrations. As such, pharmacokinetic interactions between ULORIC and drugs metabolized by these CYP enzymes are unlikely.

Effect of Other Drugs on ULORIC

Febuxostat is metabolized by conjugation and oxidation via multiple metabolizing enzymes. The relative contribution of each enzyme isoform is not clear. Drug interactions between ULORIC and a drug that inhibits or induces one particular enzyme isoform is in general not expected.

In Vivo Drug Interaction Studies

Colchicine: No dose adjustment is necessary for either ULORIC or colchicine when the two drugs are co-administered. Administration of ULORIC (40 mg once daily) with colchicine (0.6 mg twice daily) resulted in an increase of 12% in C_{max} and 7% in AUC_{24} of febuxostat. In addition, administration of colchicine (0.6 mg twice daily) with ULORIC (120 mg daily) resulted in less than 11% change in C_{max} or AUC of colchicine for both AM and PM doses. These changes were not considered clinically significant.

Naproxen: No dose adjustment is necessary for ULORIC or naproxen when the two drugs are co-administered. Administration of ULORIC (80 mg once daily) with naproxen (500 mg twice daily) resulted in a 28% increase in C_{max} and a 40% increase in AUC of febuxostat. The increases were

not considered clinically significant. In addition, there were no significant changes in the C_{max} or AUC of naproxen (less than 2%).

Indomethacin: No dose adjustment is necessary for either ULORIC or indomethacin when these two drugs are co-administered. Administration of ULORIC (80 mg once daily) with indomethacin (50 mg twice daily) did not result in any significant changes in C_{max} or AUC of febuxostat or indomethacin (less than 7%).

Hydrochlorothiazide: No dose adjustment is necessary for ULORIC when co-administered with hydrochlorothiazide. Administration of ULORIC (80 mg) with hydrochlorothiazide (50 mg) did not result in any clinically significant changes in C_{max} or AUC of febuxostat (less than 4%), and serum uric acid concentrations were not substantially affected.

Warfarin: No dose adjustment is necessary for warfarin when co-administered with ULORIC. Administration of ULORIC (80 mg once daily) with warfarin had no effect on the pharmacokinetics of warfarin in healthy subjects. INR and Factor VII activity were also not affected by the co-administration of ULORIC.

Desipramine: Co-administration of drugs that are CYP2D6 substrates (such as desipramine) with ULORIC are not expected to require dose adjustment. Febuxostat was shown to be a weak inhibitor of CYP2D6 *in vitro* and *in vivo*. Administration of ULORIC (120 mg once daily) with desipramine (25 mg) resulted in an increase in C_{max} (16%) and AUC (22%) of desipramine, which was associated with a 17% decrease in the 2-hydroxydesipramine to desipramine metabolic ratio (based on AUC).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Two-year carcinogenicity studies were conducted in F344 rats and B6C3F1 mice. Increased transitional cell papilloma and carcinoma of urinary bladder was observed at 24 mg per kg (25 times the human plasma exposure at maximum recommended human dose of 80 mg per day) and 18.75 mg per kg (12.5 times the human plasma exposure at 80 mg per day) in male rats and female mice, respectively. The urinary bladder neoplasms were secondary to calculus formation in the kidney and urinary bladder.

Mutagenesis: Febuxostat showed a positive mutagenic response in a chromosomal aberration assay in a Chinese hamster lung fibroblast cell line with and without metabolic activation *in vitro*. Febuxostat was negative in the *in vitro* Ames assay and chromosomal aberration test in human peripheral lymphocytes, and L5178Y mouse lymphoma cell line, and *in vivo* tests in mouse micronucleus, rat unscheduled DNA synthesis and rat bone marrow cells.

Impairment of Fertility: Febuxostat at oral doses up to 48 mg per kg per day (approximately 35 times the human plasma exposure at 80 mg per day) had no effect on fertility and reproductive performance of male and female rats.

13.2 Animal Toxicology

A 12-month toxicity study in beagle dogs showed deposition of xanthine crystals and calculi in kidneys at 15 mg per kg (approximately 4 times the human plasma exposure at 80 mg per day). A similar effect of calculus formation was noted in rats in a six-month study due to deposition of xanthine crystals at 48 mg per kg (approximately 35 times the human plasma exposure at 80 mg per day).

14 CLINICAL STUDIES

A serum uric acid level of less than 6 mg per dL is the goal of anti-hyperuricemic therapy and has been established as appropriate for the treatment of gout.

14.1 Management of Hyperuricemia in Gout

The efficacy of ULORIC was demonstrated in three randomized, double-blind, controlled trials in patients with hyperuricemia and gout. Hyperuricemia was defined as a baseline serum uric acid level ≥ 8 mg per dL.

Study 1 randomized patients to: ULORIC 40 mg daily, ULORIC 80 mg daily, or allopurinol (300 mg daily for patients with estimated creatinine clearance (Cl_{cr}) ≥ 60 mL per min or 200 mg daily for patients with estimated $Cl_{cr} \geq 30$ mL per min and ≤ 59 mL per min). The duration of Study 1 was 6 months.

Study 2 randomized patients to: placebo, ULORIC 80 mg daily, ULORIC 120 mg daily, ULORIC 240 mg daily or allopurinol (300 mg daily for patients with a baseline serum creatinine ≤ 1.5 mg per dL or 100 mg daily for patients with a baseline serum creatinine greater than 1.5 mg per dL and ≤ 2 mg per dL). The duration of Study 2 was 6 months.

Study 3, a 1-year study, randomized patients to: ULORIC 80 mg daily, ULORIC 120 mg daily, or allopurinol 300 mg daily. Subjects who completed Study 2 and Study 3 were eligible to enroll in a phase 3 long-term extension study in which subjects received treatment with ULORIC for over three years.

In all three studies, subjects received naproxen 250 mg twice daily or colchicine 0.6 mg once or twice daily for gout flare prophylaxis. In Study 1 the duration of prophylaxis was 6 months; in Study 2 and Study 3 the duration of prophylaxis was 8 weeks.

The efficacy of ULORIC was also evaluated in a 4 week dose ranging study which randomized patients to: placebo, ULORIC 40 mg daily, ULORIC 80 mg daily, or ULORIC 120 mg daily. Subjects who completed this study were eligible to enroll in a long-term extension study in which subjects received treatment with ULORIC for up to five years.

Patients in these studies were representative of the patient population for which ULORIC use is intended. Table 2 summarizes the demographics and baseline characteristics for the subjects enrolled in the studies.

Table 2: Patient Demographics and Baseline Characteristics in Study 1, Study 2 and Study 3

Male	95%
Race: Caucasian African American	80%
	10%
Ethnicity: Hispanic or Latino	7%
Alcohol User	67%

Mild to Moderate Renal Insufficiency [percent with estimated Cl _{cr} less than 90 mL per min]	59%
History of Hypertension	49%
History of Hyperlipidemia	38%
BMI ≥ 30 kg per m ²	63%
Mean BMI	33 kg per m ²
Baseline sUA ≥ 10 mg per dL	36%
Mean baseline sUA	9.7 mg per dL
Experienced a gout flare in previous year	85%

Serum Uric Acid Level less than 6 mg per dL at Final Visit: ULORIC 80 mg was superior to allopurinol in lowering serum uric acid to less than 6 mg per dL at the final visit. ULORIC 40 mg daily, although not superior to allopurinol, was effective in lowering serum uric acid to less than 6 mg per dL at the final visit (Table 3).

Table 3: Proportion of Patients with Serum Uric Acid Levels Less Than 6 mg per dL at Final Visit

Study*	ULORIC 40 mg daily	ULORIC 80 mg daily	allopurinol	Placebo	Difference in Proportion (95% CI)	
					ULORIC 40 mg vs allopurinol	ULORIC 80 mg vs allopurinol
Study 1 (6 months) (N=2268)	45%	67%	42%		3% (-2%, 8%)	25% (20%, 30%)
Study 2 (6 months) (N=643)		72%	39%	1%		33% (26%, 42%)
Study 3 (12 months) (N=491)		74%	36%			38% (30%, 46%)

*Randomization was balanced between treatment groups, except in Study 2 in which twice as many patients were randomized to each of the active treatment groups compared to placebo.

In 76% of ULORIC 80 mg patients, reduction in serum uric acid levels to less than 6 mg per dL was noted by the Week 2 visit. Average serum uric acid levels were maintained at 6 mg per dL or below throughout treatment in 83% of these patients.

In all treatment groups, fewer subjects with higher baseline serum urate levels (≥ 10 mg per dL) and/or tophi achieved the goal of lowering serum uric acid to less than 6 mg per dL at the final visit; however, a higher proportion achieved a serum uric acid less than 6 mg per dL with ULORIC 80 mg than with ULORIC 40 mg or allopurinol.

Study 1 evaluated efficacy in patients with mild to moderate renal impairment (i.e., baseline estimated Cl_{cr} less than 90 mL per minute). The results in this sub-group of patients are shown in Table 4.

Table 4: Proportion of Patients with Serum Uric Acid Levels Less Than 6 mg per dL in Patients with Mild or Moderate Renal Impairment at Final Visit				
ULORIC 40 mg daily (N=479)	ULORIC 80 mg daily (N=503)	allopurinol* 300 mg daily (N=501)	Difference in Proportion (95% CI)	
			ULORIC 40 mg vs allopurinol	ULORIC 80 mg vs allopurinol
50%	72%	42%	7% (1%, 14%)	29% (23%, 35%)

* Allopurinol patients (n=145) with estimated $\text{Cl}_{\text{cr}} \geq 30 \text{ mL per min}$ and $\text{Cl}_{\text{cr}} \leq 59 \text{ mL per min}$ were dosed at 200 mg daily.

16 HOW SUPPLIED/STORAGE AND HANDLING

ULORIC 40 mg tablets are light green to green in color, round shaped, debossed with "TAP" on one side and "40" on the other side and supplied as:

NDC Number	Size
64764-918-11	Hospital Unit Dose Pack of 100 Tablets
64764-918-30	Bottle of 30 Tablets
64764-918-90	Bottle of 90 Tablets
64764-918-18	Bottle of 500 Tablets

ULORIC 80 mg tablets are light green to green in color, teardrop shaped, debossed with "TAP" on one side and "80" on the other side and supplied as:

NDC Number	Size
64764-677-11	Hospital Unit Dose Pack of 100 Tablets
64764-677-30	Bottle of 30 Tablets
64764-677-13	Bottle of 100 Tablets
64764-677-19	Bottle of 1000 Tablets

Protect from light. Store at 25°C (77°F); excursions permitted to 15°– 30°C (59°– 86°F) [See USP Controlled Room Temperature]

17 PATIENT COUNSELING INFORMATION

[see *FDA-Approved Patient Labeling (17.2)*]

17.1 General Information

Patients should be advised of the potential benefits and risks of ULORIC. Patients should be informed about the potential for gout flares, elevated liver enzymes and adverse cardiovascular events after initiation of ULORIC therapy.

Concomitant prophylaxis with an NSAID or colchicine for gout flares should be considered.

Patients should be instructed to inform their healthcare professional if they develop a rash, chest pain, shortness of breath or neurologic symptoms suggesting a stroke. Patients should be instructed to inform their healthcare professional of any other medications they are currently taking with ULORIC, including over-the-counter medications.

17.2 FDA-Approved Patient Labeling

Patient Information
ULORIC® (ü - 'lor - ik)
(febuxostat) tablets

Read the Patient Information that comes with ULORIC before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is ULORIC?

ULORIC is a prescription medicine called a xanthine oxidase (XO) inhibitor, used to lower blood uric acid levels in adults with gout.

It is not known if ULORIC is safe and effective in children under 18 years of age.

Who should not take ULORIC?

Do not take ULORIC if you:

- take Azathioprine (Azasan®, Imuran®)
- take Mercaptopurine (Purinethol®)
- take Theophylline (Theo-24®, Elixophyllin®, Theochron®, Theolair®, Uniphyll®)

It is not known if ULORIC is safe and effective in children under 18 years of age.

What should I tell my healthcare provider before taking ULORIC?

Before taking ULORIC tell your healthcare provider about all of your medical conditions, including if you:

- have liver or kidney problems
- have a history of heart disease or stroke
- are pregnant or plan to become pregnant. It is not known if ULORIC will harm your unborn baby. Talk with your healthcare provider if you are pregnant or plan to become pregnant.
- are breast-feeding or plan to breast-feed. It is not known if ULORIC passes into your breast milk. You and your healthcare provider should decide if you should take ULORIC while breast-feeding.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. ULORIC may affect the way other medicines work, and other medicines may affect how ULORIC works.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take ULORIC?

- Take ULORIC exactly as your healthcare provider tells you to take it.
- ULORIC can be taken with or without food.
- ULORIC can be taken with antacids.
- Your gout may flare up when you start taking ULORIC, do not stop taking your ULORIC even if you have a flare. Your healthcare provider may give you other medicines to help prevent your gout flares.
- Your healthcare provider may do certain tests while you take ULORIC.

What are the possible side effects of ULORIC?

Heart problems. A small number of heart attacks, strokes and heart-related deaths were seen in clinical studies. It is not certain that ULORIC caused these events.

The most common side effects of ULORIC include:

- liver problems
- nausea
- gout flares
- joint pain
- rash

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of ULORIC. For more information, ask your healthcare provider or pharmacist.

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

How should I store ULORIC?

Store ULORIC between 59°F - 86°F (15°C - 30°C).

Keep ULORIC out of the light.

Keep ULORIC and all medicines out of the reach of children.

General information about the safe and effective use of ULORIC.

Medicines are sometimes prescribed for purposes other than those listed in a patient information leaflet. Do not use ULORIC for a condition for which it was not prescribed. Do not give ULORIC to other people, even if they have the same symptoms that you have. It may harm them.

This patient information leaflet summarizes the most important information about ULORIC. If you would like more information about ULORIC talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ULORIC that is written for health professionals. For more information go to www.uloric.com, or call 1-877-825-3327.

What are the ingredients in ULORIC?

Active Ingredient: febuxostat

Inactive ingredients include: lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, sodium croscarmellose, silicon dioxide, magnesium stearate, and Opadry II, green

Distributed by

Takeda Pharmaceuticals America, Inc.

Deerfield, IL 60015

U.S. Patent Nos. - 6,225,474; 7,361,676; 5,614,520.

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PI1114 R1

February 2009

EXHIBIT E

HIGHLIGHTS OF PRESCRIBING INFORMATION

These HIGHLIGHTS do not include all the information needed to use ULORIC safely and effectively. See full prescribing information for ULORIC.

ULORIC (febuxostat) tablet for oral use

Initial U.S. Approval: 2009

INDICATIONS AND USAGE

ULORIC is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in patients with gout. (1)

ULORIC is not recommended for the treatment of asymptomatic hyperuricemia. (1)

DOSAGE AND ADMINISTRATION

- ULORIC is recommended at 40 mg or 80 mg once daily. The recommended starting dose of ULORIC is 40 mg once daily. For patients who do not achieve a serum uric acid (sUA) less than 6 mg per dL after 2 weeks with 40 mg, ULORIC 80 mg is recommended. (2.1)
- ULORIC can be administered without regard to food or antacid use. (2.1)
- No dose adjustment is necessary when administering ULORIC to patients with mild to moderate renal or hepatic impairment. (2.2)

DOSAGE FORMS AND STRENGTHS

Tablet: 40 mg, 80 mg. (3)

CONTRAINDICATIONS

ULORIC is contraindicated in patients being treated with azathioprine or mercaptopurine. (4)

WARNINGS AND PRECAUTIONS

- **Gout Flare:** An increase in gout flares is frequently observed during initiation of anti-hyperuricemic agents, including ULORIC. If a gout flare occurs during treatment, ULORIC need not be discontinued. Prophylactic therapy (i.e., non-steroidal anti-inflammatory drug

(NSAID) or colchicine upon initiation of treatment) may be beneficial for up to six months. (2.4, 5.1)

- **Cardiovascular Events:** A higher rate of cardiovascular thromboembolic events was observed in patients treated with ULORIC than allopurinol in clinical trials. Monitor for signs and symptoms of MI and stroke. (5.2)
- **Liver Enzyme Elevation:** Transaminase elevations have been observed in ULORIC-treated patients. Monitor liver function tests periodically. (5.3)

ADVERSE REACTIONS

Adverse reactions occurring in at least 1% of ULORIC-treated patients, and, at least 0.5% greater than placebo, are liver function abnormalities, nausea, arthralgia, and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-877-TAKEDA-7 (1-877-825-3327) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Concomitant administration of ULORIC with XO substrate drugs, azathioprine or mercaptopurine could increase plasma concentrations of these drugs resulting in severe toxicity. (7)

USE IN SPECIFIC POPULATIONS

- There is insufficient data in patients with severe renal impairment. No studies have been conducted in patients with severe hepatic impairment. Caution should be exercised in these patients. (8.6, 8.7)
- No studies have been conducted in patients with secondary hyperuricemia (including patients being treated for Lesch-Nyhan syndrome or malignant disease, or in organ transplant recipients); therefore, ULORIC is not recommended for use in these patients. (8.8)

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

Revised: January 2011

FULL PRESCRIBING INFORMATION: CONTENTS*

- 1 INDICATIONS AND USAGE**
- 2 DOSAGE AND ADMINISTRATION**
 - 2.1 Recommended Dose
 - 2.2 Special Populations
 - 2.3 Uric Acid Level
 - 2.4 Gout Flares
- 3 DOSAGE FORMS AND STRENGTHS**
- 4 CONTRAINDICATIONS**
- 5 WARNINGS AND PRECAUTIONS**
 - 5.1 Gout Flare
 - 5.2 Cardiovascular Events
 - 5.3 Liver Enzyme Elevations
- 6 ADVERSE REACTIONS**
 - 6.1 Clinical Trials Experience
 - 6.2 Postmarketing Experience
- 7 DRUG INTERACTIONS**
 - 7.1 Xanthine Oxidase Substrate Drugs
 - 7.2 Cytotoxic Chemotherapy Drugs
 - 7.3 *In Vivo* Drug Interaction Studies
- 8 USE IN SPECIFIC POPULATIONS**
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers

- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment
- 8.8 Secondary Hyperuricemia

10 OVERDOSAGE**11 DESCRIPTION****12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology

14 CLINICAL STUDIES

- 14.1 Management of Hyperuricemia in Gout

16 HOW SUPPLIED/STORAGE AND HANDLING**17 PATIENT COUNSELING INFORMATION**

- 17.1 General Information

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ULORIC is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in patients with gout.

ULORIC is not recommended for the treatment of asymptomatic hyperuricemia.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

For treatment of hyperuricemia in patients with gout, ULORIC is recommended at 40 mg or 80 mg once daily.

The recommended starting dose of ULORIC is 40 mg once daily. For patients who do not achieve a serum uric acid (sUA) less than 6 mg per dL after 2 weeks with 40 mg, ULORIC 80 mg is recommended.

ULORIC can be taken without regard to food or antacid use [see *Clinical Pharmacology (12.3)*].

2.2 Special Populations

No dose adjustment is necessary when administering ULORIC in patients with mild to moderate renal impairment [see *Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)*]. The recommended starting dose of ULORIC is 40 mg once daily. For patients who do not achieve a SUA less than 6 mg per dL after 2 weeks with 40 mg, ULORIC 80 mg is recommended.

No dose adjustment is necessary in patients with mild to moderate hepatic impairment [see *Use in Specific Populations (8.7)* and *Clinical Pharmacology (12.3)*].

2.3 Uric Acid Level

Testing for the target serum uric acid level of less than 6 mg per dL may be performed as early as 2 weeks after initiating ULORIC therapy.

2.4 Gout Flares

Gout flares may occur after initiation of ULORIC due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. Flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended upon initiation of ULORIC. Prophylactic therapy may be beneficial for up to six months [see *Clinical Studies (14.1)*].

If a gout flare occurs during ULORIC treatment, ULORIC need not be discontinued. The gout flare should be managed concurrently, as appropriate for the individual patient [see *Warnings and Precautions (5.1)*].

3 DOSAGE FORMS AND STRENGTHS

- 40 mg tablets, light green to green, round shaped, debossed with “TAP” and “40”
- 80 mg tablets, light green to green, teardrop shaped, debossed with “TAP” and “80”

4 CONTRAINDICATIONS

ULORIC is contraindicated in patients being treated with azathioprine or mercaptopurine [see *Drug Interactions (7)*].

5 WARNINGS AND PRECAUTIONS

5.1 Gout Flare

After initiation of ULORIC, an increase in gout flares is frequently observed. This increase is due to reduction in serum uric acid levels resulting in mobilization of urate from tissue deposits.

In order to prevent gout flares when ULORIC is initiated, concurrent prophylactic treatment with an NSAID or colchicine is recommended [see *Dosage and Administration* (2.4)].

5.2 Cardiovascular Events

In the randomized controlled studies, there was a higher rate of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) in patients treated with ULORIC [0.74 per 100 P-Y (95% Confidence Interval (CI) 0.36-1.37)] than allopurinol [0.60 per 100 P-Y (95% CI 0.16-1.53)] [see *Adverse Reactions* (6.1)]. A causal relationship with ULORIC has not been established. Monitor for signs and symptoms of myocardial infarction (MI) and stroke.

5.3 Liver Enzyme Elevations

During randomized controlled studies, transaminase elevations greater than 3 times the upper limit of normal (ULN) were observed (AST: 2%, 2%, and ALT: 3%, 2% in ULORIC and allopurinol-treated patients, respectively). No dose-effect relationship for these transaminase elevations was noted. Laboratory assessment of liver function is recommended at, for example, 2 and 4 months following initiation of ULORIC and periodically thereafter.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

A total of 2757 subjects with hyperuricemia and gout were treated with ULORIC 40 mg or 80 mg daily in clinical studies. For ULORIC 40 mg, 559 patients were treated for \geq 6 months. For ULORIC 80 mg, 1377 subjects were treated for \geq 6 months, 674 patients were treated for \geq 1 year and 515 patients were treated for \geq 2 years.

Most Common Adverse Reactions

In three randomized, controlled clinical studies (Studies 1, 2 and 3), which were 6 to 12 months in duration, the following adverse reactions were reported by the treating physician as related to study drug. Table 1 summarizes adverse reactions reported at a rate of at least 1% in ULORIC treatment groups and at least 0.5% greater than placebo.

Table 1: Adverse Reactions Occurring in ≥ 1% of ULORIC-Treated Patients and at Least 0.5% Greater than Seen in Patients Receiving Placebo in Controlled Studies

Adverse Reactions	Placebo	ULORIC		allopurinol*
	(N=134)	40 mg daily (N=757)	80 mg daily (N=1279)	(N=1277)
Liver Function Abnormalities	0.7%	6.6%	4.6%	4.2%
Nausea	0.7%	1.1%	1.3%	0.8%
Arthralgia	0%	1.1%	0.7%	0.7%
Rash	0.7%	0.5%	1.6%	1.6%

* Of the subjects who received allopurinol, 10 received 100 mg, 145 received 200 mg, and 1122 received 300 mg, based on level of renal impairment.

The most common adverse reaction leading to discontinuation from therapy was liver function abnormalities in 1.8% of ULORIC 40 mg, 1.2% of ULORIC 80 mg, and in 0.9% of allopurinol-treated subjects.

In addition to the adverse reactions presented in Table 1, dizziness was reported in more than 1% of ULORIC-treated subjects although not at a rate more than 0.5% greater than placebo.

Less Common Adverse Reactions

In Phase 2 and 3 clinical studies the following adverse reactions occurred in less than 1% of subjects and in more than one subject treated with doses ranging from 40 mg to 240 mg of ULORIC. This list also includes adverse reactions (less than 1% of subjects) associated with organ systems from Warnings and Precautions.

Blood and Lymphatic System Disorders: anemia, idiopathic thrombocytopenic purpura, leukocytosis/leukopenia, neutropenia, pancytopenia, splenomegaly, thrombocytopenia.

Cardiac Disorders: angina pectoris, atrial fibrillation/flutter, cardiac murmur, ECG abnormal, palpitations, sinus bradycardia, tachycardia.

Ear and Labyrinth Disorders: deafness, tinnitus, vertigo.

Eye Disorders: vision blurred.

Gastrointestinal Disorders: abdominal distention, abdominal pain, constipation, dry mouth, dyspepsia, flatulence, frequent stools, gastritis, gastroesophageal reflux disease, gastrointestinal discomfort, gingival pain, haematemesis, hyperchlorhydria, hematochezia, mouth ulceration, pancreatitis, peptic ulcer, vomiting.

General Disorders and Administration Site Conditions: asthenia, chest pain/discomfort, edema, fatigue, feeling abnormal, gait disturbance, influenza-like symptoms, mass, pain, thirst.

Hepatobiliary Disorders: cholelithiasis/cholecystitis, hepatic steatosis, hepatitis, hepatomegaly.

Immune System Disorder: hypersensitivity.

Infections and Infestations: herpes zoster.

Procedural Complications: contusion.

Metabolism and Nutrition Disorders: anorexia, appetite decreased/increased, dehydration, diabetes mellitus, hypercholesterolemia, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypokalemia, weight decreased/increased.

Musculoskeletal and Connective Tissue Disorders: arthritis, joint stiffness, joint swelling, muscle spasms/twitching/tightness/weakness, musculoskeletal pain/stiffness, myalgia.

Nervous System Disorders: altered taste, balance disorder, cerebrovascular accident, Guillain-Barré syndrome, headache, hemiparesis, hypoesthesia, hyposmia, lacunar infarction, lethargy, mental impairment, migraine, paresthesia, somnolence, transient ischemic attack, tremor.

Psychiatric Disorders: agitation, anxiety, depression, insomnia, irritability, libido decreased, nervousness, panic attack, personality change.

Renal and Urinary Disorders: hematuria, nephrolithiasis, pollakiuria, proteinuria, renal failure, renal insufficiency, urgency, incontinence.

Reproductive System and Breast Changes: breast pain, erectile dysfunction, gynecomastia.

Respiratory, Thoracic and Mediastinal Disorders: bronchitis, cough, dyspnea, epistaxis, nasal dryness, paranasal sinus hypersecretion, pharyngeal edema, respiratory tract congestion, sneezing, throat irritation, upper respiratory tract infection.

Skin and Subcutaneous Tissue Disorders: alopecia, angio-edema, dermatitis, dermographism, ecchymosis, eczema, hair color changes, hair growth abnormal, hyperhidrosis, peeling skin, petechiae, photosensitivity, pruritus, purpura, skin discoloration/alteration in pigmentation, skin lesion, skin odor abnormal, urticaria.

Vascular Disorders: flushing, hot flush, hypertension, hypotension.

Laboratory Parameters: activated partial thromboplastin time prolonged, creatine increased, bicarbonate decreased, sodium increased, EEG abnormal, glucose increased, cholesterol increased, triglycerides increased, amylase increased, potassium increased, TSH increased, platelet count decreased, hematocrit decreased, hemoglobin decreased, MCV increased, RBC decreased, creatinine increased, blood urea increased, BUN/creatinine ratio increased, creatine phosphokinase (CPK) increased, alkaline phosphatase increased, LDH increased, PSA increased, urine output increased/decreased, lymphocyte count decreased, neutrophil count decreased, WBC increased/decreased, coagulation test abnormal, low density lipoprotein (LDL) increased, prothrombin time prolonged, urinary casts, urine positive for white blood cells and protein.

Cardiovascular Safety

Cardiovascular events and deaths were adjudicated to one of the pre-defined endpoints from the Anti-Platelet Trialists' Collaborations (APTC) (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) in the randomized controlled and long-term extension studies. In the Phase 3 randomized controlled studies, the incidences of adjudicated APTC events per 100 patient-years of exposure were: Placebo 0 (95% CI 0.00-6.16), ULORIC 40 mg 0 (95% CI 0.00-1.08), ULORIC 80 mg 1.09 (95% CI 0.44-2.24), and allopurinol 0.60 (95% CI 0.16-1.53).

In the long-term extension studies, the incidences of adjudicated APTC events were: ULORIC 80 mg 0.97 (95% CI 0.57-1.56), and allopurinol 0.58 (95% CI 0.02-3.24).

Overall, a higher rate of APTC events was observed in ULORIC than in allopurinol-treated patients. A causal relationship with ULORIC has not been established. Monitor for signs and symptoms of MI and stroke.

6.2 Postmarketing Experience

Adverse reactions have been identified during post approval use of ULORIC. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship.

Immune System Disorders: anaphylaxis, anaphylactic reaction.

Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis.

Psychiatric Disorders: psychotic behavior including aggressive thoughts.

Renal and Urinary Disorders: tubulointerstitial nephritis.

Skin and Subcutaneous Tissue Disorders: generalized rash, Stevens Johnson Syndrome, hypersensitivity skin reactions.

7 DRUG INTERACTIONS

7.1 Xanthine Oxidase Substrate Drugs

ULORIC is an XO inhibitor. Based on a drug interaction study in healthy subjects, febuxostat altered the metabolism of theophylline (a substrate of XO) in humans [see *Clinical Pharmacology (12.3)*]. Therefore, use with caution when co-administering ULORIC with theophylline.

Drug interaction studies of ULORIC with other drugs that are metabolized by XO (e.g., mercaptopurine and azathioprine) have not been conducted. Inhibition of XO by ULORIC may cause increased plasma concentrations of these drugs leading to toxicity [see *Clinical Pharmacology (12.3)*]. ULORIC is contraindicated in patients being treated with azathioprine or mercaptopurine [see *Contraindications (4)*].

7.2 Cytotoxic Chemotherapy Drugs

Drug interaction studies of ULORIC with cytotoxic chemotherapy have not been conducted. No data are available regarding the safety of ULORIC during cytotoxic chemotherapy.

7.3 *In Vivo* Drug Interaction Studies

Based on drug interaction studies in healthy subjects, ULORIC does not have clinically significant interactions with colchicine, naproxen, indomethacin, hydrochlorothiazide, warfarin or desipramine [see *Clinical Pharmacology (12.3)*]. Therefore, ULORIC may be used concomitantly with these medications.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. ULORIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Febuxostat was not teratogenic in rats and rabbits at oral doses up to 48 mg per kg (40 and 51 times the human plasma exposure at 80 mg per day for equal body surface area, respectively) during organogenesis. However, increased neonatal mortality and a reduction in the neonatal body weight gain were observed when pregnant rats were treated with oral doses up to 48 mg per kg (40 times the human plasma exposure at 80 mg per day) during organogenesis and through lactation period.

8.3 Nursing Mothers

Febuxostat is excreted in the milk of rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ULORIC is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients under 18 years of age have not been established.

8.5 Geriatric Use

No dose adjustment is necessary in elderly patients. Of the total number of subjects in clinical studies of ULORIC, 16 percent were 65 and over, while 4 percent were 75 and over. Comparing subjects in different age groups, no clinically significant differences in safety or effectiveness were observed but greater sensitivity of some older individuals cannot be ruled out. The C_{max} and AUC_{24} of febuxostat following multiple oral doses of ULORIC in geriatric subjects (≥ 65 years) were similar to those in younger subjects (18-40 years) [see *Clinical Pharmacology* (12.3)].

8.6 Renal Impairment

No dose adjustment is necessary in patients with mild or moderate renal impairment (Cl_{cr} 30-89 mL per min). The recommended starting dose of ULORIC is 40 mg once daily. For patients who do not achieve a sUA less than 6 mg per dL after 2 weeks with 40 mg, ULORIC 80 mg is recommended.

There are insufficient data in patients with severe renal impairment (Cl_{cr} less than 30 mL per min); therefore, caution should be exercised in these patients [see *Clinical Pharmacology* (12.3)].

8.7 Hepatic Impairment

No dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh Class A or B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C); therefore, caution should be exercised in these patients [see *Clinical Pharmacology* (12.3)].

8.8 Secondary Hyperuricemia

No studies have been conducted in patients with secondary hyperuricemia (including organ transplant recipients); ULORIC is not recommended for use in patients whom the rate of urate formation is greatly increased (e.g., malignant disease and its treatment, Lesch-Nyhan syndrome). The concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract.

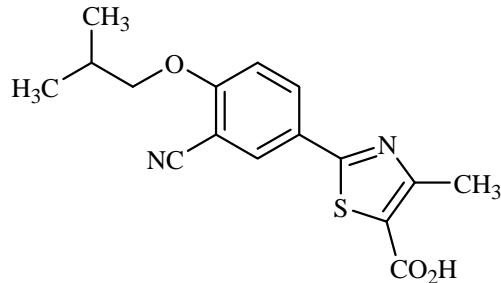
10 OVERDOSAGE

ULORIC was studied in healthy subjects in doses up to 300 mg daily for seven days without evidence of dose-limiting toxicities. No overdose of ULORIC was reported in clinical studies. Patients should be managed by symptomatic and supportive care should there be an overdose.

11 DESCRIPTION

ULORIC (febuxostat) is a xanthine oxidase inhibitor. The active ingredient in ULORIC is 2-[3-cyano-4-(2-methylpropoxy) phenyl]-4-methylthiazole-5-carboxylic acid, with a molecular weight of 316.38. The empirical formula is $C_{16}H_{16}N_2O_3S$.

The chemical structure is:



Febuxostat is a non-hygroscopic, white crystalline powder that is freely soluble in dimethylformamide; soluble in dimethylsulfoxide; sparingly soluble in ethanol; slightly soluble in methanol and acetonitrile; and practically insoluble in water. The melting range is 205°C to 208°C.

ULORIC tablets for oral use contain the active ingredient, febuxostat, and are available in two dosage strengths, 40 mg and 80 mg. Inactive ingredients include lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, sodium croscarmellose, silicon dioxide and magnesium stearate. ULORIC tablets are coated with Opadry II, green.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ULORIC, a xanthine oxidase inhibitor, achieves its therapeutic effect by decreasing serum uric acid. ULORIC is not expected to inhibit other enzymes involved in purine and pyrimidine synthesis and metabolism at therapeutic concentrations.

12.2 Pharmacodynamics

Effect on Uric Acid and Xanthine Concentrations: In healthy subjects, ULORIC resulted in a dose dependent decrease in 24-hour mean serum uric acid concentrations, and an increase in 24-hour mean serum xanthine concentrations. In addition, there was a decrease in the total daily urinary uric acid excretion. Also, there was an increase in total daily urinary xanthine excretion. Percent reduction in 24-hour mean serum uric acid concentrations was between 40% to 55% at the exposure levels of 40 mg and 80 mg daily doses.

Effect on Cardiac Repolarization: The effect of ULORIC on cardiac repolarization as assessed by the QTc interval was evaluated in normal healthy subjects and in patients with gout. ULORIC in doses up to 300 mg daily, at steady state, did not demonstrate an effect on the QTc interval.

12.3 Pharmacokinetics

In healthy subjects, maximum plasma concentrations (C_{max}) and AUC of febuxostat increased in a dose proportional manner following single and multiple doses of 10 mg to 120 mg. There is no accumulation when therapeutic doses are administered every 24 hours. Febuxostat has an apparent mean terminal elimination half-life ($t_{1/2}$) of approximately 5 to 8 hours. Febuxostat pharmacokinetic parameters for patients with hyperuricemia and gout estimated by population pharmacokinetic analyses were similar to those estimated in healthy subjects.

Absorption: The absorption of radiolabeled febuxostat following oral dose administration was estimated to be at least 49% (based on total radioactivity recovered in urine). Maximum plasma concentrations of febuxostat occurred between 1 to 1.5 hours post-dose. After multiple oral 40 mg and 80 mg once daily doses, C_{max} is approximately 1.6 ± 0.6 mcg per mL (N=30), and 2.6 ± 1.7 mcg per mL (N=227), respectively. Absolute bioavailability of the febuxostat tablet has not been studied.

Following multiple 80 mg once daily doses with a high fat meal, there was a 49% decrease in C_{max} and an 18% decrease in AUC, respectively. However, no clinically significant change in the percent decrease in serum uric acid concentration was observed (58% fed vs. 51% fasting). Thus, ULORIC may be taken without regard to food.

Concomitant ingestion of an antacid containing magnesium hydroxide and aluminum hydroxide with an 80 mg single dose of ULORIC has been shown to delay absorption of febuxostat (approximately 1 hour) and to cause a 31% decrease in C_{max} and a 15% decrease in AUC_∞. As AUC rather than C_{max} was related to drug effect, change observed in AUC was not considered clinically significant. Therefore, ULORIC may be taken without regard to antacid use.

Distribution: The mean apparent steady state volume of distribution (V_{ss}/F) of febuxostat was approximately 50 L (CV ~40%). The plasma protein binding of febuxostat is approximately 99.2%, (primarily to albumin), and is constant over the concentration range achieved with 40 mg and 80 mg doses.

Metabolism: Febuxostat is extensively metabolized by both conjugation via uridine diphosphate glucuronosyltransferase (UGT) enzymes including UGT1A1, UGT1A3, UGT1A9, and UGT2B7 and oxidation via cytochrome P450 (CYP) enzymes including CYP1A2, 2C8 and 2C9 and non-P450 enzymes. The relative contribution of each enzyme isoform in the metabolism of febuxostat is not clear. The oxidation of the isobutyl side chain leads to the formation of four pharmacologically active hydroxy metabolites, all of which occur in plasma of humans at a much lower extent than febuxostat.

In urine and feces, acyl glucuronide metabolites of febuxostat (~35% of the dose), and oxidative metabolites, 67M-1 (~10% of the dose), 67M-2 (~11% of the dose), and 67M-4, a secondary metabolite from 67M-1, (~14% of the dose) appeared to be the major metabolites of febuxostat *in vivo*.

Elimination: Febuxostat is eliminated by both hepatic and renal pathways. Following an 80 mg oral dose of ¹⁴C-labeled febuxostat, approximately 49% of the dose was recovered in the urine as unchanged febuxostat (3%), the acyl glucuronide of the drug (30%), its known oxidative metabolites and their conjugates (13%), and other unknown metabolites (3%). In addition to the urinary excretion, approximately 45% of the dose was recovered in the feces as the unchanged febuxostat (12%), the acyl glucuronide of the drug (1%), its known oxidative metabolites and their conjugates (25%), and other unknown metabolites (7%).

The apparent mean terminal elimination half-life ($t_{1/2}$) of febuxostat was approximately 5 to 8 hours.

Special Populations

Pediatric Use: The pharmacokinetics of ULORIC in patients under the age of 18 years have not been studied.

Geriatric Use: The C_{max} and AUC of febuxostat and its metabolites following multiple oral doses of ULORIC in geriatric subjects (\geq 65 years) were similar to those in younger subjects (18-40 years). In addition, the percent decrease in serum uric acid concentration was similar between elderly and younger subjects. No dose adjustment is necessary in geriatric patients [see *Use in Specific Populations (8.5)*].

Renal Impairment: Following multiple 80 mg doses of ULORIC in healthy subjects with mild (Cl_{cr} 50-80 mL per min), moderate (Cl_{cr} 30-49 mL per min) or severe renal impairment (Cl_{cr} 10-29 mL per min), the C_{max} of febuxostat did not change relative to subjects with normal renal function (Cl_{cr} greater than 80 mL per min). AUC and half-life of febuxostat increased in subjects with renal impairment in comparison to subjects with normal renal function, but values were similar among

three renal impairment groups. Mean febuxostat AUC values were up to 1.8 times higher in subjects with renal impairment compared to those with normal renal function. Mean C_{max} and AUC values for 3 active metabolites increased up to 2- and 4-fold, respectively. However, the percent decrease in serum uric acid concentration for subjects with renal impairment was comparable to those with normal renal function (58% in normal renal function group and 55% in the severe renal function group).

No dose adjustment is necessary in patients with mild to moderate renal impairment [see *Dosage and Administration (2) and Use in Specific Populations (8.6)*]. The recommended starting dose of ULORIC is 40 mg once daily. For patients who do not achieve a sUA less than 6 mg per dL after 2 weeks with 40 mg, ULORIC 80 mg is recommended. There is insufficient data in patients with severe renal impairment; caution should be exercised in those patients [see *Use in Specific Populations (8.6)*].

ULORIC has not been studied in end stage renal impairment patients who are on dialysis.

Hepatic Impairment: Following multiple 80 mg doses of ULORIC in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, an average of 20-30% increase was observed for both C_{max} and AUC_{24} (total and unbound) in hepatic impairment groups compared to subjects with normal hepatic function. In addition, the percent decrease in serum uric acid concentration was comparable between different hepatic groups (62% in healthy group, 49% in mild hepatic impairment group, and 48% in moderate hepatic impairment group). No dose adjustment is necessary in patients with mild or moderate hepatic impairment. No studies have been conducted in subjects with severe hepatic impairment (Child-Pugh Class C); caution should be exercised in those patients [see *Use in Specific Populations (8.7)*].

Gender: Following multiple oral doses of ULORIC, the C_{max} and AUC_{24} of febuxostat were 30% and 14% higher in females than in males, respectively. However, weight-corrected C_{max} and AUC were similar between the genders. In addition, the percent decrease in serum uric acid concentrations was similar between genders. No dose adjustment is necessary based on gender.

Race: No specific pharmacokinetic study was conducted to investigate the effects of race.

Drug-Drug Interactions

Effect of ULORIC on Other Drugs

Xanthine Oxidase Substrate Drugs-Azathioprine, Mercaptopurine, and Theophylline: Febuxostat is an XO inhibitor. A drug-drug interaction study evaluating the effect of ULORIC upon the pharmacokinetics of theophylline (an XO substrate) in healthy subjects showed that co-administration of febuxostat with theophylline resulted in an approximately 400-fold increase in the amount of 1-methylxanthine, one of the major metabolites of theophylline, excreted in the urine. Since the long-term safety of exposure to 1-methylxanthine in humans is unknown, use with caution when co-administering febuxostat with theophylline.

Drug interaction studies of ULORIC with other drugs that are metabolized by XO (e.g., mercaptopurine and azathioprine) have not been conducted. Inhibition of XO by ULORIC may cause increased plasma concentrations of these drugs leading to toxicity. ULORIC is contraindicated in patients being treated with azathioprine or mercaptopurine [see *Contraindications (4) and Drug Interactions (7)*].

Azathioprine and mercaptopurine undergo metabolism via three major metabolic pathways, one of which is mediated by XO. Although ULORIC drug interaction studies with azathioprine and mercaptopurine have not been conducted, concomitant administration of allopurinol [a xanthine oxidase inhibitor] with azathioprine or mercaptopurine has been reported to substantially increase

plasma concentrations of these drugs. Because ULORIC is a xanthine oxidase inhibitor, it could inhibit the XO-mediated metabolism of azathioprine and mercaptopurine leading to increased plasma concentrations of azathioprine or mercaptopurine that could result in severe toxicity.

P450 Substrate Drugs: *In vitro* studies have shown that febuxostat does not inhibit P450 enzymes CYP1A2, 2C9, 2C19, 2D6, or 3A4 and it also does not induce CYP1A2, 2B6, 2C9, 2C19, or 3A4 at clinically relevant concentrations. As such, pharmacokinetic interactions between ULORIC and drugs metabolized by these CYP enzymes are unlikely.

Effect of Other Drugs on ULORIC

Febuxostat is metabolized by conjugation and oxidation via multiple metabolizing enzymes. The relative contribution of each enzyme isoform is not clear. Drug interactions between ULORIC and a drug that inhibits or induces one particular enzyme isoform is in general not expected.

In Vivo Drug Interaction Studies

Theophylline: No dose adjustment is necessary for theophylline when co-administered with ULORIC. Administration of ULORIC (80 mg once daily) with theophylline resulted in an increase of 6% in C_{max} and 6.5% in AUC of theophylline. These changes were not considered statistically significant. However, the study also showed an approximately 400-fold increase in the amount of 1-methylxanthine (one of the major theophylline metabolites) excreted in urine as a result of XO inhibition by ULORIC. The safety of long-term exposure to 1-methylxanthine has not been evaluated. This should be taken into consideration when deciding to co-administer ULORIC and theophylline.

Colchicine: No dose adjustment is necessary for either ULORIC or colchicine when the two drugs are co-administered. Administration of ULORIC (40 mg once daily) with colchicine (0.6 mg twice daily) resulted in an increase of 12% in C_{max} and 7% in AUC_{24} of febuxostat. In addition, administration of colchicine (0.6 mg twice daily) with ULORIC (120 mg daily) resulted in less than 11% change in C_{max} or AUC of colchicine for both AM and PM doses. These changes were not considered clinically significant.

Naproxen: No dose adjustment is necessary for ULORIC or naproxen when the two drugs are co-administered. Administration of ULORIC (80 mg once daily) with naproxen (500 mg twice daily) resulted in a 28% increase in C_{max} and a 40% increase in AUC of febuxostat. The increases were not considered clinically significant. In addition, there were no significant changes in the C_{max} or AUC of naproxen (less than 2%).

Indomethacin: No dose adjustment is necessary for either ULORIC or indomethacin when these two drugs are co-administered. Administration of ULORIC (80 mg once daily) with indomethacin (50 mg twice daily) did not result in any significant changes in C_{max} or AUC of febuxostat or indomethacin (less than 7%).

Hydrochlorothiazide: No dose adjustment is necessary for ULORIC when co-administered with hydrochlorothiazide. Administration of ULORIC (80 mg) with hydrochlorothiazide (50 mg) did not result in any clinically significant changes in C_{max} or AUC of febuxostat (less than 4%), and serum uric acid concentrations were not substantially affected.

Warfarin: No dose adjustment is necessary for warfarin when co-administered with ULORIC. Administration of ULORIC (80 mg once daily) with warfarin had no effect on the pharmacokinetics of warfarin in healthy subjects. INR and Factor VII activity were also not affected by the co-administration of ULORIC.

Desipramine: Co-administration of drugs that are CYP2D6 substrates (such as desipramine) with ULORIC are not expected to require dose adjustment. Febuxostat was shown to be a weak inhibitor of CYP2D6 *in vitro* and *in vivo*. Administration of ULORIC (120 mg once daily) with desipramine (25 mg) resulted in an increase in C_{max} (16%) and AUC (22%) of desipramine, which was associated with a 17% decrease in the 2-hydroxydesipramine to desipramine metabolic ratio (based on AUC).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Two-year carcinogenicity studies were conducted in F344 rats and B6C3F1 mice. Increased transitional cell papilloma and carcinoma of urinary bladder was observed at 24 mg per kg (25 times the human plasma exposure at maximum recommended human dose of 80 mg per day) and 18.75 mg per kg (12.5 times the human plasma exposure at 80 mg per day) in male rats and female mice, respectively. The urinary bladder neoplasms were secondary to calculus formation in the kidney and urinary bladder.

Mutagenesis: Febuxostat showed a positive mutagenic response in a chromosomal aberration assay in a Chinese hamster lung fibroblast cell line with and without metabolic activation *in vitro*. Febuxostat was negative in the *in vitro* Ames assay and chromosomal aberration test in human peripheral lymphocytes, and L5178Y mouse lymphoma cell line, and *in vivo* tests in mouse micronucleus, rat unscheduled DNA synthesis and rat bone marrow cells.

Impairment of Fertility: Febuxostat at oral doses up to 48 mg per kg per day (approximately 35 times the human plasma exposure at 80 mg per day) had no effect on fertility and reproductive performance of male and female rats.

13.2 Animal Toxicology

A 12-month toxicity study in beagle dogs showed deposition of xanthine crystals and calculi in kidneys at 15 mg per kg (approximately 4 times the human plasma exposure at 80 mg per day). A similar effect of calculus formation was noted in rats in a six-month study due to deposition of xanthine crystals at 48 mg per kg (approximately 35 times the human plasma exposure at 80 mg per day).

14 CLINICAL STUDIES

A serum uric acid level of less than 6 mg per dL is the goal of anti-hyperuricemic therapy and has been established as appropriate for the treatment of gout.

14.1 Management of Hyperuricemia in Gout

The efficacy of ULORIC was demonstrated in three randomized, double-blind, controlled trials in patients with hyperuricemia and gout. Hyperuricemia was defined as a baseline serum uric acid level \geq 8 mg per dL.

Study 1 randomized patients to: ULORIC 40 mg daily, ULORIC 80 mg daily, or allopurinol (300 mg daily for patients with estimated creatinine clearance (Cl_{cr}) \geq 60 mL per min or 200 mg daily for patients with estimated Cl_{cr} \geq 30 mL per min and \leq 59 mL per min). The duration of Study 1 was 6 months.

Study 2 randomized patients to: placebo, ULORIC 80 mg daily, ULORIC 120 mg daily, ULORIC 240 mg daily or allopurinol (300 mg daily for patients with a baseline serum creatinine \leq 1.5 mg per

dL or 100 mg daily for patients with a baseline serum creatinine greater than 1.5 mg per dL and ≤ 2 mg per dL). The duration of Study 2 was 6 months.

Study 3, a 1-year study, randomized patients to: ULORIC 80 mg daily, ULORIC 120 mg daily, or allopurinol 300 mg daily. Subjects who completed Study 2 and Study 3 were eligible to enroll in a phase 3 long-term extension study in which subjects received treatment with ULORIC for over three years.

In all three studies, subjects received naproxen 250 mg twice daily or colchicine 0.6 mg once or twice daily for gout flare prophylaxis. In Study 1 the duration of prophylaxis was 6 months; in Study 2 and Study 3 the duration of prophylaxis was 8 weeks.

The efficacy of ULORIC was also evaluated in a 4 week dose ranging study which randomized patients to: placebo, ULORIC 40 mg daily, ULORIC 80 mg daily, or ULORIC 120 mg daily. Subjects who completed this study were eligible to enroll in a long-term extension study in which subjects received treatment with ULORIC for up to five years.

Patients in these studies were representative of the patient population for which ULORIC use is intended. Table 2 summarizes the demographics and baseline characteristics for the subjects enrolled in the studies.

Table 2: Patient Demographics and Baseline Characteristics in Study 1, Study 2 and Study 3

Male	95%
Race: Caucasian	80%
African American	10%
Ethnicity: Hispanic or Latino	7%
Alcohol User	67%
Mild to Moderate Renal Insufficiency [percent with estimated Cl _{cr} less than 90 mL per min]	59%
History of Hypertension	49%
History of Hyperlipidemia	38%
BMI ≥ 30 kg per m ²	63%
Mean BMI	33 kg per m ²
Baseline sUA ≥ 10 mg per dL	36%
Mean baseline sUA	9.7 mg per dL
Experienced a gout flare in previous year	85%

Serum Uric Acid Level less than 6 mg per dL at Final Visit: ULORIC 80 mg was superior to allopurinol in lowering serum uric acid to less than 6 mg per dL at the final visit. ULORIC 40 mg daily, although not superior to allopurinol, was effective in lowering serum uric acid to less than 6 mg per dL at the final visit (Table 3).

Table 3: Proportion of Patients with Serum Uric Acid Levels Less Than 6 mg per dL at Final Visit

	ULORIC	ULORIC			Difference in Proportion (95% CI)
					ULORIC

Study*	40 mg daily	80 mg daily	allopurinol	Placebo	40 mg vs allopurinol	80 mg vs allopurinol
Study 1 (6 months) (N=2268)	45%	67%	42%		3% (-2%, 8%)	25% (20%, 30%)
Study 2 (6 months) (N=643)		72%	39%	1%		33% (26%, 42%)
Study 3 (12 months) (N=491)		74%	36%			38% (30%, 46%)

*Randomization was balanced between treatment groups, except in Study 2 in which twice as many patients were randomized to each of the active treatment groups compared to placebo.

In 76% of ULORIC 80 mg patients, reduction in serum uric acid levels to less than 6 mg per dL was noted by the Week 2 visit. Average serum uric acid levels were maintained at 6 mg per dL or below throughout treatment in 83% of these patients.

In all treatment groups, fewer subjects with higher baseline serum urate levels (≥ 10 mg per dL) and/or tophi achieved the goal of lowering serum uric acid to less than 6 mg per dL at the final visit; however, a higher proportion achieved a serum uric acid less than 6 mg per dL with ULORIC 80 mg than with ULORIC 40 mg or allopurinol.

Study 1 evaluated efficacy in patients with mild to moderate renal impairment (i.e., baseline estimated Cl_{cr} less than 90 mL per minute). The results in this sub-group of patients are shown in Table 4.

Table 4: Proportion of Patients with Serum Uric Acid Levels Less Than 6 mg per dL in Patients with Mild or Moderate Renal Impairment at Final Visit				
ULORIC 40 mg daily (N=479)	ULORIC 80 mg daily (N=503)	allopurinol* 300 mg daily (N=501)	Difference in Proportion (95% CI)	
			ULORIC 40 mg vs allopurinol	ULORIC 80 mg vs allopurinol
50%	72%	42%	7% (1%, 14%)	29% (23%, 35%)

* Allopurinol patients (n=145) with estimated $\text{Cl}_{\text{cr}} \geq 30$ mL per min and $\text{Cl}_{\text{cr}} \leq 59$ mL per min were dosed at 200 mg daily.

16 HOW SUPPLIED/STORAGE AND HANDLING

ULORIC 40 mg tablets are light green to green in color, round shaped, debossed with "TAP" on one side and "40" on the other side and supplied as:

NDC Number Size

64764-918-11	Hospital Unit Dose Pack of 100 Tablets
64764-918-30	Bottle of 30 Tablets
64764-918-90	Bottle of 90 Tablets
64764-918-18	Bottle of 500 Tablets

ULORIC 80 mg tablets are light green to green in color, teardrop shaped, debossed with "TAP" on one side and "80" on the other side and supplied as:

NDC Number	Size
64764-677-11	Hospital Unit Dose Pack of 100 Tablets
64764-677-30	Bottle of 30 Tablets
64764-677-13	Bottle of 100 Tablets
64764-677-19	Bottle of 1000 Tablets

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

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information)

17.1 General Information

Patients should be advised of the potential benefits and risks of ULORIC. Patients should be informed about the potential for gout flares, elevated liver enzymes and adverse cardiovascular events after initiation of ULORIC therapy.

Concomitant prophylaxis with an NSAID or colchicine for gout flares should be considered.

Patients should be instructed to inform their healthcare professional if they develop a rash, chest pain, shortness of breath or neurologic symptoms suggesting a stroke. Patients should be instructed to inform their healthcare professional of any other medications they are currently taking with ULORIC, including over-the-counter medications.

Patient Information
ULORIC (Ü – 'Ior – ik)
(febuxostat) tablets

Read the Patient Information that comes with ULORIC before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is ULORIC?

ULORIC is a prescription medicine called a xanthine oxidase (XO) inhibitor, used to lower blood uric acid levels in adults with gout.

It is not known if ULORIC is safe and effective in children under 18 years of age.

Who should not take ULORIC?

Do not take ULORIC if you:

- take Azathioprine (Azasan[®], Imuran[®])
- take Mercaptopurine (Purinethol[®])

It is not known if ULORIC is safe and effective in children under 18 years of age.

What should I tell my healthcare provider before taking ULORIC?

Before taking ULORIC tell your healthcare provider about all of your medical conditions, including if you:

- have liver or kidney problems
- have a history of heart disease or stroke
- are pregnant or plan to become pregnant. It is not known if ULORIC will harm your unborn baby. Talk with your healthcare provider if you are pregnant or plan to become pregnant.
- are breast-feeding or plan to breast-feed. It is not known if ULORIC passes into your breast milk. You and your healthcare provider should decide if you should take ULORIC while breast-feeding.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. ULORIC may affect the way other medicines work, and other medicines may affect how ULORIC works.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take ULORIC?

- Take ULORIC exactly as your healthcare provider tells you to take it.
- ULORIC can be taken with or without food.
- ULORIC can be taken with antacids.
- Your gout may flare up when you start taking ULORIC, do not stop taking your ULORIC even if you have a flare. Your healthcare provider may give you other medicines to help prevent your gout flares.
- Your healthcare provider may do certain tests while you take ULORIC.

What are the possible side effects of ULORIC?

Heart problems. A small number of heart attacks, strokes and heart-related deaths were seen in clinical studies. It is not certain that ULORIC caused these events.

The most common side effects of ULORIC include:

- liver problems
- nausea
- gout flares
- joint pain
- rash

Tell your healthcare provider if you develop a rash, have any side effect that bothers you, or that

does not go away. These are not all of the possible side effects of ULORIC. For more information, ask your healthcare provider or pharmacist.

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

How should I store ULORIC?

Store ULORIC between 59°F to 86°F (15°C to 30°C).

Keep ULORIC out of the light.

Keep ULORIC and all medicines out of the reach of children.

General information about the safe and effective use of ULORIC.

Medicines are sometimes prescribed for purposes other than those listed in a patient information leaflet. Do not use ULORIC for a condition for which it was not prescribed. Do not give ULORIC to other people, even if they have the same symptoms that you have. It may harm them.

This patient information leaflet summarizes the most important information about ULORIC. If you would like more information about ULORIC talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ULORIC that is written for health professionals. For more information go to www.uloric.com, or call 1-877-825-3327.

What are the ingredients in ULORIC?

Active Ingredient: febuxostat

Inactive ingredients include: lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, sodium croscarmellose, silicon dioxide, magnesium stearate, and Opadry II, green

Distributed by

Takeda Pharmaceuticals America, Inc.

Deerfield, IL 60015

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ULR015 R2

EXHIBIT F

HIGHLIGHTS OF PRESCRIBING INFORMATION

These HIGHLIGHTS do not include all the information needed to use ULORIC safely and effectively. See full prescribing information for ULORIC.

ULORIC (febuxostat) tablet for oral use

Initial U.S. Approval: 2009

RECENT MAJOR CHANGES

Warnings and Precautions

Hepatic Effects (5.3) 11/2012

INDICATIONS AND USAGE

ULORIC is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in patients with gout. (1)

ULORIC is not recommended for the treatment of asymptomatic hyperuricemia. (1)

DOSAGE AND ADMINISTRATION

- ULORIC is recommended at 40 mg or 80 mg once daily. The recommended starting dose of ULORIC is 40 mg once daily. For patients who do not achieve a serum uric acid (sUA) less than 6 mg/dL after 2 weeks with 40 mg, ULORIC 80 mg is recommended. (2.1)
- ULORIC can be administered without regard to food or antacid use. (2.1)
- No dose adjustment is necessary when administering ULORIC to patients with mild to moderate renal or hepatic impairment. (2.2)

DOSAGE FORMS AND STRENGTHS

Tablet: 40 mg, 80 mg. (3)

CONTRAINDICATIONS

ULORIC is contraindicated in patients being treated with azathioprine or mercaptopurine. (4)

WARNINGS AND PRECAUTIONS

- Gout Flare:** An increase in gout flares is frequently observed during initiation of anti-hyperuricemic agents, including ULORIC. If a gout flare occurs during treatment, ULORIC need not be discontinued. Prophylactic therapy (i.e., non-steroidal anti-inflammatory drug

[NSAID] or colchicine upon initiation of treatment) may be beneficial for up to six months. (2.4, 5.1)

- Cardiovascular Events:** A higher rate of cardiovascular thromboembolic events was observed in patients treated with ULORIC than allopurinol in clinical trials. Monitor for signs and symptoms of MI and stroke. (5.2)
- Hepatic Effects:** Postmarketing reports of hepatic failure, sometimes fatal. Causality cannot be excluded. If liver injury is detected, promptly interrupt ULORIC and assess patient for probable cause, then treat cause if possible, to resolution or stabilization. Do not restart ULORIC if liver injury is confirmed and no alternate etiology can be found. (5.3)

ADVERSE REACTIONS

Adverse reactions occurring in at least 1% of ULORIC-treated patients, and at least 0.5% greater than placebo, are liver function abnormalities, nausea, arthralgia, and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-877-TAKEDA-7 (1-877-825-3327) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Concomitant administration of ULORIC with XO substrate drugs, azathioprine or mercaptopurine could increase plasma concentrations of these drugs resulting in severe toxicity. (7)

USE IN SPECIFIC POPULATIONS

- There is insufficient data in patients with severe renal impairment. No studies have been conducted in patients with severe hepatic impairment. Caution should be exercised in these patients. (8.6, 8.7)
- No studies have been conducted in patients with secondary hyperuricemia (including patients being treated for Lesch-Nyhan syndrome or malignant disease, or in organ transplant recipients); therefore, ULORIC is not recommended for use in these patients. (8.8)

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Patient Labeling.

Revised: November 2012

FULL PRESCRIBING INFORMATION: CONTENTS***1 INDICATIONS AND USAGE****2 DOSAGE AND ADMINISTRATION**

- Recommended Dose
- Special Populations
- Uric Acid Level
- Gout Flares

3 DOSAGE FORMS AND STRENGTHS**4 CONTRAINDICATIONS****5 WARNINGS AND PRECAUTIONS**

- Gout Flare
- Cardiovascular Events
- Hepatic Effects

6 ADVERSE REACTIONS

- Clinical Trials Experience
- Postmarketing Experience

7 DRUG INTERACTIONS

- Xanthine Oxidase Substrate Drugs
- Cytotoxic Chemotherapy Drugs
- In Vivo Drug Interaction Studies

8 USE IN SPECIFIC POPULATIONS

- Pregnancy
- Nursing Mothers

8.4 Pediatric Use**8.5 Geriatric Use****8.6 Renal Impairment****8.7 Hepatic Impairment****8.8 Secondary Hyperuricemia****10 OVERDOSAGE****11 DESCRIPTION****12 CLINICAL PHARMACOLOGY**

- Mechanism of Action
- Pharmacodynamics
- Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- Carcinogenesis, Mutagenesis, Impairment of Fertility
- Animal Toxicology

14 CLINICAL STUDIES

- Management of Hyperuricemia in Gout

16 HOW SUPPLIED/STORAGE AND HANDLING**17 PATIENT COUNSELING INFORMATION**

- General Information

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ULORIC is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in patients with gout.

ULORIC is not recommended for the treatment of asymptomatic hyperuricemia.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

For treatment of hyperuricemia in patients with gout, ULORIC is recommended at 40 mg or 80 mg once daily.

The recommended starting dose of ULORIC is 40 mg once daily. For patients who do not achieve a serum uric acid (sUA) less than 6 mg/dL after two weeks with 40 mg, ULORIC 80 mg is recommended.

ULORIC can be taken without regard to food or antacid use [*see Clinical Pharmacology (12.3)*].

2.2 Special Populations

No dose adjustment is necessary when administering ULORIC in patients with mild to moderate renal impairment [*see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*]. The recommended starting dose of ULORIC is 40 mg once daily. For patients who do not achieve a sUA less than 6 mg/dL after two weeks with 40 mg, ULORIC 80 mg is recommended.

No dose adjustment is necessary in patients with mild to moderate hepatic impairment [*see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)*].

2.3 Uric Acid Level

Testing for the target serum uric acid level of less than 6 mg/dL may be performed as early as two weeks after initiating ULORIC therapy.

2.4 Gout Flares

Gout flares may occur after initiation of ULORIC due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. Flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended upon initiation of ULORIC. Prophylactic therapy may be beneficial for up to six months [*see Clinical Studies (14.1)*].

If a gout flare occurs during ULORIC treatment, ULORIC need not be discontinued. The gout flare should be managed concurrently, as appropriate for the individual patient [*see Warnings and Precautions (5.1)*].

3 DOSAGE FORMS AND STRENGTHS

- 40 mg tablets, light green to green, round, debossed with “TAP” and “40”
- 80 mg tablets, light green to green, teardrop shaped, debossed with “TAP” and “80”

4 CONTRAINDICATIONS

ULORIC is contraindicated in patients being treated with azathioprine or mercaptopurine [*see Drug Interactions (7)*].

5 WARNINGS AND PRECAUTIONS

5.1 Gout Flare

After initiation of ULORIC, an increase in gout flares is frequently observed. This increase is due to reduction in serum uric acid levels, resulting in mobilization of urate from tissue deposits.

In order to prevent gout flares when ULORIC is initiated, concurrent prophylactic treatment with an NSAID or colchicine is recommended [see *Dosage and Administration* (2.4)].

5.2 Cardiovascular Events

In the randomized controlled studies, there was a higher rate of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) in patients treated with ULORIC (0.74 per 100 P-Y [95% Confidence Interval (CI) 0.36-1.37]) than allopurinol (0.60 per 100 P-Y [95% CI 0.16-1.53]) [see *Adverse Reactions* (6.1)]. A causal relationship with ULORIC has not been established. Monitor for signs and symptoms of myocardial infarction (MI) and stroke.

5.3 Hepatic Effects

There have been postmarketing reports of fatal and non-fatal hepatic failure in patients taking ULORIC, although the reports contain insufficient information necessary to establish the probable cause. During randomized controlled studies, transaminase elevations greater than three times the upper limit of normal (ULN) were observed (AST: 2%, 2%, and ALT: 3%, 2% in ULORIC and allopurinol-treated patients, respectively). No dose-effect relationship for these transaminase elevations was noted [see *Clinical Pharmacology* (12.3)].

Obtain a liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) as a baseline before initiating ULORIC.

Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. In this clinical context, if the patient is found to have abnormal liver tests (ALT greater than three times the upper limit of the reference range), ULORIC treatment should be interrupted and investigation done to establish the probable cause. ULORIC should not be restarted in these patients without another explanation for the liver test abnormalities.

Patients who have serum ALT greater than three times the reference range with serum total bilirubin greater than two times the reference range without alternative etiologies are at risk for severe drug-induced liver injury and should not be restarted on ULORIC. For patients with lesser elevations of serum ALT or bilirubin and with an alternate probable cause, treatment with ULORIC can be used with caution.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

A total of 2757 subjects with hyperuricemia and gout were treated with ULORIC 40 mg or 80 mg daily in clinical studies. For ULORIC 40 mg, 559 patients were treated for ≥ 6 months. For ULORIC 80 mg, 1377 subjects were treated for ≥ 6 months, 674 patients were treated for ≥ 1 year and 515 patients were treated for ≥ 2 years.

Most Common Adverse Reactions

In three randomized, controlled clinical studies (Studies 1, 2 and 3), which were six to 12 months in duration, the following adverse reactions were reported by the treating physician as related to study drug. Table 1 summarizes adverse reactions reported at a rate of at least 1% in ULORIC treatment groups and at least 0.5% greater than placebo.

Table 1: Adverse Reactions Occurring in ≥1% of ULORIC-Treated Patients and at Least 0.5% Greater than Seen in Patients Receiving Placebo in Controlled Studies

Adverse Reactions	Placebo	ULORIC		allopurinol*
	(N=134)	40 mg daily (N=757)	80 mg daily (N=1279)	(N=1277)
Liver Function Abnormalities	0.7%	6.6%	4.6%	4.2%
Nausea	0.7%	1.1%	1.3%	0.8%
Arthralgia	0%	1.1%	0.7%	0.7%
Rash	0.7%	0.5%	1.6%	1.6%

*Of the subjects who received allopurinol, 10 received 100 mg, 145 received 200 mg, and 1122 received 300 mg, based on level of renal impairment.

The most common adverse reaction leading to discontinuation from therapy was liver function abnormalities in 1.8% of ULORIC 40 mg, 1.2% of ULORIC 80 mg, and in 0.9% of allopurinol-treated subjects.

In addition to the adverse reactions presented in Table 1, dizziness was reported in more than 1% of ULORIC-treated subjects although not at a rate more than 0.5% greater than placebo.

Less Common Adverse Reactions

In Phase 2 and 3 clinical studies the following adverse reactions occurred in less than 1% of subjects and in more than one subject treated with doses ranging from 40 mg to 240 mg of ULORIC. This list also includes adverse reactions (less than 1% of subjects) associated with organ systems from Warnings and Precautions.

Blood and Lymphatic System Disorders: anemia, idiopathic thrombocytopenic purpura, leukocytosis/leukopenia, neutropenia, pancytopenia, splenomegaly, thrombocytopenia.

Cardiac Disorders: angina pectoris, atrial fibrillation/flutter, cardiac murmur, ECG abnormal, palpitations, sinus bradycardia, tachycardia.

Ear and Labyrinth Disorders: deafness, tinnitus, vertigo.

Eye Disorders: vision blurred.

Gastrointestinal Disorders: abdominal distention, abdominal pain, constipation, dry mouth, dyspepsia, flatulence, frequent stools, gastritis, gastroesophageal reflux disease, gastrointestinal discomfort, gingival pain, haematemesis, hyperchlorhydria, hematochezia, mouth ulceration, pancreatitis, peptic ulcer, vomiting.

General Disorders and Administration Site Conditions: asthenia, chest pain/discomfort, edema, fatigue, feeling abnormal, gait disturbance, influenza-like symptoms, mass, pain, thirst.

Hepatobiliary Disorders: cholelithiasis/cholecystitis, hepatic steatosis, hepatitis, hepatomegaly.

Immune System Disorder: hypersensitivity.

Infections and Infestations: herpes zoster.

Procedural Complications: contusion.

Metabolism and Nutrition Disorders: anorexia, appetite decreased/increased, dehydration, diabetes mellitus, hypercholesterolemia, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypokalemia, weight decreased/increased.

Musculoskeletal and Connective Tissue Disorders: arthritis, joint stiffness, joint swelling, muscle spasms/twitching/tightness/weakness, musculoskeletal pain/stiffness, myalgia.

Nervous System Disorders: altered taste, balance disorder, cerebrovascular accident, Guillain-Barré syndrome, headache, hemiparesis, hypoesthesia, hyposmia, lacunar infarction, lethargy, mental impairment, migraine, paresthesia, somnolence, transient ischemic attack, tremor.

Psychiatric Disorders: agitation, anxiety, depression, insomnia, irritability, libido decreased, nervousness, panic attack, personality change.

Renal and Urinary Disorders: hematuria, nephrolithiasis, pollakiuria, proteinuria, renal failure, renal insufficiency, urgency, incontinence.

Reproductive System and Breast Changes: breast pain, erectile dysfunction, gynecomastia.

Respiratory, Thoracic and Mediastinal Disorders: bronchitis, cough, dyspnea, epistaxis, nasal dryness, paranasal sinus hypersecretion, pharyngeal edema, respiratory tract congestion, sneezing, throat irritation, upper respiratory tract infection.

Skin and Subcutaneous Tissue Disorders: alopecia, angio-edema, dermatitis, dermographism, ecchymosis, eczema, hair color changes, hair growth abnormal, hyperhidrosis, peeling skin, petechiae, photosensitivity, pruritus, purpura, skin discoloration/alteration in pigmentation, skin lesion, skin odor abnormal, urticaria.

Vascular Disorders: flushing, hot flush, hypertension, hypotension.

Laboratory Parameters: activated partial thromboplastin time prolonged, creatine increased, bicarbonate decreased, sodium increased, EEG abnormal, glucose increased, cholesterol increased, triglycerides increased, amylase increased, potassium increased, TSH increased, platelet count decreased, hematocrit decreased, hemoglobin decreased, MCV increased, RBC decreased, creatinine increased, blood urea increased, BUN/creatinine ratio increased, creatine phosphokinase (CPK) increased, alkaline phosphatase increased, LDH increased, PSA increased, urine output increased/decreased, lymphocyte count decreased, neutrophil count decreased, WBC increased/decreased, coagulation test abnormal, low density lipoprotein (LDL) increased, prothrombin time prolonged, urinary casts, urine positive for white blood cells and protein.

Cardiovascular Safety

Cardiovascular events and deaths were adjudicated to one of the pre-defined endpoints from the Anti-Platelet Trialists' Collaborations (APTC) (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) in the randomized controlled and long-term extension studies. In the Phase 3 randomized controlled studies, the incidences of adjudicated APTC events per 100 patient-years of exposure were: Placebo 0 (95% CI 0.00-6.16), ULORIC 40 mg 0 (95% CI 0.00-1.08), ULORIC 80 mg 1.09 (95% CI 0.44-2.24), and allopurinol 0.60 (95% CI 0.16-1.53).

In the long-term extension studies, the incidences of adjudicated APTC events were: ULORIC 80 mg 0.97 (95% CI 0.57-1.56), and allopurinol 0.58 (95% CI 0.02-3.24).

Overall, a higher rate of APTC events was observed in ULORIC than in allopurinol-treated patients. A causal relationship with ULORIC has not been established. Monitor for signs and symptoms of MI and stroke.

6.2 Postmarketing Experience

Adverse reactions have been identified during postapproval use of ULORIC. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship.

Hepatobiliary Disorders: hepatic failure (some fatal), jaundice, serious cases of abnormal liver function test results, liver disorder.

Immune System Disorders: anaphylaxis, anaphylactic reaction.

Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis.

Psychiatric Disorders: psychotic behavior including aggressive thoughts.

Renal and Urinary Disorders: tubulointerstitial nephritis.

Skin and Subcutaneous Tissue Disorders: generalized rash, Stevens Johnson Syndrome, hypersensitivity skin reactions.

7 DRUG INTERACTIONS

7.1 Xanthine Oxidase Substrate Drugs

ULORIC is an XO inhibitor. Based on a drug interaction study in healthy subjects, febuxostat altered the metabolism of theophylline (a substrate of XO) in humans [see *Clinical Pharmacology (12.3)*]. Therefore, use with caution when coadministering ULORIC with theophylline.

Drug interaction studies of ULORIC with other drugs that are metabolized by XO (e.g., mercaptopurine and azathioprine) have not been conducted. Inhibition of XO by ULORIC may cause increased plasma concentrations of these drugs leading to toxicity [see *Clinical Pharmacology (12.3)*]. ULORIC is contraindicated in patients being treated with azathioprine or mercaptopurine [see *Contraindications (4)*].

7.2 Cytotoxic Chemotherapy Drugs

Drug interaction studies of ULORIC with cytotoxic chemotherapy have not been conducted. No data are available regarding the safety of ULORIC during cytotoxic chemotherapy.

7.3 In Vivo Drug Interaction Studies

Based on drug interaction studies in healthy subjects, ULORIC does not have clinically significant interactions with colchicine, naproxen, indomethacin, hydrochlorothiazide, warfarin or desipramine [see *Clinical Pharmacology (12.3)*]. Therefore, ULORIC may be used concomitantly with these medications.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. ULORIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Febuxostat was not teratogenic in rats and rabbits at oral doses up to 48 mg/kg (40 and 51 times the human plasma exposure at 80 mg/day for equal body surface area, respectively) during

organogenesis. However, increased neonatal mortality and a reduction in the neonatal body weight gain were observed when pregnant rats were treated with oral doses up to 48 mg/kg (40 times the human plasma exposure at 80 mg/day) during organogenesis and through lactation period.

8.3 Nursing Mothers

Febuxostat is excreted in the milk of rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ULORIC is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients under 18 years of age have not been established.

8.5 Geriatric Use

No dose adjustment is necessary in elderly patients. Of the total number of subjects in clinical studies of ULORIC, 16% were 65 and over, while 4% were 75 and over. Comparing subjects in different age groups, no clinically significant differences in safety or effectiveness were observed but greater sensitivity of some older individuals cannot be ruled out. The C_{max} and AUC_{24} of febuxostat following multiple oral doses of ULORIC in geriatric subjects (≥ 65 years) were similar to those in younger subjects (18 to 40 years) [see *Clinical Pharmacology* (12.3)].

8.6 Renal Impairment

No dose adjustment is necessary in patients with mild or moderate renal impairment (Cl_{cr} 30 to 89 mL/min). The recommended starting dose of ULORIC is 40 mg once daily. For patients who do not achieve a sUA less than 6 mg/dL after two weeks with 40 mg, ULORIC 80 mg is recommended.

There are insufficient data in patients with severe renal impairment (Cl_{cr} less than 30 mL/min); therefore, caution should be exercised in these patients [see *Clinical Pharmacology* (12.3)].

8.7 Hepatic Impairment

No dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh Class A or B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C); therefore, caution should be exercised in these patients [see *Clinical Pharmacology* (12.3)].

8.8 Secondary Hyperuricemia

No studies have been conducted in patients with secondary hyperuricemia (including organ transplant recipients); ULORIC is not recommended for use in patients whom the rate of urate formation is greatly increased (e.g., malignant disease and its treatment, Lesch-Nyhan syndrome). The concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract.

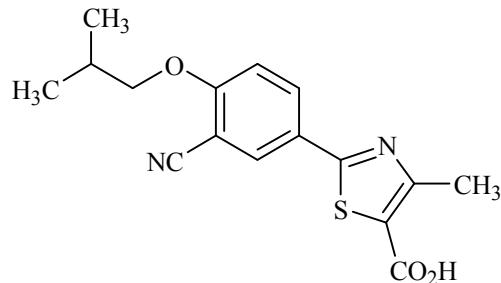
10 OVERDOSAGE

ULORIC was studied in healthy subjects in doses up to 300 mg daily for seven days without evidence of dose-limiting toxicities. No overdose of ULORIC was reported in clinical studies. Patients should be managed by symptomatic and supportive care should there be an overdose.

11 DESCRIPTION

ULORIC (febuxostat) is a xanthine oxidase inhibitor. The active ingredient in ULORIC is 2-[3-cyano-4-(2-methylpropoxy) phenyl]-4-methylthiazole-5-carboxylic acid, with a molecular weight of 316.38. The empirical formula is C₁₆H₁₆N₂O₃S.

The chemical structure is:



Febuxostat is a non-hygroscopic, white crystalline powder that is freely soluble in dimethylformamide; soluble in dimethylsulfoxide; sparingly soluble in ethanol; slightly soluble in methanol and acetonitrile; and practically insoluble in water. The melting range is 205°C to 208°C.

ULORIC tablets for oral use contain the active ingredient, febuxostat, and are available in two dosage strengths, 40 mg and 80 mg. Inactive ingredients include lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, sodium croscarmellose, silicon dioxide and magnesium stearate. ULORIC tablets are coated with Opadry II, green.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ULORIC, a xanthine oxidase inhibitor, achieves its therapeutic effect by decreasing serum uric acid. ULORIC is not expected to inhibit other enzymes involved in purine and pyrimidine synthesis and metabolism at therapeutic concentrations.

12.2 Pharmacodynamics

Effect on Uric Acid and Xanthine Concentrations: In healthy subjects, ULORIC resulted in a dose dependent decrease in 24-hour mean serum uric acid concentrations and an increase in 24-hour mean serum xanthine concentrations. In addition, there was a decrease in the total daily urinary uric acid excretion. Also, there was an increase in total daily urinary xanthine excretion. Percent reduction in 24-hour mean serum uric acid concentrations was between 40% and 55% at the exposure levels of 40 mg and 80 mg daily doses.

Effect on Cardiac Repolarization: The effect of ULORIC on cardiac repolarization as assessed by the QTc interval was evaluated in normal healthy subjects and in patients with gout. ULORIC in doses up to 300 mg daily, at steady-state, did not demonstrate an effect on the QTc interval.

12.3 Pharmacokinetics

In healthy subjects, maximum plasma concentrations (C_{max}) and AUC of febuxostat increased in a dose proportional manner following single and multiple doses of 10 mg to 120 mg. There is no accumulation when therapeutic doses are administered every 24 hours. Febuxostat has an apparent mean terminal elimination half-life (t_{1/2}) of approximately 5 to 8 hours. Febuxostat pharmacokinetic parameters for patients with hyperuricemia and gout estimated by population pharmacokinetic analyses were similar to those estimated in healthy subjects.

Absorption: The absorption of radiolabeled febuxostat following oral dose administration was estimated to be at least 49% (based on total radioactivity recovered in urine). Maximum plasma concentrations of febuxostat occurred between 1 and 1.5 hours post-dose. After multiple oral 40 mg and 80 mg once daily doses, C_{max} is approximately 1.6 ± 0.6 mcg/mL (N=30), and 2.6 ± 1.7 mcg/mL (N=227), respectively. Absolute bioavailability of the febuxostat tablet has not been studied.

Following multiple 80 mg once daily doses with a high fat meal, there was a 49% decrease in C_{max} and an 18% decrease in AUC, respectively. However, no clinically significant change in the percent decrease in serum uric acid concentration was observed (58% fed vs. 51% fasting). Thus, ULORIC may be taken without regard to food.

Concomitant ingestion of an antacid containing magnesium hydroxide and aluminum hydroxide with an 80 mg single dose of ULORIC has been shown to delay absorption of febuxostat (approximately one hour) and to cause a 31% decrease in C_{max} and a 15% decrease in AUC ∞ . As AUC rather than C_{max} was related to drug effect, change observed in AUC was not considered clinically significant. Therefore, ULORIC may be taken without regard to antacid use.

Distribution: The mean apparent steady state volume of distribution (V_{ss}/F) of febuxostat was approximately 50 L (CV ~40%). The plasma protein binding of febuxostat is approximately 99.2%, (primarily to albumin), and is constant over the concentration range achieved with 40 mg and 80 mg doses.

Metabolism: Febuxostat is extensively metabolized by both conjugation via uridine diphosphate glucuronosyltransferase (UGT) enzymes including UGT1A1, UGT1A3, UGT1A9, and UGT2B7 and oxidation via cytochrome P450 (CYP) enzymes including CYP1A2, 2C8 and 2C9 and non-P450 enzymes. The relative contribution of each enzyme isoform in the metabolism of febuxostat is not clear. The oxidation of the isobutyl side chain leads to the formation of four pharmacologically active hydroxy metabolites, all of which occur in plasma of humans at a much lower extent than febuxostat.

In urine and feces, acyl glucuronide metabolites of febuxostat (~35% of the dose), and oxidative metabolites, 67M-1 (~10% of the dose), 67M-2 (~11% of the dose), and 67M-4, a secondary metabolite from 67M-1 (~14% of the dose), appeared to be the major metabolites of febuxostat *in vivo*.

Elimination: Febuxostat is eliminated by both hepatic and renal pathways. Following an 80 mg oral dose of ^{14}C -labeled febuxostat, approximately 49% of the dose was recovered in the urine as unchanged febuxostat (3%), the acyl glucuronide of the drug (30%), its known oxidative metabolites and their conjugates (13%), and other unknown metabolites (3%). In addition to the urinary excretion, approximately 45% of the dose was recovered in the feces as the unchanged febuxostat (12%), the acyl glucuronide of the drug (1%), its known oxidative metabolites and their conjugates (25%), and other unknown metabolites (7%).

The apparent mean terminal elimination half-life ($t_{1/2}$) of febuxostat was approximately 5 to 8 hours.

Special Populations

Pediatric Use: The pharmacokinetics of ULORIC in patients under the age of 18 years have not been studied.

Geriatric Use: The C_{max} and AUC of febuxostat and its metabolites following multiple oral doses of ULORIC in geriatric subjects (≥ 65 years) were similar to those in younger subjects (18 to 40 years). In addition, the percent decrease in serum uric acid concentration was similar between elderly and younger subjects. No dose adjustment is necessary in geriatric patients [see *Use in Specific Populations (8.5)*].

Renal Impairment: Following multiple 80 mg doses of ULORIC in healthy subjects with mild (Cl_{cr} 50 to 80 mL/min), moderate (Cl_{cr} 30 to 49 mL/min) or severe renal impairment (Cl_{cr} 10 to 29 mL/min), the C_{max} of febuxostat did not change relative to subjects with normal renal function (Cl_{cr} greater than 80 mL/min). AUC and half-life of febuxostat increased in subjects with renal impairment in comparison to subjects with normal renal function, but values were similar among three renal impairment groups. Mean febuxostat AUC values were up to 1.8 times higher in subjects with renal impairment compared to those with normal renal function. Mean C_{max} and AUC values for three active metabolites increased up to 2- and 4-fold, respectively. However, the percent decrease in serum uric acid concentration for subjects with renal impairment was comparable to those with normal renal function (58% in normal renal function group and 55% in the severe renal function group).

No dose adjustment is necessary in patients with mild to moderate renal impairment [see *Dosage and Administration (2)* and *Use in Specific Populations (8.6)*]. The recommended starting dose of ULORIC is 40 mg once daily. For patients who do not achieve a sUA less than 6 mg/dL after two weeks with 40 mg, ULORIC 80 mg is recommended. There is insufficient data in patients with severe renal impairment; caution should be exercised in those patients [see *Use in Specific Populations (8.6)*].

ULORIC has not been studied in end stage renal impairment patients who are on dialysis.

Hepatic Impairment: Following multiple 80 mg doses of ULORIC in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, an average of 20% to 30% increase was observed for both C_{max} and AUC_{24} (total and unbound) in hepatic impairment groups compared to subjects with normal hepatic function. In addition, the percent decrease in serum uric acid concentration was comparable between different hepatic groups (62% in healthy group, 49% in mild hepatic impairment group, and 48% in moderate hepatic impairment group). No dose adjustment is necessary in patients with mild or moderate hepatic impairment. No studies have been conducted in subjects with severe hepatic impairment (Child-Pugh Class C); caution should be exercised in those patients [see *Use in Specific Populations (8.7)*].

Gender: Following multiple oral doses of ULORIC, the C_{max} and AUC_{24} of febuxostat were 30% and 14% higher in females than in males, respectively. However, weight-corrected C_{max} and AUC were similar between the genders. In addition, the percent decrease in serum uric acid concentrations was similar between genders. No dose adjustment is necessary based on gender.

Race: No specific pharmacokinetic study was conducted to investigate the effects of race.

Drug-Drug Interactions

Effect of ULORIC on Other Drugs

Xanthine Oxidase Substrate Drugs-Azathioprine, Mercaptopurine, and Theophylline: Febuxostat is an XO inhibitor. A drug-drug interaction study evaluating the effect of ULORIC upon the pharmacokinetics of theophylline (an XO substrate) in healthy subjects showed that coadministration of febuxostat with theophylline resulted in an approximately 400-fold increase in the amount of 1-methylxanthine, one of the major metabolites of theophylline, excreted in the urine. Since the long-term safety of exposure to 1-methylxanthine in humans is unknown, use with caution when coadministering febuxostat with theophylline.

Drug interaction studies of ULORIC with other drugs that are metabolized by XO (e.g., mercaptopurine and azathioprine) have not been conducted. Inhibition of XO by ULORIC may cause increased plasma concentrations of these drugs leading to toxicity. ULORIC is

contraindicated in patients being treated with azathioprine or mercaptopurine [see *Contraindications* (4) and *Drug Interactions* (7)].

Azathioprine and mercaptopurine undergo metabolism via three major metabolic pathways, one of which is mediated by XO. Although ULORIC drug interaction studies with azathioprine and mercaptopurine have not been conducted, concomitant administration of allopurinol [a xanthine oxidase inhibitor] with azathioprine or mercaptopurine has been reported to substantially increase plasma concentrations of these drugs. Because ULORIC is a xanthine oxidase inhibitor, it could inhibit the XO-mediated metabolism of azathioprine and mercaptopurine leading to increased plasma concentrations of azathioprine or mercaptopurine that could result in severe toxicity.

P450 Substrate Drugs: *In vitro* studies have shown that febuxostat does not inhibit P450 enzymes CYP1A2, 2C9, 2C19, 2D6, or 3A4 and it also does not induce CYP1A2, 2B6, 2C9, 2C19, or 3A4 at clinically relevant concentrations. As such, pharmacokinetic interactions between ULORIC and drugs metabolized by these CYP enzymes are unlikely.

Effect of Other Drugs on ULORIC

Febuxostat is metabolized by conjugation and oxidation via multiple metabolizing enzymes. The relative contribution of each enzyme isoform is not clear. Drug interactions between ULORIC and a drug that inhibits or induces one particular enzyme isoform is in general not expected.

In Vivo Drug Interaction Studies

Theophylline: No dose adjustment is necessary for theophylline when coadministered with ULORIC. Administration of ULORIC (80 mg once daily) with theophylline resulted in an increase of 6% in C_{max} and 6.5% in AUC of theophylline. These changes were not considered statistically significant. However, the study also showed an approximately 400-fold increase in the amount of 1-methylxanthine (one of the major theophylline metabolites) excreted in urine as a result of XO inhibition by ULORIC. The safety of long-term exposure to 1-methylxanthine has not been evaluated. This should be taken into consideration when deciding to coadminister Uloric and theophylline.

Colchicine: No dose adjustment is necessary for either ULORIC or colchicine when the two drugs are coadministered. Administration of ULORIC (40 mg once daily) with colchicine (0.6 mg twice daily) resulted in an increase of 12% in C_{max} and 7% in AUC_{24} of febuxostat. In addition, administration of colchicine (0.6 mg twice daily) with ULORIC (120 mg daily) resulted in a less than 11% change in C_{max} or AUC of colchicine for both AM and PM doses. These changes were not considered clinically significant.

Naproxen: No dose adjustment is necessary for ULORIC or naproxen when the two drugs are coadministered. Administration of ULORIC (80 mg once daily) with naproxen (500 mg twice daily) resulted in a 28% increase in C_{max} and a 40% increase in AUC of febuxostat. The increases were not considered clinically significant. In addition, there were no significant changes in the C_{max} or AUC of naproxen (less than 2%).

Indomethacin: No dose adjustment is necessary for either ULORIC or indomethacin when these two drugs are coadministered. Administration of ULORIC (80 mg once daily) with indomethacin (50 mg twice daily) did not result in any significant changes in C_{max} or AUC of febuxostat or indomethacin (less than 7%).

Hydrochlorothiazide: No dose adjustment is necessary for ULORIC when coadministered with hydrochlorothiazide. Administration of ULORIC (80 mg) with hydrochlorothiazide (50 mg) did not result in any clinically significant changes in C_{max} or AUC of febuxostat (less than 4%), and serum uric acid concentrations were not substantially affected.

Warfarin: No dose adjustment is necessary for warfarin when coadministered with ULORIC. Administration of ULORIC (80 mg once daily) with warfarin had no effect on the pharmacokinetics of warfarin in healthy subjects. INR and Factor VII activity were also not affected by the coadministration of ULORIC.

Desipramine: Coadministration of drugs that are CYP2D6 substrates (such as desipramine) with ULORIC are not expected to require dose adjustment. Febuxostat was shown to be a weak inhibitor of CYP2D6 *in vitro* and *in vivo*. Administration of ULORIC (120 mg once daily) with desipramine (25 mg) resulted in an increase in C_{max} (16%) and AUC (22%) of desipramine, which was associated with a 17% decrease in the 2-hydroxydesipramine to desipramine metabolic ratio (based on AUC).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Two-year carcinogenicity studies were conducted in F344 rats and B6C3F1 mice. Increased transitional cell papilloma and carcinoma of urinary bladder was observed at 24 mg/kg (25 times the human plasma exposure at maximum recommended human dose of 80 mg/day) and 18.75 mg/kg (12.5 times the human plasma exposure at 80 mg/day) in male rats and female mice, respectively. The urinary bladder neoplasms were secondary to calculus formation in the kidney and urinary bladder.

Mutagenesis: Febuxostat showed a positive mutagenic response in a chromosomal aberration assay in a Chinese hamster lung fibroblast cell line with and without metabolic activation *in vitro*. Febuxostat was negative in the *in vitro* Ames assay and chromosomal aberration test in human peripheral lymphocytes, and L5178Y mouse lymphoma cell line, and *in vivo* tests in mouse micronucleus, rat unscheduled DNA synthesis and rat bone marrow cells.

Impairment of Fertility: Febuxostat at oral doses up to 48 mg/kg/day (approximately 35 times the human plasma exposure at 80 mg/day) had no effect on fertility and reproductive performance of male and female rats.

13.2 Animal Toxicology

A 12-month toxicity study in beagle dogs showed deposition of xanthine crystals and calculi in kidneys at 15 mg/kg (approximately four times the human plasma exposure at 80 mg/day). A similar effect of calculus formation was noted in rats in a six-month study due to deposition of xanthine crystals at 48 mg/kg (approximately 35 times the human plasma exposure at 80 mg/day).

14 CLINICAL STUDIES

A serum uric acid level of less than 6 mg/dL is the goal of anti-hyperuricemic therapy and has been established as appropriate for the treatment of gout.

14.1 Management of Hyperuricemia in Gout

The efficacy of ULORIC was demonstrated in three randomized, double-blind, controlled trials in patients with hyperuricemia and gout. Hyperuricemia was defined as a baseline serum uric acid level ≥ 8 mg/dL.

Study 1 randomized patients to: ULORIC 40 mg daily, ULORIC 80 mg daily, or allopurinol (300 mg daily for patients with estimated creatinine clearance (Cl_{cr}) ≥ 60 mL/min or 200 mg daily for patients with estimated $Cl_{cr} \geq 30$ mL/min and ≤ 59 mL/min). The duration of Study 1 was six months.

Study 2 randomized patients to: placebo, ULORIC 80 mg daily, ULORIC 120 mg daily, ULORIC 240 mg daily or allopurinol (300 mg daily for patients with a baseline serum creatinine ≤ 1.5 mg/dL or 100

mg daily for patients with a baseline serum creatinine greater than 1.5 mg/dL and ≤ 2 mg/dL). The duration of Study 2 was six months.

Study 3, a 1-year study, randomized patients to: ULORIC 80 mg daily, ULORIC 120 mg daily, or allopurinol 300 mg daily. Subjects who completed Study 2 and Study 3 were eligible to enroll in a phase 3 long-term extension study in which subjects received treatment with ULORIC for over three years.

In all three studies, subjects received naproxen 250 mg twice daily or colchicine 0.6 mg once or twice daily for gout flare prophylaxis. In Study 1 the duration of prophylaxis was six months; in Study 2 and Study 3 the duration of prophylaxis was eight weeks.

The efficacy of ULORIC was also evaluated in a 4 week dose ranging study which randomized patients to: placebo, ULORIC 40 mg daily, ULORIC 80 mg daily, or ULORIC 120 mg daily. Subjects who completed this study were eligible to enroll in a long-term extension study in which subjects received treatment with ULORIC for up to five years.

Patients in these studies were representative of the patient population for which ULORIC use is intended. Table 2 summarizes the demographics and baseline characteristics for the subjects enrolled in the studies.

Table 2: Patient Demographics and Baseline Characteristics in Study 1, Study 2 and Study 3

Male	95%
Race: Caucasian African American	80%
	10%
Ethnicity: Hispanic or Latino	7%
Alcohol User	67%
Mild to Moderate Renal Insufficiency (percent with estimated Cl_{cr} less than 90 mL/min)	59%
History of Hypertension	49%
History of Hyperlipidemia	38%
BMI ≥ 30 kg/m ²	63%
Mean BMI	33 kg/m ²
Baseline sUA ≥ 10 mg/dL	36%
Mean baseline sUA	9.7 mg/dL
Experienced a gout flare in previous year	85%

Serum Uric Acid Level less than 6 mg/dL at Final Visit: ULORIC 80 mg was superior to allopurinol in lowering serum uric acid to less than 6 mg/dL at the final visit. ULORIC 40 mg daily, although not superior to allopurinol, was effective in lowering serum uric acid to less than 6 mg/dL at the final visit ([Table 3](#)).

Table 3: Proportion of Patients with Serum Uric Acid Levels less than 6 mg/dL at Final Visit

Study*	ULORIC 40 mg daily	ULORIC 80 mg daily	allopurinol	Placebo	Difference in Proportion (95% CI)	
					ULORIC 40 mg vs allopurinol	ULORIC 80 mg vs allopurinol
Study 1 (6 months) (N=2268)	45%	67%	42%		3% (-2%, 8%)	25% (20%, 30%)
Study 2 (6 months) (N=643)		72%	39%	1%		33% (26%, 42%)
Study 3 (12 months) (N=491)		74%	36%			38% (30%, 46%)

*Randomization was balanced between treatment groups, except in Study 2 in which twice as many patients were randomized to each of the active treatment groups compared to placebo.

In 76% of ULORIC 80 mg patients, reduction in serum uric acid levels to less than 6 mg/dL was noted by the Week 2 visit. Average serum uric acid levels were maintained at 6 mg/dL or below throughout treatment in 83% of these patients.

In all treatment groups, fewer subjects with higher baseline serum urate levels (≥ 10 mg/dL) and/or tophi achieved the goal of lowering serum uric acid to less than 6 mg/dL at the final visit; however, a higher proportion achieved a serum uric acid less than 6 mg/dL with ULORIC 80 mg than with ULORIC 40 mg or allopurinol.

Study 1 evaluated efficacy in patients with mild to moderate renal impairment (i.e., baseline estimated Cl_{cr} less than 90 mL/min). The results in this sub-group of patients are shown in Table 4.

Table 4: Proportion of Patients with Serum Uric Acid Levels less than 6 mg/dL in Patients with Mild or Moderate Renal Impairment at Final Visit

ULORIC 40 mg daily (N=479)	ULORIC 80 mg daily (N=503)	allopurinol* 300 mg daily (N=501)	Difference in Proportion (95% CI)	
			ULORIC 40 mg vs allopurinol	ULORIC 80 mg vs allopurinol
50%	72%	42%	7% (1%, 14%)	29% (23%, 35%)

*Allopurinol patients (n=145) with estimated $\text{Cl}_{\text{cr}} \geq 30$ mL/min and $\text{Cl}_{\text{cr}} \leq 59$ mL/min were dosed at 200 mg daily.

16 HOW SUPPLIED/STORAGE AND HANDLING

ULORIC 40 mg tablets are light green to green in color, round, debossed with "TAP" on one side and "40" on the other side and supplied as:

<u>NDC Number</u>	<u>Size</u>
64764-918-11	Hospital Unit Dose Pack of 100 Tablets
64764-918-30	Bottle of 30 Tablets
64764-918-90	Bottle of 90 Tablets
64764-918-18	Bottle of 500 Tablets

ULORIC 80 mg tablets are light green to green in color, teardrop shaped, debossed with "TAP" on one side and "80" on the other side and supplied as:

<u>NDC Number</u>	<u>Size</u>
64764-677-11	Hospital Unit Dose Pack of 100 Tablets
64764-677-30	Bottle of 30 Tablets
64764-677-13	Bottle of 100 Tablets
64764-677-19	Bottle of 1000 Tablets

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

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information)

17.1 General Information

Patients should be advised of the potential benefits and risks of ULORIC. Patients should be informed about the potential for gout flares, elevated liver enzymes and adverse cardiovascular events after initiation of ULORIC therapy.

Concomitant prophylaxis with an NSAID or colchicine for gout flares should be considered.

Patients should be instructed to inform their healthcare professional if they develop a rash, chest pain, shortness of breath or neurologic symptoms suggesting a stroke. Patients should be instructed to inform their healthcare professional of any other medications they are currently taking with ULORIC, including over-the-counter medications.

Patient Information

ULORIC (ü-lor-ik) (febuxostat) tablets

Read the Patient Information that comes with ULORIC before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is ULORIC?

ULORIC is a prescription medicine called a xanthine oxidase (XO) inhibitor, used to lower blood uric acid levels in adults with gout.

It is not known if ULORIC is safe and effective in children under 18 years of age.

Who should not take ULORIC?

Do not take ULORIC if you:

- take azathioprine (Azasan, Imuran)
- take mercaptopurine (Purinethol)

It is not known if ULORIC is safe and effective in children under 18 years of age.

What should I tell my healthcare provider before taking ULORIC?

Before taking ULORIC tell your healthcare provider about all of your medical conditions, including if you:

- have liver or kidney problems
- have a history of heart disease or stroke
- are pregnant or plan to become pregnant. It is not known if ULORIC will harm your unborn baby. Talk with your healthcare provider if you are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. It is not known if ULORIC passes into your breast milk. You and your healthcare provider should decide if you should take ULORIC while breastfeeding.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. ULORIC may affect the way other medicines work, and other medicines may affect how ULORIC works.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take ULORIC?

- Take ULORIC exactly as your healthcare provider tells you to take it.
- ULORIC can be taken with or without food.
- ULORIC can be taken with antacids.
- Your gout may flare up when you start taking ULORIC, do not stop taking your ULORIC even if you have a flare. Your healthcare provider may give you other medicines to help prevent your gout flares.

- Your healthcare provider may do certain tests while you take ULORIC.

What are the possible side effects of ULORIC?

Heart problems. A small number of heart attacks, strokes and heart-related deaths were seen in clinical studies. It is not certain that ULORIC caused these events.

The most common side effects of ULORIC include:

- liver problems
- nausea
- gout flares
- joint pain
- rash

Tell your healthcare provider if you develop a rash, have any side effect that bothers you, or that does not go away. These are not all of the possible side effects of ULORIC. For more information, ask your healthcare provider or pharmacist.

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

How should I store ULORIC?

Store ULORIC between 59°F and 86°F (15°C to 30°C).

Keep ULORIC out of the light.

Keep ULORIC and all medicines out of the reach of children.

General information about the safe and effective use of ULORIC.

Medicines are sometimes prescribed for purposes other than those listed in a patient information leaflet. Do not use ULORIC for a condition for which it was not prescribed. Do not give ULORIC to other people, even if they have the same symptoms that you have. It may harm them.

This patient information leaflet summarizes the most important information about ULORIC. If you would like more information about ULORIC talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ULORIC that is written for health professionals. For more information go to www.uloric.com, or call 1-877-825-3327.

What are the ingredients in ULORIC?

Active Ingredient: febuxostat

Inactive ingredients include: lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, sodium croscarmellose, silicon dioxide, magnesium stearate, and Opadry II, green

Distributed by:

Takeda Pharmaceuticals America, Inc.

Deerfield, IL 60015

Revised: November 2012

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ULR015 R3

EXHIBIT G

HIGHLIGHTS OF PRESCRIBING INFORMATION

These HIGHLIGHTS do not include all the information needed to use ULORIC safely and effectively. See full prescribing information for ULORIC.

ULORIC (febuxostat) tablet for oral use

Initial U.S. Approval: 2009

RECENT MAJOR CHANGES**Dosage and Administration**

Special Populations (2.2) 8/2017

INDICATIONS AND USAGE

ULORIC is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in patients with gout. (1)

ULORIC is not recommended for the treatment of asymptomatic hyperuricemia. (1)

DOSAGE AND ADMINISTRATION

- ULORIC is recommended at 40 mg or 80 mg once daily. The recommended starting dose of ULORIC is 40 mg once daily. For patients who do not achieve a serum uric acid (sUA) less than 6 mg/dL after 2 weeks with 40 mg, ULORIC 80 mg is recommended. (2.1)
- ULORIC can be administered without regard to food or antacid use. (2.1)
- Limit the dose of ULORIC to 40 mg once daily in patients with severe renal impairment. (2.2, 8.6)

DOSAGE FORMS AND STRENGTHS

Tablet: 40 mg, 80 mg. (3)

CONTRAINDICATIONS

ULORIC is contraindicated in patients being treated with azathioprine or mercaptopurine. (4)

WARNINGS AND PRECAUTIONS

- Gout Flare:** An increase in gout flares is frequently observed during initiation of anti-hyperuricemic agents, including ULORIC. If a gout flare occurs during treatment, ULORIC need not be discontinued. Prophylactic therapy (i.e., non-steroidal anti-inflammatory drug

[NSAID] or colchicine upon initiation of treatment) may be beneficial for up to six months. (2.4, 5.1)

- Cardiovascular Events:** A higher rate of cardiovascular thromboembolic events was observed in patients treated with ULORIC than allopurinol in clinical trials. Monitor for signs and symptoms of MI and stroke. (5.2)
- Hepatic Effects:** Postmarketing reports of hepatic failure, sometimes fatal. Causality cannot be excluded. If liver injury is detected, promptly interrupt ULORIC and assess patient for probable cause, then treat cause if possible, to resolution or stabilization. Do not restart ULORIC if liver injury is confirmed and no alternate etiology can be found. (5.3)

ADVERSE REACTIONS

Adverse reactions occurring in at least 1% of patients treated with ULORIC, and at least 0.5% greater than placebo, are liver function abnormalities, nausea, arthralgia, and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-877-TAKEDA-7 (1-877-825-3327) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Concomitant administration of ULORIC with XO substrate drugs, azathioprine or mercaptopurine could increase plasma concentrations of these drugs resulting in severe toxicity. (7)

USE IN SPECIFIC POPULATIONS

- No studies have been conducted in patients with severe hepatic impairment. Caution should be exercised in these patients. (8.6, 8.7)
- No studies have been conducted in patients with secondary hyperuricemia (including patients being treated for Lesch-Nyhan syndrome or malignant disease, or in organ transplant recipients); therefore, ULORIC is not recommended for use in these patients. (8.8)

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

Revised: 8/2017

FULL PRESCRIBING INFORMATION: CONTENTS***1 INDICATIONS AND USAGE****2 DOSAGE AND ADMINISTRATION**

- Recommended Dose
- Special Populations
- Uric Acid Level
- Gout Flares

3 DOSAGE FORMS AND STRENGTHS**4 CONTRAINDICATIONS****5 WARNINGS AND PRECAUTIONS**

- Gout Flare
- Cardiovascular Events
- Hepatic Effects

6 ADVERSE REACTIONS

- Clinical Trials Experience
- Postmarketing Experience

7 DRUG INTERACTIONS

- Xanthine Oxidase Substrate Drugs
- Cytotoxic Chemotherapy Drugs
- In Vivo Drug Interaction Studies

8 USE IN SPECIFIC POPULATIONS

- Pregnancy

- Lactation
- Pediatric Use
- Geriatric Use
- Renal Impairment
- Hepatic Impairment
- Secondary Hyperuricemia

10 OVERDOSAGE**11 DESCRIPTION****12 CLINICAL PHARMACOLOGY**

- Mechanism of Action
- Pharmacodynamics
- Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- Carcinogenesis, Mutagenesis, Impairment of Fertility
- Animal Toxicology

14 CLINICAL STUDIES

- Management of Hyperuricemia in Gout

16 HOW SUPPLIED/STORAGE AND HANDLING**17 PATIENT COUNSELING INFORMATION**

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ULORIC is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in patients with gout.

ULORIC is not recommended for the treatment of asymptomatic hyperuricemia.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

For treatment of hyperuricemia in patients with gout, ULORIC is recommended at 40 mg or 80 mg once daily.

The recommended starting dose of ULORIC is 40 mg once daily. For patients who do not achieve a serum uric acid (sUA) less than 6 mg/dL after two weeks with 40 mg, ULORIC 80 mg is recommended.

ULORIC can be taken without regard to food or antacid use [see *Clinical Pharmacology (12.3)*].

2.2 Special Populations

No dose adjustment is necessary when administering ULORIC in patients with mild or moderate renal impairment. The recommended starting dose of ULORIC is 40 mg once daily. For patients who do not achieve a sUA less than 6 mg/dL after two weeks with 40 mg, ULORIC 80 mg is recommended.

The dose of ULORIC is limited to 40 mg once daily in patients with severe renal impairment [see *Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)*].

No dose adjustment is necessary in patients with mild to moderate hepatic impairment [see *Use in Specific Populations (8.7)* and *Clinical Pharmacology (12.3)*].

2.3 Uric Acid Level

Testing for the target serum uric acid level of less than 6 mg/dL may be performed as early as two weeks after initiating ULORIC therapy.

2.4 Gout Flares

Gout flares may occur after initiation of ULORIC due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. Flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended upon initiation of ULORIC. Prophylactic therapy may be beneficial for up to six months [see *Clinical Studies (14.1)*].

If a gout flare occurs during ULORIC treatment, ULORIC need not be discontinued. The gout flare should be managed concurrently, as appropriate for the individual patient [see *Warnings and Precautions (5.1)*].

3 DOSAGE FORMS AND STRENGTHS

- 40 mg tablets, light green to green, round, debossed with “TAP” and “40”
- 80 mg tablets, light green to green, teardrop shaped, debossed with “TAP” and “80”

4 CONTRAINDICATIONS

ULORIC is contraindicated in patients being treated with azathioprine or mercaptopurine [see *Drug Interactions* (7)].

5 WARNINGS AND PRECAUTIONS

5.1 Gout Flare

After initiation of ULORIC, an increase in gout flares is frequently observed. This increase is due to reduction in serum uric acid levels, resulting in mobilization of urate from tissue deposits.

In order to prevent gout flares when ULORIC is initiated, concurrent prophylactic treatment with an NSAID or colchicine is recommended [see *Dosage and Administration* (2.4)].

5.2 Cardiovascular Events

In the randomized controlled studies, there was a higher rate of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) in patients treated with ULORIC (0.74 per 100 P-Y [95% Confidence Interval (CI) 0.36-1.37]) than allopurinol (0.60 per 100 P-Y [95% CI 0.16-1.53]) [see *Adverse Reactions* (6.1)]. A causal relationship with ULORIC has not been established. Monitor for signs and symptoms of myocardial infarction (MI) and stroke.

5.3 Hepatic Effects

There have been postmarketing reports of fatal and non-fatal hepatic failure in patients taking ULORIC, although the reports contain insufficient information necessary to establish the probable cause. During randomized controlled studies, transaminase elevations greater than three times the upper limit of normal (ULN) were observed (AST: 2%, 2%, and ALT: 3%, 2% in ULORIC and allopurinol-treated patients, respectively). No dose-effect relationship for these transaminase elevations was noted [see *Clinical Pharmacology* (12.3)].

Obtain a liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) as a baseline before initiating ULORIC.

Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. In this clinical context, if the patient is found to have abnormal liver tests (ALT greater than three times the upper limit of the reference range), ULORIC treatment should be interrupted and investigation done to establish the probable cause. ULORIC should not be restarted in these patients without another explanation for the liver test abnormalities.

Patients who have serum ALT greater than three times the reference range with serum total bilirubin greater than two times the reference range without alternative etiologies are at risk for severe drug-induced liver injury and should not be restarted on ULORIC. For patients with lesser elevations of serum ALT or bilirubin and with an alternate probable cause, treatment with ULORIC can be used with caution.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

A total of 2757 patients with hyperuricemia and gout were treated with ULORIC 40 mg or 80 mg daily in clinical studies. For ULORIC 40 mg, 559 patients were treated for ≥6 months. For ULORIC 80 mg, 1377 patients were treated for ≥6 months, 674 patients were treated for ≥1 year and 515 patients were treated for ≥2 years.

Most Common Adverse Reactions

In three randomized, controlled clinical studies (Studies 1, 2 and 3), which were six to 12 months in duration, the following adverse reactions were reported by the treating physician as related to study drug. Table 1 summarizes adverse reactions reported at a rate of at least 1% in ULORIC treatment groups and at least 0.5% greater than placebo.

Table 1: Adverse Reactions Occurring in ≥1% of Patients Treated with ULORIC and at Least 0.5% Greater than Seen in Patients Receiving Placebo in Controlled Studies

Adverse Reactions	Placebo	ULORIC		allopurinol*
	(N=134)	40 mg daily (N=757)	80 mg daily (N=1279)	(N=1277)
Liver Function Abnormalities	0.7%	6.6%	4.6%	4.2%
Nausea	0.7%	1.1%	1.3%	0.8%
Arthralgia	0%	1.1%	0.7%	0.7%
Rash	0.7%	0.5%	1.6%	1.6%

*Of the patients who received allopurinol, 10 received 100 mg, 145 received 200 mg, and 1122 received 300 mg, based on level of renal impairment.

The most common adverse reaction leading to discontinuation from therapy was liver function abnormalities in 1.8% of ULORIC 40 mg, 1.2% of ULORIC 80 mg, and in 0.9% of patients treated with allopurinol.

In addition to the adverse reactions presented in Table 1, dizziness was reported in more than 1% of patients treated with ULORIC although not at a rate more than 0.5% greater than placebo.

Less Common Adverse Reactions

In Phase 2 and 3 clinical studies the following adverse reactions occurred in less than 1% of patients and in more than one subject treated with doses ranging from 40 mg to 240 mg of ULORIC. This list also includes adverse reactions (less than 1% of patients) associated with organ systems from Warnings and Precautions.

Blood and Lymphatic System Disorders: anemia, idiopathic thrombocytopenic purpura, leukocytosis/leukopenia, neutropenia, pancytopenia, splenomegaly, thrombocytopenia.

Cardiac Disorders: angina pectoris, atrial fibrillation/flutter, cardiac murmur, ECG abnormal, palpitations, sinus bradycardia, tachycardia.

Ear and Labyrinth Disorders: deafness, tinnitus, vertigo.

Eye Disorders: vision blurred.

Gastrointestinal Disorders: abdominal distention, abdominal pain, constipation, dry mouth, dyspepsia, flatulence, frequent stools, gastritis, gastroesophageal reflux disease, gastrointestinal discomfort, gingival pain, haematemesis, hyperchlorhydria, hematochezia, mouth ulceration, pancreatitis, peptic ulcer, vomiting.

General Disorders and Administration Site Conditions: asthenia, chest pain/discomfort, edema, fatigue, feeling abnormal, gait disturbance, influenza-like symptoms, mass, pain, thirst.

Hepatobiliary Disorders: cholelithiasis/cholecystitis, hepatic steatosis, hepatitis, hepatomegaly.

Immune System Disorder: hypersensitivity.

Infections and Infestations: herpes zoster.

Procedural Complications: contusion.

Metabolism and Nutrition Disorders: anorexia, appetite decreased/increased, dehydration, diabetes mellitus, hypercholesterolemia, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypokalemia, weight decreased/increased.

Musculoskeletal and Connective Tissue Disorders: arthritis, joint stiffness, joint swelling, muscle spasms/twitching/tightness/weakness, musculoskeletal pain/stiffness, myalgia.

Nervous System Disorders: altered taste, balance disorder, cerebrovascular accident, Guillain-Barré syndrome, headache, hemiparesis, hypoesthesia, hyposmia, lacunar infarction, lethargy, mental impairment, migraine, paresthesia, somnolence, transient ischemic attack, tremor.

Psychiatric Disorders: agitation, anxiety, depression, insomnia, irritability, libido decreased, nervousness, panic attack, personality change.

Renal and Urinary Disorders: hematuria, nephrolithiasis, pollakiuria, proteinuria, renal failure, renal insufficiency, urgency, incontinence.

Reproductive System and Breast Changes: breast pain, erectile dysfunction, gynecomastia.

Respiratory, Thoracic and Mediastinal Disorders: bronchitis, cough, dyspnea, epistaxis, nasal dryness, paranasal sinus hypersecretion, pharyngeal edema, respiratory tract congestion, sneezing, throat irritation, upper respiratory tract infection.

Skin and Subcutaneous Tissue Disorders: alopecia, angio-edema, dermatitis, dermographism, ecchymosis, eczema, hair color changes, hair growth abnormal, hyperhidrosis, peeling skin, petechiae, photosensitivity, pruritus, purpura, skin discoloration/alteration/pigmentation, skin lesion, skin odor abnormal, urticaria.

Vascular Disorders: flushing, hot flush, hypertension, hypotension.

Laboratory Parameters: activated partial thromboplastin time prolonged, creatine increased, bicarbonate decreased, sodium increased, EEG abnormal, glucose increased, cholesterol increased, triglycerides increased, amylase increased, potassium increased, TSH increased, platelet count decreased, hematocrit decreased, hemoglobin decreased, MCV increased, RBC decreased, creatinine increased, blood urea increased, BUN/creatinine ratio increased, creatine phosphokinase (CPK) increased, alkaline phosphatase increased, LDH increased, PSA increased, urine output increased/decreased, lymphocyte count decreased, neutrophil count decreased, WBC increased/decreased, coagulation test abnormal, low density lipoprotein (LDL) increased, prothrombin time prolonged, urinary casts, urine positive for white blood cells and protein.

Cardiovascular Safety

Cardiovascular events and deaths were adjudicated to one of the pre-defined endpoints from the Anti-Platelet Trialists' Collaborations (APTC) (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) in the randomized controlled and long-term extension studies. In the Phase 3 randomized controlled studies, the incidences of adjudicated APTC events per 100 patient-years of

exposure were: Placebo 0 (95% CI 0.00-6.16), ULORIC 40 mg 0 (95% CI 0.00-1.08), ULORIC 80 mg 1.09 (95% CI 0.44-2.24), and allopurinol 0.60 (95% CI 0.16-1.53).

In the long-term extension studies, the incidences of adjudicated APTC events were: ULORIC 80 mg 0.97 (95% CI 0.57-1.56), and allopurinol 0.58 (95% CI 0.02-3.24).

Overall, a higher rate of APTC events was observed in ULORIC than in patients treated with allopurinol. A causal relationship with ULORIC has not been established. Monitor for signs and symptoms of MI and stroke.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of ULORIC. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hepatobiliary Disorders: hepatic failure (some fatal), jaundice, serious cases of abnormal liver function test results, liver disorder.

Immune System Disorders: anaphylaxis, anaphylactic reaction.

Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis.

Psychiatric Disorders: psychotic behavior including aggressive thoughts.

Renal and Urinary Disorders: tubulointerstitial nephritis.

Skin and Subcutaneous Tissue Disorders: generalized rash, Stevens Johnson Syndrome, hypersensitivity skin reactions.

7 DRUG INTERACTIONS

7.1 Xanthine Oxidase Substrate Drugs

ULORIC is an XO inhibitor. Based on a drug interaction study in healthy patients, febuxostat altered the metabolism of theophylline (a substrate of XO) in humans [see *Clinical Pharmacology (12.3)*]. Therefore, use with caution when coadministering ULORIC with theophylline.

Drug interaction studies of ULORIC with other drugs that are metabolized by XO (e.g., mercaptopurine and azathioprine) have not been conducted. Inhibition of XO by ULORIC may cause increased plasma concentrations of these drugs leading to toxicity [see *Clinical Pharmacology (12.3)*]. ULORIC is contraindicated in patients being treated with azathioprine or mercaptopurine [see *Contraindications (4)*].

7.2 Cytotoxic Chemotherapy Drugs

Drug interaction studies of ULORIC with cytotoxic chemotherapy have not been conducted. No data are available regarding the safety of ULORIC during cytotoxic chemotherapy.

7.3 *In Vivo* Drug Interaction Studies

Based on drug interaction studies in healthy patients, ULORIC does not have clinically significant interactions with colchicine, naproxen, indomethacin, hydrochlorothiazide, warfarin or desipramine [see *Clinical Pharmacology (12.3)*]. Therefore, ULORIC may be used concomitantly with these medications.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited available data with ULORIC use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes. No adverse developmental effects were observed in embryo-fetal development studies with oral administration of febuxostat to pregnant rats and rabbits during organogenesis at doses that produced maternal exposures up to 40 and 51 times, respectively, the exposure at the maximum recommended human dose (MRHD). No adverse developmental effects were observed in a pre- and postnatal development study with administration of febuxostat to pregnant rats from organogenesis through lactation at an exposure approximately 11 times the MRHD (see *Data*).

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

Data

Animal Data

In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation Days 7 – 17, febuxostat was not teratogenic and did not affect fetal development or survival at exposures up to approximately 40 times the MRHD (on an AUC basis at maternal oral doses up to 48 mg/kg/day). In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation Days 6 – 18, febuxostat was not teratogenic and did not affect fetal development at exposures up to approximately 51 times the MRHD (on an AUC basis at maternal oral doses up to 48 mg/kg/day).

In a pre- and postnatal development study in pregnant female rats dosed orally from gestation Day 7 through lactation Day 20, febuxostat had no effects on delivery or growth and development of offspring at a dose approximately 11 times the MRHD (on an AUC basis at a maternal oral dose of 12 mg/kg/day). However, increased neonatal mortality and a reduction in neonatal body weight gain were observed in the presence of maternal toxicity at a dose approximately 40 times the MRHD (on an AUC basis at a maternal oral dose of 48 mg/kg/day).

Febuxostat crossed the placental barrier following oral administration to pregnant rats and was detected in fetal tissues.

8.2 Lactation

Risk Summary

There are no data on the presence of febuxostat in human milk, the effects on the breastfed infant, or the effects on milk production. Febuxostat is present in rat milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ULORIC and any potential adverse effects on the breastfed child from ULORIC or from the underlying maternal condition.

Data

Animal Data

Orally administered febuxostat was detected in the milk of lactating rats at up to approximately 7 times the plasma concentration.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients under 18 years of age have not been established.

8.5 Geriatric Use

No dose adjustment is necessary in elderly patients. Of the total number of patients in clinical studies of ULORIC, 16% were 65 and over, while 4% were 75 and over. Comparing patients in different age groups, no clinically significant differences in safety or effectiveness were observed but greater sensitivity of some older individuals cannot be ruled out. The C_{max} and AUC_{24} of febuxostat following multiple oral doses of ULORIC in geriatric patients (≥ 65 years) were similar to those in younger patients (18 to 40 years) [see *Clinical Pharmacology* (12.3)].

8.6 Renal Impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment (Cl_{cr} 30 to 89 mL/min). The recommended starting dose of ULORIC is 40 mg once daily. For patients who do not achieve a sUA less than 6 mg/dL after two weeks with 40 mg, ULORIC 80 mg is recommended. For patients with severe renal impairment (Cl_{cr} 15 to 29 mL/min), the dose of ULORIC is limited to 40 mg once daily [see *Dosage and Administration* (2.2) and *Clinical Pharmacology* (12.3)].

8.7 Hepatic Impairment

No dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh Class A or B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C); therefore, caution should be exercised in these patients [see *Clinical Pharmacology* (12.3)].

8.8 Secondary Hyperuricemia

No studies have been conducted in patients with secondary hyperuricemia (including organ transplant recipients); ULORIC is not recommended for use in patients whom the rate of urate formation is greatly increased (e.g., malignant disease and its treatment, Lesch-Nyhan syndrome). The concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract.

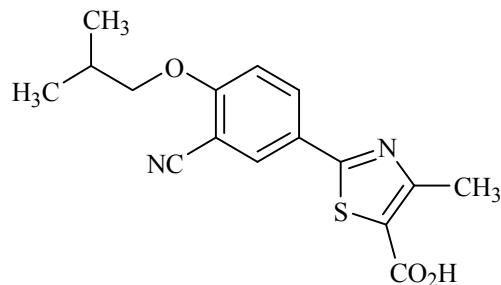
10 OVERDOSAGE

ULORIC was studied in healthy patients in doses up to 300 mg daily for seven days without evidence of dose-limiting toxicities. No overdose of ULORIC was reported in clinical studies. Patients should be managed by symptomatic and supportive care should there be an overdose.

11 DESCRIPTION

ULORIC (febuxostat) is a xanthine oxidase inhibitor. The active ingredient in ULORIC is 2-[3-cyano-4-(2-methylpropoxy) phenyl]-4-methylthiazole-5-carboxylic acid, with a molecular weight of 316.38. The empirical formula is $C_{16}H_{16}N_2O_3S$.

The chemical structure is:



Febuxostat is a non-hygroscopic, white crystalline powder that is freely soluble in dimethylformamide; soluble in dimethylsulfoxide; sparingly soluble in ethanol; slightly soluble in methanol and acetonitrile; and practically insoluble in water. The melting range is 205°C to 208°C.

ULORIC tablets for oral use contain the active ingredient, febuxostat, and are available in two dosage strengths, 40 mg and 80 mg. Inactive ingredients include lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, sodium croscarmellose, silicon dioxide and magnesium stearate. ULORIC tablets are coated with Opadry II, green.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ULORIC, a xanthine oxidase inhibitor, achieves its therapeutic effect by decreasing serum uric acid. ULORIC is not expected to inhibit other enzymes involved in purine and pyrimidine synthesis and metabolism at therapeutic concentrations.

12.2 Pharmacodynamics

Effect on Uric Acid and Xanthine Concentrations

In healthy patients, ULORIC resulted in a dose dependent decrease in 24 hour mean serum uric acid concentrations and an increase in 24 hour mean serum xanthine concentrations. In addition, there was a decrease in the total daily urinary uric acid excretion. Also, there was an increase in total daily urinary xanthine excretion. Percent reduction in 24 hour mean serum uric acid concentrations was between 40% and 55% at the exposure levels of 40 mg and 80 mg daily doses.

Effect on Cardiac Repolarization

The effect of ULORIC on cardiac repolarization as assessed by the QTc interval was evaluated in normal healthy patients and in patients with gout. ULORIC in doses up to 300 mg daily, at steady-state, did not demonstrate an effect on the QTc interval.

12.3 Pharmacokinetics

In healthy patients, maximum plasma concentrations (C_{\max}) and AUC of febuxostat increased in a dose proportional manner following single and multiple doses of 10 mg to 120 mg. There is no accumulation when therapeutic doses are administered every 24 hours. Febuxostat has an apparent mean terminal elimination half-life ($t_{1/2}$) of approximately 5 to 8 hours. Febuxostat pharmacokinetic parameters for patients with hyperuricemia and gout estimated by population pharmacokinetic analyses were similar to those estimated in healthy patients.

Absorption

The absorption of radiolabeled febuxostat following oral dose administration was estimated to be at least 49% (based on total radioactivity recovered in urine). Maximum plasma concentrations of febuxostat occurred between 1 and 1.5 hours post-dose. After multiple oral 40 mg and 80 mg once daily doses, C_{\max} is approximately $1.6 \pm 0.6 \text{ mcg/mL}$ ($N=30$), and $2.6 \pm 1.7 \text{ mcg/mL}$ ($N=227$), respectively. Absolute bioavailability of the febuxostat tablet has not been studied.

Following multiple 80 mg once daily doses with a high fat meal, there was a 49% decrease in C_{max} and an 18% decrease in AUC, respectively. However, no clinically significant change in the percent decrease in serum uric acid concentration was observed (58% fed vs. 51% fasting). Thus, ULORIC may be taken without regard to food.

Concomitant ingestion of an antacid containing magnesium hydroxide and aluminum hydroxide with an 80 mg single dose of ULORIC has been shown to delay absorption of febuxostat (approximately one hour) and to cause a 31% decrease in C_{max} and a 15% decrease in AUC ∞ . As AUC rather than C_{max} was related to drug effect, change observed in AUC was not considered clinically significant. Therefore, ULORIC may be taken without regard to antacid use.

Distribution

The mean apparent steady state volume of distribution (V_{ss}/F) of febuxostat was approximately 50 L (CV ~40%). The plasma protein binding of febuxostat is approximately 99.2% (primarily to albumin), and is constant over the concentration range achieved with 40 mg and 80 mg doses.

Metabolism

Febuxostat is extensively metabolized by both conjugation via uridine diphosphate glucuronosyltransferase (UGT) enzymes including UGT1A1, UGT1A3, UGT1A9, and UGT2B7 and oxidation via cytochrome P450 (CYP) enzymes including CYP1A2, 2C8 and 2C9 and non-P450 enzymes. The relative contribution of each enzyme isoform in the metabolism of febuxostat is not clear. The oxidation of the isobutyl side chain leads to the formation of four pharmacologically active hydroxy metabolites, all of which occur in plasma of humans at a much lower extent than febuxostat.

In urine and feces, acyl glucuronide metabolites of febuxostat (~35% of the dose), and oxidative metabolites, 67M-1 (~10% of the dose), 67M-2 (~11% of the dose), and 67M-4, a secondary metabolite from 67M-1 (~14% of the dose), appeared to be the major metabolites of febuxostat *in vivo*.

Elimination

Febuxostat is eliminated by both hepatic and renal pathways. Following an 80 mg oral dose of ^{14}C -labeled febuxostat, approximately 49% of the dose was recovered in the urine as unchanged febuxostat (3%), the acyl glucuronide of the drug (30%), its known oxidative metabolites and their conjugates (13%), and other unknown metabolites (3%). In addition to the urinary excretion, approximately 45% of the dose was recovered in the feces as the unchanged febuxostat (12%), the acyl glucuronide of the drug (1%), its known oxidative metabolites and their conjugates (25%), and other unknown metabolites (7%).

The apparent mean terminal elimination half-life ($t_{1/2}$) of febuxostat was approximately 5 to 8 hours.

Special Populations

Pediatric Use

The pharmacokinetics of ULORIC in patients under the age of 18 years have not been studied.

Geriatric Use

The C_{max} and AUC of febuxostat and its metabolites following multiple oral doses of ULORIC in geriatric patients (≥ 65 years) were similar to those in younger patients (18 to 40 years). In addition, the percent decrease in serum uric acid concentration was similar between elderly and younger patients. No dose adjustment is necessary in geriatric patients [see *Use in Specific Populations (8.5)*].

Renal Impairment

In a dedicated phase I pharmacokinetics study, following multiple 80 mg doses of ULORIC in healthy patients with mild (Cl_{cr} 50 to 80 mL/min), moderate (Cl_{cr} 30 to 49 mL/min) or severe renal impairment (Cl_{cr} 10 to 29 mL/min), the C_{max} of febuxostat did not change relative to patients with normal renal function (Cl_{cr} greater than 80 mL/min). AUC and half-life of febuxostat increased in patients with renal impairment in comparison to patients with normal renal function, but values were similar among three renal impairment groups. Mean febuxostat AUC values were up to 1.8 times higher in patients with renal impairment compared to those with normal renal function. Mean C_{max} and AUC values for three active metabolites increased up to 2- and 4-fold, respectively. However, the percent decrease in serum uric acid concentration for patients with renal impairment was comparable to those with normal renal function (58% in normal renal function group and 55% in the severe renal function group).

Based on population pharmacokinetic analysis, following multiple 40 mg or 80 mg doses of ULORIC, the mean oral clearance (CL/F) values of febuxostat in patients with gout and mild (n=334), moderate (n=232) or severe (n=34) renal impairment were decreased by 14%, 34%, and 48%, respectively, compared to patients with normal (n=89) renal function. The corresponding median AUC values of febuxostat at steady-state in patients with renal impairment were increased by 18%, 49%, and 96% after 40 mg dose, and 7%, 45% and 98% after 80 mg dose, respectively, compared to patients with normal renal function.

ULORIC has not been studied in end stage renal impairment patients who are on dialysis.

Hepatic Impairment

Following multiple 80 mg doses of ULORIC in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, an average of 20% to 30% increase was observed for both C_{max} and AUC_{24} (total and unbound) in hepatic impairment groups compared to patients with normal hepatic function. In addition, the percent decrease in serum uric acid concentration was comparable between different hepatic groups (62% in healthy group, 49% in mild hepatic impairment group, and 48% in moderate hepatic impairment group). No dose adjustment is necessary in patients with mild or moderate hepatic impairment. No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C); caution should be exercised in those patients [see *Use in Specific Populations* (8.7)].

Gender

Following multiple oral doses of ULORIC, the C_{max} and AUC_{24} of febuxostat were 30% and 14% higher in females than in males, respectively. However, weight-corrected C_{max} and AUC were similar between the genders. In addition, the percent decrease in serum uric acid concentrations was similar between genders. No dose adjustment is necessary based on gender.

Race

No specific pharmacokinetic study was conducted to investigate the effects of race.

Drug-Drug Interactions

Effect of ULORIC on Other Drugs

Xanthine Oxidase Substrate Drugs-Azathioprine, Mercaptopurine, and Theophylline

Febuxostat is an XO inhibitor. A drug-drug interaction study evaluating the effect of ULORIC upon the pharmacokinetics of theophylline (an XO substrate) in healthy patients showed that coadministration of febuxostat with theophylline resulted in an approximately 400-fold increase in the amount of 1-methylxanthine, one of the major metabolites of theophylline, excreted in the urine. Since the long-term safety of exposure to 1-methylxanthine in humans is unknown, use with caution when coadministering febuxostat with theophylline.

Drug interaction studies of ULORIC with other drugs that are metabolized by XO (e.g., mercaptopurine and azathioprine) have not been conducted. Inhibition of XO by ULORIC may cause increased plasma concentrations of these drugs leading to toxicity. ULORIC is contraindicated in patients being treated with azathioprine or mercaptopurine [see *Contraindications (4)* and *Drug Interactions (7)*].

Azathioprine and mercaptopurine undergo metabolism via three major metabolic pathways, one of which is mediated by XO. Although ULORIC drug interaction studies with azathioprine and mercaptopurine have not been conducted, concomitant administration of allopurinol [a xanthine oxidase inhibitor] with azathioprine or mercaptopurine has been reported to substantially increase plasma concentrations of these drugs. Because ULORIC is a xanthine oxidase inhibitor, it could inhibit the XO-mediated metabolism of azathioprine and mercaptopurine leading to increased plasma concentrations of azathioprine or mercaptopurine that could result in severe toxicity.

P450 Substrate Drugs

In vitro studies have shown that febuxostat does not inhibit P450 enzymes CYP1A2, 2C9, 2C19, 2D6, or 3A4 and it also does not induce CYP1A2, 2B6, 2C9, 2C19, or 3A4 at clinically relevant concentrations. As such, pharmacokinetic interactions between ULORIC and drugs metabolized by these CYP enzymes are unlikely.

Effect of Other Drugs on ULORIC

Febuxostat is metabolized by conjugation and oxidation via multiple metabolizing enzymes. The relative contribution of each enzyme isoform is not clear. Drug interactions between ULORIC and a drug that inhibits or induces one particular enzyme isoform is in general not expected.

In Vivo Drug Interaction Studies

Theophylline

No dose adjustment is necessary for theophylline when coadministered with ULORIC. Administration of ULORIC (80 mg once daily) with theophylline resulted in an increase of 6% in C_{max} and 6.5% in AUC of theophylline. These changes were not considered statistically significant. However, the study also showed an approximately 400-fold increase in the amount of 1-methylxanthine (one of the major theophylline metabolites) excreted in urine as a result of XO inhibition by ULORIC. The safety of long-term exposure to 1-methylxanthine has not been evaluated. This should be taken into consideration when deciding to coadminister ULORIC and theophylline.

Colchicine

No dose adjustment is necessary for either ULORIC or colchicine when the two drugs are coadministered. Administration of ULORIC (40 mg once daily) with colchicine (0.6 mg twice daily) resulted in an increase of 12% in C_{max} and 7% in AUC_{24} of febuxostat. In addition, administration of colchicine (0.6 mg twice daily) with ULORIC (120 mg daily) resulted in a less than 11% change in C_{max} or AUC of colchicine for both AM and PM doses. These changes were not considered clinically significant.

Naproxen

No dose adjustment is necessary for ULORIC or naproxen when the two drugs are coadministered. Administration of ULORIC (80 mg once daily) with naproxen (500 mg twice daily) resulted in a 28% increase in C_{max} and a 40% increase in AUC of febuxostat. The increases were not considered clinically significant. In addition, there were no significant changes in the C_{max} or AUC of naproxen (less than 2%).

Indomethacin

No dose adjustment is necessary for either ULORIC or indomethacin when these two drugs are coadministered. Administration of ULORIC (80 mg once daily) with indomethacin (50 mg twice daily) did not result in any significant changes in C_{max} or AUC of febuxostat or indomethacin (less than 7%).

Hydrochlorothiazide

No dose adjustment is necessary for ULORIC when coadministered with hydrochlorothiazide. Administration of ULORIC (80 mg) with hydrochlorothiazide (50 mg) did not result in any clinically significant changes in C_{max} or AUC of febuxostat (less than 4%), and serum uric acid concentrations were not substantially affected.

Warfarin

No dose adjustment is necessary for warfarin when coadministered with ULORIC. Administration of ULORIC (80 mg once daily) with warfarin had no effect on the pharmacokinetics of warfarin in healthy patients. INR and Factor VII activity were also not affected by the coadministration of ULORIC.

Desipramine

Coadministration of drugs that are CYP2D6 substrates (such as desipramine) with ULORIC are not expected to require dose adjustment. Febuxostat was shown to be a weak inhibitor of CYP2D6 *in vitro* and *in vivo*. Administration of ULORIC (120 mg once daily) with desipramine (25 mg) resulted in an increase in C_{max} (16%) and AUC (22%) of desipramine, which was associated with a 17% decrease in the 2-hydroxydesipramine to desipramine metabolic ratio (based on AUC).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies were conducted in F344 rats and B6C3F1 mice. Increased transitional cell papilloma and carcinoma of the urinary bladder was observed at 24 mg/kg (25 times the MRHD on an AUC basis and 18.75 mg/kg (12.5 times the MRHD on an AUC basis) in male rats and female mice, respectively. The urinary bladder neoplasms were secondary to calculus formation in the kidney and urinary bladder.

Febuxostat showed a positive clastogenic response in a chromosomal aberration assay in a Chinese hamster lung fibroblast cell line with and without metabolic activation *in vitro*. Febuxostat was negative in the following genotoxicity assays: the *in vitro* Ames assay, *in vitro* chromosomal aberration assay in human peripheral lymphocytes, the L5178Y mouse lymphoma cell line assay, the *in vivo* mouse micronucleus assay, and the rat unscheduled DNA synthesis assay.

Fertility and reproductive performance were unaffected in male or female rats that received febuxostat at oral doses up to 48 mg/kg/day (approximately 31 and 40 times the MRHD on an AUC basis in males and females respectively).

13.2 Animal Toxicology

A 12 month toxicity study in beagle dogs showed deposition of xanthine crystals and calculi in kidneys at 15 mg/kg (approximately 4 times the MRHD on an AUC basis). A similar effect of calculus formation was noted in rats in a six-month study due to deposition of xanthine crystals at 48 mg/kg (approximately 31 and 40 times the MRHD on an AUC basis in males and females respectively).

14 CLINICAL STUDIES

A serum uric acid level of less than 6 mg/dL is the goal of anti-hyperuricemic therapy and has been established as appropriate for the treatment of gout.

14.1 Management of Hyperuricemia in Gout

The efficacy of ULORIC was demonstrated in three randomized, double-blind, controlled trials in patients with hyperuricemia and gout. Hyperuricemia was defined as a baseline serum uric acid level ≥ 8 mg/dL.

Study 1 randomized patients to: ULORIC 40 mg daily, ULORIC 80 mg daily, or allopurinol (300 mg daily for patients with estimated creatinine clearance (Cl_{cr}) ≥ 60 mL/min or 200 mg daily for patients with estimated $\text{Cl}_{\text{cr}} \geq 30$ mL/min and ≤ 59 mL/min). The duration of Study 1 was six months.

Study 2 randomized patients to: placebo, ULORIC 80 mg daily, ULORIC 120 mg daily, ULORIC 240 mg daily or allopurinol (300 mg daily for patients with a baseline serum creatinine ≤ 1.5 mg/dL or 100 mg daily for patients with a baseline serum creatinine greater than 1.5 mg/dL and ≤ 2 mg/dL). The duration of Study 2 was six months.

Study 3, a 1 year study, randomized patients to: ULORIC 80 mg daily, ULORIC 120 mg daily, or allopurinol 300 mg daily. Patients who completed Study 2 and Study 3 were eligible to enroll in a Phase 3 long-term extension study in which patients received treatment with ULORIC for over three years.

In all three studies, patients received naproxen 250 mg twice daily or colchicine 0.6 mg once or twice daily for gout flare prophylaxis. In Study 1 the duration of prophylaxis was six months; in Study 2 and Study 3 the duration of prophylaxis was eight weeks.

The efficacy of ULORIC was also evaluated in a four week dose ranging study which randomized patients to: placebo, ULORIC 40 mg daily, ULORIC 80 mg daily, or ULORIC 120 mg daily. Patients who completed this study were eligible to enroll in a long-term extension study in which patients received treatment with ULORIC for up to five years.

Patients in these studies were representative of the patient population for which ULORIC use is intended. Table 2 summarizes the demographics and baseline characteristics for the patients enrolled in the studies.

Table 2: Patient Demographics and Baseline Characteristics in Study 1, Study 2 and Study 3

Male	95%
Race: Caucasian	80%
African American	10%
Ethnicity: Hispanic or Latino	7%
Alcohol User	67%
Mild to Moderate Renal Insufficiency (percent with estimated Cl _{cr} less than 90 mL/min)	59%
History of Hypertension	49%
History of Hyperlipidemia	38%
BMI ≥30 kg/m ²	63%
Mean BMI	33 kg/m ²
Baseline sUA ≥10 mg/dL	36%
Mean baseline sUA	9.7 mg/dL
Experienced a gout flare in previous year	85%

Serum Uric Acid Level less than 6 mg/dL at Final Visit

ULORIC 80 mg was superior to allopurinol in lowering serum uric acid to less than 6 mg/dL at the final visit. ULORIC 40 mg daily, although not superior to allopurinol, was effective in lowering serum uric acid to less than 6 mg/dL at the final visit (*Table 3*).

Table 3: Proportion of Patients with Serum Uric Acid Levels less than 6 mg/dL at Final Visit

Study*	ULORIC 40 mg daily	ULORIC 80 mg daily	allopurinol	Placebo	Difference in Proportion (95% CI)	
					ULORIC 40 mg vs allopurinol	ULORIC 80 mg vs allopurinol
Study 1 (6 months) (N=2268)	45%	67%	42%		3% (-2%, 8%)	25% (20%, 30%)
Study 2 (6 months) (N=643)		72%	39%	1%		33% (26%, 42%)
Study 3 (12 months) (N=491)		74%	36%			38% (30%, 46%)

*Randomization was balanced between treatment groups, except in Study 2 in which twice as many patients were randomized to each of the active treatment groups compared to placebo.

In 76% of ULORIC 80 mg patients, reduction in serum uric acid levels to less than 6 mg/dL was noted by the Week 2 visit. Average serum uric acid levels were maintained at 6 mg/dL or below throughout treatment in 83% of these patients.

In all treatment groups, fewer patients with higher baseline serum urate levels (≥ 10 mg/dL) and/or tophi achieved the goal of lowering serum uric acid to less than 6 mg/dL at the final visit; however, a higher proportion achieved a serum uric acid less than 6 mg/dL with ULORIC 80 mg than with ULORIC 40 mg or allopurinol.

Study 1 evaluated efficacy in patients with mild to moderate renal impairment (i.e., baseline estimated Cl_{cr} less than 90 mL/min). The results in this sub-group of patients are shown in Table 4.

			Difference in Proportion (95% CI)	
ULORIC 40 mg daily (N=479)	ULORIC 80 mg daily (N=503)	allopurinol* 300 mg daily (N=501)	ULORIC 40 mg vs allopurinol	ULORIC 80 mg vs allopurinol
50%	72%	42%	7% (1%, 14%)	29% (23%, 35%)

*Allopurinol patients (n=145) with estimated $\text{Cl}_{\text{cr}} \geq 30$ mL/min and $\text{Cl}_{\text{cr}} \leq 59$ mL/min were dosed at 200 mg daily.

16 HOW SUPPLIED/STORAGE AND HANDLING

ULORIC 40 mg tablets are light green to green in color, round, debossed with "TAP" on one side and "40" on the other side and supplied as:

NDC Number	Size
64764-918-11	Hospital Unit Dose Pack of 100 Tablets
64764-918-30	Bottle of 30 Tablets
64764-918-90	Bottle of 90 Tablets
64764-918-18	Bottle of 500 Tablets

ULORIC 80 mg tablets are light green to green in color, teardrop shaped, debossed with "TAP" on one side and "80" on the other side and supplied as:

NDC Number	Size
64764-677-11	Hospital Unit Dose Pack of 100 Tablets
64764-677-30	Bottle of 30 Tablets
64764-677-13	Bottle of 100 Tablets
64764-677-19	Bottle of 1000 Tablets

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information). Patients should be advised of the potential benefits and risks of ULORIC. Patients should be informed about the potential for gout flares, elevated liver enzymes and adverse cardiovascular events after initiation of ULORIC therapy.

Concomitant prophylaxis with an NSAID or colchicine for gout flares should be considered.

Patients should be instructed to inform their healthcare professional if they develop a rash, chest pain, shortness of breath or neurologic symptoms suggesting a stroke. Patients should be instructed to inform their healthcare professional of any other medications they are currently taking with ULORIC, including over-the-counter medications.

Patient Information

ULORIC (ü-lor-ik)

(febuxostat) tablets

Read the Patient Information that comes with ULORIC before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is ULORIC?

ULORIC is a prescription medicine called a xanthine oxidase (XO) inhibitor, used to lower blood uric acid levels in adults with gout.

It is not known if ULORIC is safe and effective in children under 18 years of age.

Who should not take ULORIC?

Do not take ULORIC if you:

- take azathioprine (Azasan, Imuran)
- take mercaptopurine (Purinethol)

It is not known if ULORIC is safe and effective in children under 18 years of age.

What should I tell my healthcare provider before taking ULORIC?

Before taking ULORIC tell your healthcare provider about all of your medical conditions, including if you:

- have liver or kidney problems
- have a history of heart disease or stroke
- are pregnant or plan to become pregnant. It is not known if ULORIC will harm your unborn baby. Talk with your healthcare provider if you are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. It is not known if ULORIC passes into your breast milk. You and your healthcare provider should decide if you should take ULORIC while breastfeeding.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. ULORIC may affect the way other medicines work, and other medicines may affect how ULORIC works.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take ULORIC?

- Take ULORIC exactly as your healthcare provider tells you to take it.
- ULORIC can be taken with or without food.
- ULORIC can be taken with antacids.
- Your gout may flare up when you start taking ULORIC, do not stop taking your ULORIC even if you have a flare. Your healthcare provider may give you other medicines to help prevent your gout flares.
- Your healthcare provider may do certain tests while you take ULORIC.

What are the possible side effects of ULORIC?

Heart problems. A small number of heart attacks, strokes and heart-related deaths were seen in clinical studies. It is not certain that ULORIC caused these events.

The most common side effects of ULORIC include:

- liver problems
- nausea
- gout flares
- joint pain
- rash

Tell your healthcare provider if you develop a rash, have any side effect that bothers you, or that does not go away. These are not all of the possible side effects of ULORIC. For more information, ask your healthcare provider or pharmacist.

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

How should I store ULORIC?

Store ULORIC between 59°F and 86°F (15°C to 30°C).

Keep ULORIC out of the light.

Keep ULORIC and all medicines out of the reach of children.

General information about the safe and effective use of ULORIC.

Medicines are sometimes prescribed for purposes other than those listed in a patient information leaflet. Do not use ULORIC for a condition for which it was not prescribed. Do not give ULORIC to other people, even if they have the same symptoms that you have. It may harm them.

This patient information leaflet summarizes the most important information about ULORIC. If you would like more information about ULORIC talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ULORIC that is written for health professionals. For more information go to www.uloric.com, or call 1-877-825-3327.

What are the ingredients in ULORIC?

Active Ingredient: febuxostat

Inactive ingredients include: lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, sodium croscarmellose, silicon dioxide, magnesium stearate, and Opadry II, green

Distributed by:

Takeda Pharmaceuticals America, Inc.

Deerfield, IL 60015

Revised: March 2013

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ULR015 R5

EXHIBIT H

HIGHLIGHTS OF PRESCRIBING INFORMATION

These HIGHLIGHTS do not include all the information needed to use ULORIC safely and effectively. See full prescribing information for ULORIC.

ULORIC (febuxostat) tablet for oral use

Initial U.S. Approval: 2009

RECENT MAJOR CHANGES

Dosage and Administration

Special Populations (2.2)	8/2017
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Warnings and Precautions

Serious Skin Reactions (5.4)	2/2018
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INDICATIONS AND USAGE

ULORIC is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in patients with gout. (1)

ULORIC is not recommended for the treatment of asymptomatic hyperuricemia. (1)

DOSAGE AND ADMINISTRATION

- ULORIC is recommended at 40 mg or 80 mg once daily. The recommended starting dose of ULORIC is 40 mg once daily. For patients who do not achieve a serum uric acid (sUA) less than 6 mg/dL after 2 weeks with 40 mg, ULORIC 80 mg is recommended. (2.1)
- ULORIC can be administered without regard to food or antacid use. (2.1)
- Limit the dose of ULORIC to 40 mg once daily in patients with severe renal impairment. (2.2, 8.6)

DOSAGE FORMS AND STRENGTHS

Tablet: 40 mg, 80 mg. (3)

CONTRAINDICATIONS

ULORIC is contraindicated in patients being treated with azathioprine or mercaptopurine. (4)

WARNINGS AND PRECAUTIONS

- **Gout Flare:** An increase in gout flares is frequently observed during initiation of anti-hyperuricemic agents, including ULORIC. If a gout flare occurs during treatment, ULORIC need not be discontinued. Prophylactic therapy (i.e., non-steroidal anti-inflammatory drug [NSAID] or colchicine upon initiation of treatment) may be beneficial for up to six months. (2.4, 5.1)

FULL PRESCRIBING INFORMATION: CONTENTS***1 INDICATIONS AND USAGE****2 DOSAGE AND ADMINISTRATION**

- 2.1 Recommended Dose
- 2.2 Special Populations
- 2.3 Uric Acid Level
- 2.4 Gout Flares

3 DOSAGE FORMS AND STRENGTHS**4 CONTRAINDICATIONS****5 WARNINGS AND PRECAUTIONS**

- 5.1 Gout Flare
- 5.2 Cardiovascular Events
- 5.3 Hepatic Effects
- 5.4 Serious Skin Reactions

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Xanthine Oxidase Substrate Drugs
- 7.2 Cytotoxic Chemotherapy Drugs
- 7.3 *In Vivo* Drug Interaction Studies

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy

- **Cardiovascular Events:** A higher rate of cardiovascular thromboembolic events was observed in patients treated with ULORIC than allopurinol in clinical trials. Monitor for signs and symptoms of MI and stroke. (5.2)
- **Hepatic Effects:** Postmarketing reports of hepatic failure, sometimes fatal. Causality cannot be excluded. If liver injury is detected, promptly interrupt ULORIC and assess patient for probable cause, then treat cause if possible, to resolution or stabilization. Do not restart ULORIC if liver injury is confirmed and no alternate etiology can be found. (5.3)
- **Serious Skin Reactions:** Postmarketing reports of serious skin and hypersensitivity reactions, including Stevens-Johnson Syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis (TEN) have been reported in patients taking ULORIC. Discontinue ULORIC if serious skin reactions are suspected. (5.4)

ADVERSE REACTIONS

Adverse reactions occurring in at least 1% of patients treated with ULORIC, and at least 0.5% greater than placebo, are liver function abnormalities, nausea, arthralgia, and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-877-TAKEDA-7 (1-877-825-3327) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Concomitant administration of ULORIC with XO substrate drugs, azathioprine or mercaptopurine could increase plasma concentrations of these drugs resulting in severe toxicity. (7)

USE IN SPECIFIC POPULATIONS

- No studies have been conducted in patients with severe hepatic impairment. Caution should be exercised in these patients. (8.6, 8.7)
- No studies have been conducted in patients with secondary hyperuricemia (including patients being treated for Lesch-Nyhan syndrome or malignant disease, or in organ transplant recipients); therefore, ULORIC is not recommended for use in these patients. (8.8)

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

Revised: 2/2018

8.2 Lactation

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Renal Impairment

8.7 Hepatic Impairment

8.8 Secondary Hyperuricemia

10 OVERDOSAGE**11 DESCRIPTION****12 CLINICAL PHARMACOLOGY**

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology

14 CLINICAL STUDIES

14.1 Management of Hyperuricemia in Gout

16 HOW SUPPLIED/STORAGE AND HANDLING**17 PATIENT COUNSELING INFORMATION**

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ULORIC is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in patients with gout.

ULORIC is not recommended for the treatment of asymptomatic hyperuricemia.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

For treatment of hyperuricemia in patients with gout, ULORIC is recommended at 40 mg or 80 mg once daily.

The recommended starting dose of ULORIC is 40 mg once daily. For patients who do not achieve a serum uric acid (sUA) less than 6 mg/dL after two weeks with 40 mg, ULORIC 80 mg is recommended.

ULORIC can be taken without regard to food or antacid use [see *Clinical Pharmacology (12.3)*].

2.2 Special Populations

No dose adjustment is necessary when administering ULORIC in patients with mild or moderate renal impairment. The recommended starting dose of ULORIC is 40 mg once daily. For patients who do not achieve a sUA less than 6 mg/dL after two weeks with 40 mg, ULORIC 80 mg is recommended.

The dose of ULORIC is limited to 40 mg once daily in patients with severe renal impairment [see *Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)*].

No dose adjustment is necessary in patients with mild to moderate hepatic impairment [see *Use in Specific Populations (8.7)* and *Clinical Pharmacology (12.3)*].

2.3 Uric Acid Level

Testing for the target serum uric acid level of less than 6 mg/dL may be performed as early as two weeks after initiating ULORIC therapy.

2.4 Gout Flares

Gout flares may occur after initiation of ULORIC due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. Flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended upon initiation of ULORIC. Prophylactic therapy may be beneficial for up to six months [see *Clinical Studies (14.1)*].

If a gout flare occurs during ULORIC treatment, ULORIC need not be discontinued. The gout flare should be managed concurrently, as appropriate for the individual patient [see *Warnings and Precautions (5.1)*].

3 DOSAGE FORMS AND STRENGTHS

- 40 mg tablets, light green to green, round, debossed with “TAP” and “40”
- 80 mg tablets, light green to green, teardrop shaped, debossed with “TAP” and “80”

4 CONTRAINDICATIONS

ULORIC is contraindicated in patients being treated with azathioprine or mercaptopurine [see *Drug Interactions* (7)].

5 WARNINGS AND PRECAUTIONS

5.1 Gout Flare

After initiation of ULORIC, an increase in gout flares is frequently observed. This increase is due to reduction in serum uric acid levels, resulting in mobilization of urate from tissue deposits.

In order to prevent gout flares when ULORIC is initiated, concurrent prophylactic treatment with an NSAID or colchicine is recommended [see *Dosage and Administration* (2.4)].

5.2 Cardiovascular Events

In the randomized controlled studies, there was a higher rate of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) in patients treated with ULORIC (0.74 per 100 P-Y [95% Confidence Interval (CI) 0.36-1.37]) than allopurinol (0.60 per 100 P-Y [95% CI 0.16-1.53]) [see *Adverse Reactions* (6.1)]. A causal relationship with ULORIC has not been established. Monitor for signs and symptoms of myocardial infarction (MI) and stroke.

5.3 Hepatic Effects

There have been postmarketing reports of fatal and non-fatal hepatic failure in patients taking ULORIC, although the reports contain insufficient information necessary to establish the probable cause. During randomized controlled studies, transaminase elevations greater than three times the upper limit of normal (ULN) were observed (AST: 2%, 2%, and ALT: 3%, 2% in ULORIC and allopurinol-treated patients, respectively). No dose-effect relationship for these transaminase elevations was noted [see *Clinical Pharmacology* (12.3)].

Obtain a liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) as a baseline before initiating ULORIC.

Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. In this clinical context, if the patient is found to have abnormal liver tests (ALT greater than three times the upper limit of the reference range), ULORIC treatment should be interrupted and investigation done to establish the probable cause. ULORIC should not be restarted in these patients without another explanation for the liver test abnormalities.

Patients who have serum ALT greater than three times the reference range with serum total bilirubin greater than two times the reference range without alternative etiologies are at risk for severe drug-induced liver injury and should not be restarted on ULORIC. For patients with lesser elevations of serum ALT or bilirubin and with an alternate probable cause, treatment with ULORIC can be used with caution.

5.4 Serious Skin Reactions

Postmarketing reports of serious skin and hypersensitivity reactions, including Stevens-Johnson Syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis (TEN) have been reported in patients taking ULORIC. Discontinue ULORIC if serious skin reactions are suspected [see *Patient Counseling Information* (17)]. Many of these patients had reported previous similar skin reactions to allopurinol. ULORIC should be used with caution in these patients.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

A total of 2757 patients with hyperuricemia and gout were treated with ULORIC 40 mg or 80 mg daily in clinical studies. For ULORIC 40 mg, 559 patients were treated for ≥6 months. For ULORIC 80 mg, 1377 patients were treated for ≥6 months, 674 patients were treated for ≥1 year and 515 patients were treated for ≥2 years.

Most Common Adverse Reactions

In three randomized, controlled clinical studies (Studies 1, 2 and 3), which were six to 12 months in duration, the following adverse reactions were reported by the treating physician as related to study drug. Table 1 summarizes adverse reactions reported at a rate of at least 1% in ULORIC treatment groups and at least 0.5% greater than placebo.

Table 1: Adverse Reactions Occurring in ≥1% of Patients Treated with ULORIC and at Least 0.5% Greater than Seen in Patients Receiving Placebo in Controlled Studies

Adverse Reactions	Placebo	ULORIC		allopurinol*
	(N=134)	40 mg daily (N=757)	80 mg daily (N=1279)	(N=1277)
Liver Function Abnormalities	0.7%	6.6%	4.6%	4.2%
Nausea	0.7%	1.1%	1.3%	0.8%
Arthralgia	0%	1.1%	0.7%	0.7%
Rash	0.7%	0.5%	1.6%	1.6%

*Of the patients who received allopurinol, 10 received 100 mg, 145 received 200 mg, and 1122 received 300 mg, based on level of renal impairment.

The most common adverse reaction leading to discontinuation from therapy was liver function abnormalities in 1.8% of ULORIC 40 mg, 1.2% of ULORIC 80 mg, and in 0.9% of patients treated with allopurinol.

In addition to the adverse reactions presented in Table 1, dizziness was reported in more than 1% of patients treated with ULORIC although not at a rate more than 0.5% greater than placebo.

Less Common Adverse Reactions

In Phase 2 and 3 clinical studies the following adverse reactions occurred in less than 1% of patients and in more than one subject treated with doses ranging from 40 mg to 240 mg of ULORIC. This list also includes adverse reactions (less than 1% of patients) associated with organ systems from Warnings and Precautions.

Blood and Lymphatic System Disorders: anemia, idiopathic thrombocytopenic purpura, leukocytosis/leukopenia, neutropenia, pancytopenia, splenomegaly, thrombocytopenia.

Cardiac Disorders: angina pectoris, atrial fibrillation/flutter, cardiac murmur, ECG abnormal, palpitations, sinus bradycardia, tachycardia.

Ear and Labyrinth Disorders: deafness, tinnitus, vertigo.

Eye Disorders: vision blurred.

Gastrointestinal Disorders: abdominal distention, abdominal pain, constipation, dry mouth, dyspepsia, flatulence, frequent stools, gastritis, gastroesophageal reflux disease, gastrointestinal discomfort, gingival pain, haematemesis, hyperchlorhydria, hematochezia, mouth ulceration, pancreatitis, peptic ulcer, vomiting.

General Disorders and Administration Site Conditions: asthenia, chest pain/discomfort, edema, fatigue, feeling abnormal, gait disturbance, influenza-like symptoms, mass, pain, thirst.

Hepatobiliary Disorders: cholelithiasis/cholecystitis, hepatic steatosis, hepatitis, hepatomegaly.

Immune System Disorder: hypersensitivity.

Infections and Infestations: herpes zoster.

Procedural Complications: contusion.

Metabolism and Nutrition Disorders: anorexia, appetite decreased/increased, dehydration, diabetes mellitus, hypercholesterolemia, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypokalemia, weight decreased/increased.

Musculoskeletal and Connective Tissue Disorders: arthritis, joint stiffness, joint swelling, muscle spasms/twitching/tightness/weakness, musculoskeletal pain/stiffness, myalgia.

Nervous System Disorders: altered taste, balance disorder, cerebrovascular accident, Guillain-Barré syndrome, headache, hemiparesis, hypoesthesia, hyposmia, lacunar infarction, lethargy, mental impairment, migraine, paresthesia, somnolence, transient ischemic attack, tremor.

Psychiatric Disorders: agitation, anxiety, depression, insomnia, irritability, libido decreased, nervousness, panic attack, personality change.

Renal and Urinary Disorders: hematuria, nephrolithiasis, pollakiuria, proteinuria, renal failure, renal insufficiency, urgency, incontinence.

Reproductive System and Breast Changes: breast pain, erectile dysfunction, gynecomastia.

Respiratory, Thoracic and Mediastinal Disorders: bronchitis, cough, dyspnea, epistaxis, nasal dryness, paranasal sinus hypersecretion, pharyngeal edema, respiratory tract congestion, sneezing, throat irritation, upper respiratory tract infection.

Skin and Subcutaneous Tissue Disorders: alopecia, angio-edema, dermatitis, dermographism, ecchymosis, eczema, hair color changes, hair growth abnormal, hyperhidrosis, peeling skin, petechiae, photosensitivity, pruritus, purpura, skin discoloration/changed pigmentation, skin lesion, skin odor abnormal, urticaria.

Vascular Disorders: flushing, hot flush, hypertension, hypotension.

Laboratory Parameters: activated partial thromboplastin time prolonged, creatine increased, bicarbonate decreased, sodium increased, EEG abnormal, glucose increased, cholesterol increased, triglycerides increased, amylase increased, potassium increased, TSH increased, platelet count decreased, hematocrit decreased, hemoglobin decreased, MCV increased, RBC decreased, creatinine increased, blood urea increased, BUN/creatinine ratio increased, creatine phosphokinase (CPK) increased, alkaline phosphatase increased, LDH increased, PSA increased, urine output increased/decreased, lymphocyte count decreased, neutrophil count decreased, WBC increased/decreased, coagulation test abnormal, low density lipoprotein (LDL) increased, prothrombin time prolonged, urinary casts, urine positive for white blood cells and protein.

Cardiovascular Safety

Cardiovascular events and deaths were adjudicated to one of the pre-defined endpoints from the Anti-Platelet Trialists' Collaborations (APTC) (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) in the randomized controlled and long-term extension studies. In the Phase 3 randomized controlled studies, the incidences of adjudicated APTC events per 100 patient-years of exposure were: Placebo 0 (95% CI 0.00-6.16), ULORIC 40 mg 0 (95% CI 0.00-1.08), ULORIC 80 mg 1.09 (95% CI 0.44-2.24), and allopurinol 0.60 (95% CI 0.16-1.53).

In the long-term extension studies, the incidences of adjudicated APTC events were: ULORIC 80 mg 0.97 (95% CI 0.57-1.56), and allopurinol 0.58 (95% CI 0.02-3.24).

Overall, a higher rate of APTC events was observed in ULORIC than in patients treated with allopurinol. A causal relationship with ULORIC has not been established. Monitor for signs and symptoms of MI and stroke.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of ULORIC. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: agranulocytosis, eosinophilia.

Hepatobiliary Disorders: hepatic failure (some fatal), jaundice, serious cases of abnormal liver function test results, liver disorder.

Immune System Disorders: anaphylaxis, anaphylactic reaction.

Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis.

Psychiatric Disorders: psychotic behavior including aggressive thoughts.

Renal and Urinary Disorders: tubulointerstitial nephritis.

Skin and Subcutaneous Tissue Disorders: generalized rash, Stevens-Johnson Syndrome, hypersensitivity skin reactions, erythema multiforme, drug reaction with eosinophilia and systemic symptoms, toxic epidermal necrolysis.

7 DRUG INTERACTIONS

7.1 Xanthine Oxidase Substrate Drugs

ULORIC is an XO inhibitor. Based on a drug interaction study in healthy patients, febuxostat altered the metabolism of theophylline (a substrate of XO) in humans [see *Clinical Pharmacology* (12.3)]. Therefore, use with caution when coadministering ULORIC with theophylline.

Drug interaction studies of ULORIC with other drugs that are metabolized by XO (e.g., mercaptopurine and azathioprine) have not been conducted. Inhibition of XO by ULORIC may cause increased plasma concentrations of these drugs leading to toxicity [see *Clinical Pharmacology* (12.3)]. ULORIC is contraindicated in patients being treated with azathioprine or mercaptopurine [see *Contraindications* (4)].

7.2 Cytotoxic Chemotherapy Drugs

Drug interaction studies of ULORIC with cytotoxic chemotherapy have not been conducted. No data are available regarding the safety of ULORIC during cytotoxic chemotherapy.

7.3 *In Vivo* Drug Interaction Studies

Based on drug interaction studies in healthy patients, ULORIC does not have clinically significant interactions with colchicine, naproxen, indomethacin, hydrochlorothiazide, warfarin or desipramine [see *Clinical Pharmacology* (12.3)]. Therefore, ULORIC may be used concomitantly with these medications.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited available data with ULORIC use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes. No adverse developmental effects were observed in embryo-fetal development studies with oral administration of febuxostat to pregnant rats and rabbits during organogenesis at doses that produced maternal exposures up to 40 and 51 times, respectively, the exposure at the maximum recommended human dose (MRHD). No adverse developmental effects were observed in a pre- and postnatal development study with administration of febuxostat to pregnant rats from organogenesis through lactation at an exposure approximately 11 times the MRHD (see *Data*).

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

Data

Animal Data

In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation Days 7 – 17, febuxostat was not teratogenic and did not affect fetal development or survival at exposures up to approximately 40 times the MRHD (on an AUC basis at maternal oral doses up to 48 mg/kg/day). In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation Days 6 – 18, febuxostat was not teratogenic and did not affect fetal development at exposures up to approximately 51 times the MRHD (on an AUC basis at maternal oral doses up to 48 mg/kg/day).

In a pre- and postnatal development study in pregnant female rats dosed orally from gestation Day 7 through lactation Day 20, febuxostat had no effects on delivery or growth and development of offspring at a dose approximately 11 times the MRHD (on an AUC basis at a maternal oral dose of 12 mg/kg/day). However, increased neonatal mortality and a reduction in neonatal body weight gain were observed in the presence of maternal toxicity at a dose approximately 40 times the MRHD (on an AUC basis at a maternal oral dose of 48 mg/kg/day).

Febuxostat crossed the placental barrier following oral administration to pregnant rats and was detected in fetal tissues.

8.2 Lactation

Risk Summary

There are no data on the presence of febuxostat in human milk, the effects on the breastfed infant, or the effects on milk production. Febuxostat is present in rat milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ULORIC and any potential adverse effects on the breastfed child from ULORIC or from the underlying maternal condition.

Data

Animal Data

Orally administered febuxostat was detected in the milk of lactating rats at up to approximately 7 times the plasma concentration.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients under 18 years of age have not been established.

8.5 Geriatric Use

No dose adjustment is necessary in elderly patients. Of the total number of patients in clinical studies of ULORIC, 16% were 65 and over, while 4% were 75 and over. Comparing patients in different age groups, no clinically significant differences in safety or effectiveness were observed but greater sensitivity of some older individuals cannot be ruled out. The C_{max} and AUC_{24} of febuxostat following multiple oral doses of ULORIC in geriatric patients (≥ 65 years) were similar to those in younger patients (18 to 40 years) [see *Clinical Pharmacology* (12.3)].

8.6 Renal Impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment (Cl_{cr} 30 to 89 mL/min). The recommended starting dose of ULORIC is 40 mg once daily. For patients who do not achieve a sUA less than 6 mg/dL after two weeks with 40 mg, ULORIC 80 mg is recommended. For patients with severe renal impairment (Cl_{cr} 15 to 29 mL/min), the dose of ULORIC is limited to 40 mg once daily [see *Dosage and Administration* (2.2) and *Clinical Pharmacology* (12.3)].

8.7 Hepatic Impairment

No dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh Class A or B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C); therefore, caution should be exercised in these patients [see *Clinical Pharmacology* (12.3)].

8.8 Secondary Hyperuricemia

No studies have been conducted in patients with secondary hyperuricemia (including organ transplant recipients); ULORIC is not recommended for use in patients whom the rate of urate formation is greatly increased (e.g., malignant disease and its treatment, Lesch-Nyhan syndrome). The concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract.

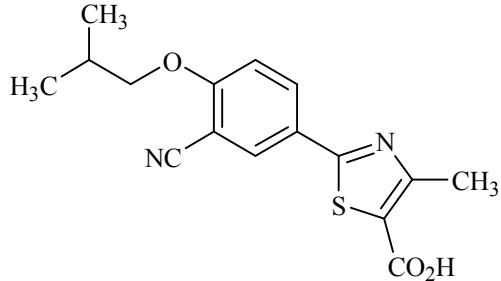
10 OVERDOSAGE

ULORIC was studied in healthy patients in doses up to 300 mg daily for seven days without evidence of dose-limiting toxicities. No overdose of ULORIC was reported in clinical studies. Patients should be managed by symptomatic and supportive care should there be an overdose.

11 DESCRIPTION

ULORIC (febuxostat) is a xanthine oxidase inhibitor. The active ingredient in ULORIC is 2-[3-cyano-4-(2-methylpropoxy) phenyl]-4-methylthiazole-5-carboxylic acid, with a molecular weight of 316.38. The empirical formula is $C_{16}H_{16}N_2O_3S$.

The chemical structure is:



Febuxostat is a non-hygroscopic, white crystalline powder that is freely soluble in dimethylformamide; soluble in dimethylsulfoxide; sparingly soluble in ethanol; slightly soluble in methanol and acetonitrile; and practically insoluble in water. The melting range is 205°C to 208°C.

ULORIC tablets for oral use contain the active ingredient, febuxostat, and are available in two dosage strengths, 40 mg and 80 mg. Inactive ingredients include lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, sodium croscarmellose, silicon dioxide and magnesium stearate. ULORIC tablets are coated with Opadry II, green.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ULORIC, a xanthine oxidase inhibitor, achieves its therapeutic effect by decreasing serum uric acid. ULORIC is not expected to inhibit other enzymes involved in purine and pyrimidine synthesis and metabolism at therapeutic concentrations.

12.2 Pharmacodynamics

Effect on Uric Acid and Xanthine Concentrations

In healthy patients, ULORIC resulted in a dose dependent decrease in 24 hour mean serum uric acid concentrations and an increase in 24 hour mean serum xanthine concentrations. In addition, there was a decrease in the total daily urinary uric acid excretion. Also, there was an increase in total daily urinary xanthine excretion. Percent reduction in 24 hour mean serum uric acid concentrations was between 40% and 55% at the exposure levels of 40 mg and 80 mg daily doses.

Effect on Cardiac Repolarization

The effect of ULORIC on cardiac repolarization as assessed by the QTc interval was evaluated in normal healthy patients and in patients with gout. ULORIC in doses up to 300 mg daily, at steady-state, did not demonstrate an effect on the QTc interval.

12.3 Pharmacokinetics

In healthy patients, maximum plasma concentrations (C_{max}) and AUC of febuxostat increased in a dose proportional manner following single and multiple doses of 10 mg to 120 mg. There is no accumulation when therapeutic doses are administered every 24 hours. Febuxostat has an apparent mean terminal elimination half-life ($t_{1/2}$) of approximately 5 to 8 hours. Febuxostat pharmacokinetic parameters for patients with hyperuricemia and gout estimated by population pharmacokinetic analyses were similar to those estimated in healthy patients.

Absorption

The absorption of radiolabeled febuxostat following oral dose administration was estimated to be at least 49% (based on total radioactivity recovered in urine). Maximum plasma concentrations of febuxostat occurred between 1 and 1.5 hours post-dose. After multiple oral 40 mg and 80 mg once daily doses, C_{max} is approximately 1.6 ± 0.6 mcg/mL (N=30), and 2.6 ± 1.7 mcg/mL (N=227), respectively. Absolute bioavailability of the febuxostat tablet has not been studied.

Following multiple 80 mg once daily doses with a high fat meal, there was a 49% decrease in C_{max} and an 18% decrease in AUC, respectively. However, no clinically significant change in the percent decrease in serum uric acid concentration was observed (58% fed vs. 51% fasting). Thus, ULORIC may be taken without regard to food.

Concomitant ingestion of an antacid containing magnesium hydroxide and aluminum hydroxide with an 80 mg single dose of ULORIC has been shown to delay absorption of febuxostat (approximately one hour) and to cause a 31% decrease in C_{max} and a 15% decrease in AUC ∞ . As AUC rather than C_{max} was related to drug effect, change observed in AUC was not considered clinically significant. Therefore, ULORIC may be taken without regard to antacid use.

Distribution

The mean apparent steady state volume of distribution (V_{ss}/F) of febuxostat was approximately 50 L (CV ~40%). The plasma protein binding of febuxostat is approximately 99.2% (primarily to albumin), and is constant over the concentration range achieved with 40 mg and 80 mg doses.

Metabolism

Febuxostat is extensively metabolized by both conjugation via uridine diphosphate glucuronosyltransferase (UGT) enzymes including UGT1A1, UGT1A3, UGT1A9, and UGT2B7 and oxidation via cytochrome P450 (CYP) enzymes including CYP1A2, 2C8 and 2C9 and non-P450 enzymes. The relative contribution of each enzyme isoform in the metabolism of febuxostat is not clear. The oxidation of the isobutyl side chain leads to the formation of four pharmacologically active hydroxy metabolites, all of which occur in plasma of humans at a much lower extent than febuxostat.

In urine and feces, acyl glucuronide metabolites of febuxostat (~35% of the dose), and oxidative metabolites, 67M-1 (~10% of the dose), 67M-2 (~11% of the dose), and 67M-4, a secondary metabolite from 67M-1 (~14% of the dose), appeared to be the major metabolites of febuxostat *in vivo*.

Elimination

Febuxostat is eliminated by both hepatic and renal pathways. Following an 80 mg oral dose of ^{14}C -labeled febuxostat, approximately 49% of the dose was recovered in the urine as unchanged febuxostat (3%), the acyl glucuronide of the drug (30%), its known oxidative metabolites and their conjugates (13%), and other unknown metabolites (3%). In addition to the urinary excretion, approximately 45% of the dose was recovered in the feces as the unchanged febuxostat (12%), the acyl glucuronide of the drug (1%), its known oxidative metabolites and their conjugates (25%), and other unknown metabolites (7%).

The apparent mean terminal elimination half-life ($t_{1/2}$) of febuxostat was approximately 5 to 8 hours.

Special Populations

Pediatric Use

The pharmacokinetics of ULORIC in patients under the age of 18 years have not been studied.

Geriatric Use

The C_{max} and AUC of febuxostat and its metabolites following multiple oral doses of ULORIC in geriatric patients (≥ 65 years) were similar to those in younger patients (18 to 40 years). In addition, the percent decrease in serum uric acid concentration was similar between elderly and younger patients. No dose adjustment is necessary in geriatric patients [see *Use in Specific Populations* (8.5)].

Renal Impairment

In a dedicated phase I pharmacokinetics study, following multiple 80 mg doses of ULORIC in healthy patients with mild (Cl_{cr} 50 to 80 mL/min), moderate (Cl_{cr} 30 to 49 mL/min) or severe renal impairment (Cl_{cr} 10 to 29 mL/min), the C_{max} of febuxostat did not change relative to patients with normal renal function (Cl_{cr} greater than 80 mL/min). AUC and half-life of febuxostat increased in patients with renal impairment in comparison to patients with normal renal function, but values were similar among three renal impairment groups. Mean febuxostat AUC values were up to 1.8 times higher in patients with renal impairment compared to those with normal renal function. Mean C_{max} and AUC values for three active metabolites increased up to 2- and 4-fold, respectively. However, the percent decrease in serum uric acid concentration for patients with renal impairment was comparable to those with normal renal function (58% in normal renal function group and 55% in the severe renal function group).

Based on population pharmacokinetic analysis, following multiple 40 mg or 80 mg doses of ULORIC, the mean oral clearance (CL/F) values of febuxostat in patients with gout and mild (n=334), moderate (n=232) or severe (n=34) renal impairment were decreased by 14%, 34%, and 48%, respectively, compared to patients with normal (n=89) renal function. The corresponding median AUC values of febuxostat at steady-state in patients with renal impairment were increased by 18%, 49%, and 96% after 40 mg dose, and 7%, 45% and 98% after 80 mg dose, respectively, compared to patients with normal renal function.

ULORIC has not been studied in end stage renal impairment patients who are on dialysis.

Hepatic Impairment

Following multiple 80 mg doses of ULORIC in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, an average of 20% to 30% increase was observed for both C_{max} and AUC_{24} (total and unbound) in hepatic impairment groups compared to patients with normal hepatic function. In addition, the percent decrease in serum uric acid concentration was comparable between different hepatic groups (62% in healthy group, 49% in mild hepatic impairment group, and 48% in moderate hepatic impairment group). No dose adjustment is necessary in patients with mild or moderate hepatic impairment. No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C); caution should be exercised in those patients [see *Use in Specific Populations (8.7)*].

Gender

Following multiple oral doses of ULORIC, the C_{max} and AUC_{24} of febuxostat were 30% and 14% higher in females than in males, respectively. However, weight-corrected C_{max} and AUC were similar between the genders. In addition, the percent decrease in serum uric acid concentrations was similar between genders. No dose adjustment is necessary based on gender.

Race

No specific pharmacokinetic study was conducted to investigate the effects of race.

Drug-Drug Interactions

Effect of ULORIC on Other Drugs

Xanthine Oxidase Substrate Drugs-Azathioprine, Mercaptopurine, and Theophylline

Febuxostat is an XO inhibitor. A drug-drug interaction study evaluating the effect of ULORIC upon the pharmacokinetics of theophylline (an XO substrate) in healthy patients showed that coadministration of febuxostat with theophylline resulted in an approximately 400-fold increase in the amount of 1-methylxanthine, one of the major metabolites of theophylline, excreted in the urine. Since the long-term safety of exposure to 1-methylxanthine in humans is unknown, use with caution when coadministering febuxostat with theophylline.

Drug interaction studies of ULORIC with other drugs that are metabolized by XO (e.g., mercaptopurine and azathioprine) have not been conducted. Inhibition of XO by ULORIC may cause increased plasma concentrations of these drugs leading to toxicity. ULORIC is contraindicated in patients being treated with azathioprine or mercaptopurine [see *Contraindications (4)* and *Drug Interactions (7)*].

Azathioprine and mercaptopurine undergo metabolism via three major metabolic pathways, one of which is mediated by XO. Although ULORIC drug interaction studies with azathioprine and mercaptopurine have not been conducted, concomitant administration of allopurinol [a xanthine oxidase inhibitor] with azathioprine or mercaptopurine has been reported to substantially increase plasma concentrations of these drugs. Because ULORIC is a xanthine oxidase inhibitor, it could inhibit the XO-mediated metabolism of azathioprine and mercaptopurine leading to increased plasma concentrations of azathioprine or mercaptopurine that could result in severe toxicity.

P450 Substrate Drugs

In vitro studies have shown that febuxostat does not inhibit P450 enzymes CYP1A2, 2C9, 2C19, 2D6, or 3A4 and it also does not induce CYP1A2, 2B6, 2C9, 2C19, or 3A4 at clinically relevant concentrations. As such, pharmacokinetic interactions between ULORIC and drugs metabolized by these CYP enzymes are unlikely.

Effect of Other Drugs on ULORIC

Febuxostat is metabolized by conjugation and oxidation via multiple metabolizing enzymes. The relative contribution of each enzyme isoform is not clear. Drug interactions between ULORIC and a drug that inhibits or induces one particular enzyme isoform is in general not expected.

In Vivo Drug Interaction Studies

Theophylline

No dose adjustment is necessary for theophylline when coadministered with ULORIC. Administration of ULORIC (80 mg once daily) with theophylline resulted in an increase of 6% in C_{max} and 6.5% in AUC of theophylline. These changes were not considered statistically significant. However, the study also showed an approximately 400-fold increase in the amount of 1-methylxanthine (one of the major theophylline metabolites) excreted in urine as a result of XO inhibition by ULORIC. The safety of long-term exposure to 1-methylxanthine has not been evaluated. This should be taken into consideration when deciding to coadminister ULORIC and theophylline.

Colchicine

No dose adjustment is necessary for either ULORIC or colchicine when the two drugs are coadministered. Administration of ULORIC (40 mg once daily) with colchicine (0.6 mg twice daily) resulted in an increase of 12% in C_{max} and 7% in AUC_{24} of febuxostat. In addition, administration of colchicine (0.6 mg twice daily) with ULORIC (120 mg daily) resulted in a less than 11% change in C_{max} or AUC of colchicine for both AM and PM doses. These changes were not considered clinically significant.

Naproxen

No dose adjustment is necessary for ULORIC or naproxen when the two drugs are coadministered. Administration of ULORIC (80 mg once daily) with naproxen (500 mg twice daily) resulted in a 28% increase in C_{max} and a 40% increase in AUC of febuxostat. The increases were not considered clinically significant. In addition, there were no significant changes in the C_{max} or AUC of naproxen (less than 2%).

Indomethacin

No dose adjustment is necessary for either ULORIC or indomethacin when these two drugs are coadministered. Administration of ULORIC (80 mg once daily) with indomethacin (50 mg twice daily) did not result in any significant changes in C_{max} or AUC of febuxostat or indomethacin (less than 7%).

Hydrochlorothiazide

No dose adjustment is necessary for ULORIC when coadministered with hydrochlorothiazide. Administration of ULORIC (80 mg) with hydrochlorothiazide (50 mg) did not result in any clinically significant changes in C_{max} or AUC of febuxostat (less than 4%), and serum uric acid concentrations were not substantially affected.

Warfarin

No dose adjustment is necessary for warfarin when coadministered with ULORIC. Administration of ULORIC (80 mg once daily) with warfarin had no effect on the pharmacokinetics of warfarin in healthy patients. INR and Factor VII activity were also not affected by the coadministration of ULORIC.

Desipramine

Coadministration of drugs that are CYP2D6 substrates (such as desipramine) with ULORIC are not expected to require dose adjustment. Febuxostat was shown to be a weak inhibitor of CYP2D6 *in vitro* and *in vivo*. Administration of ULORIC (120 mg once daily) with desipramine (25 mg) resulted in an increase in C_{max} (16%) and AUC (22%) of desipramine, which was associated with a 17% decrease in the 2-hydroxydesipramine to desipramine metabolic ratio (based on AUC).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies were conducted in F344 rats and B6C3F1 mice. Increased transitional cell papilloma and carcinoma of the urinary bladder was observed at 24 mg/kg (25 times the MRHD on an AUC basis and 18.75 mg/kg (12.5 times the MRHD on an AUC basis) in male rats and female mice, respectively. The urinary bladder neoplasms were secondary to calculus formation in the kidney and urinary bladder.

Febuxostat showed a positive clastogenic response in a chromosomal aberration assay in a Chinese hamster lung fibroblast cell line with and without metabolic activation *in vitro*. Febuxostat was negative in the following genotoxicity assays: the *in vitro* Ames assay, *in vitro* chromosomal aberration assay in human peripheral lymphocytes, the L5178Y mouse lymphoma cell line assay, the *in vivo* mouse micronucleus assay, and the rat unscheduled DNA synthesis assay.

Fertility and reproductive performance were unaffected in male or female rats that received febuxostat at oral doses up to 48 mg/kg/day (approximately 31 and 40 times the MRHD on an AUC basis in males and females respectively).

13.2 Animal Toxicology

A 12 month toxicity study in beagle dogs showed deposition of xanthine crystals and calculi in kidneys at 15 mg/kg (approximately 4 times the MRHD on an AUC basis). A similar effect of calculus formation was noted in rats in a six-month study due to deposition of xanthine crystals at 48 mg/kg (approximately 31 and 40 times the MRHD on an AUC basis in males and females respectively).

14 CLINICAL STUDIES

A serum uric acid level of less than 6 mg/dL is the goal of anti-hyperuricemic therapy and has been established as appropriate for the treatment of gout.

14.1 Management of Hyperuricemia in Gout

The efficacy of ULORIC was demonstrated in three randomized, double-blind, controlled trials in patients with hyperuricemia and gout. Hyperuricemia was defined as a baseline serum uric acid level ≥ 8 mg/dL.

Study 1 randomized patients to: ULORIC 40 mg daily, ULORIC 80 mg daily, or allopurinol (300 mg daily for patients with estimated creatinine clearance (Cl_{cr}) ≥ 60 mL/min or 200 mg daily for patients with estimated $Cl_{cr} \geq 30$ mL/min and ≤ 59 mL/min). The duration of Study 1 was six months.

Study 2 randomized patients to: placebo, ULORIC 80 mg daily, ULORIC 120 mg daily, ULORIC 240 mg daily or allopurinol (300 mg daily for patients with a baseline serum creatinine ≤ 1.5 mg/dL or 100 mg daily for patients with a baseline serum creatinine greater than 1.5 mg/dL and ≤ 2 mg/dL). The duration of Study 2 was six months.

Study 3, a 1 year study, randomized patients to: ULORIC 80 mg daily, ULORIC 120 mg daily, or allopurinol 300 mg daily. Patients who completed Study 2 and Study 3 were eligible to enroll in a Phase 3 long-term extension study in which patients received treatment with ULORIC for over three years.

In all three studies, patients received naproxen 250 mg twice daily or colchicine 0.6 mg once or twice daily for gout flare prophylaxis. In Study 1 the duration of prophylaxis was six months; in Study 2 and Study 3 the duration of prophylaxis was eight weeks.

The efficacy of ULORIC was also evaluated in a four week dose ranging study which randomized patients to: placebo, ULORIC 40 mg daily, ULORIC 80 mg daily, or ULORIC 120 mg daily. Patients who completed this study were eligible to enroll in a long-term extension study in which patients received treatment with ULORIC for up to five years.

Patients in these studies were representative of the patient population for which ULORIC use is intended. Table 2 summarizes the demographics and baseline characteristics for the patients enrolled in the studies.

Table 2: Patient Demographics and Baseline Characteristics in Study 1, Study 2 and Study 3

Male	95%
Race: Caucasian	80%
African American	10%
Ethnicity: Hispanic or Latino	7%
Alcohol User	67%
Mild to Moderate Renal Insufficiency (percent with estimated Cl _{cr} less than 90 mL/min)	59%
History of Hypertension	49%
History of Hyperlipidemia	38%
BMI ≥30 kg/m ²	63%
Mean BMI	33 kg/m ²
Baseline sUA ≥10 mg/dL	36%
Mean baseline sUA	9.7 mg/dL
Experienced a gout flare in previous year	85%

Serum Uric Acid Level less than 6 mg/dL at Final Visit

ULORIC 80 mg was superior to allopurinol in lowering serum uric acid to less than 6 mg/dL at the final visit. ULORIC 40 mg daily, although not superior to allopurinol, was effective in lowering serum uric acid to less than 6 mg/dL at the final visit (*Table 3*).

Table 3: Proportion of Patients with Serum Uric Acid Levels less than 6 mg/dL at Final Visit

Study*	ULORIC 40 mg daily	ULORIC 80 mg daily	allopurinol	Placebo	Difference in Proportion (95% CI)	
					ULORIC 40 mg vs allopurinol	ULORIC 80 mg vs allopurinol
Study 1 (6 months) (N=2268)	45%	67%	42%		3% (-2%, 8%)	25% (20%, 30%)
Study 2 (6 months) (N=643)		72%	39%	1%		33% (26%, 42%)
Study 3 (12 months) (N=491)		74%	36%			38% (30%, 46%)

*Randomization was balanced between treatment groups, except in Study 2 in which twice as many patients were randomized to each of the active treatment groups compared to placebo.

In 76% of ULORIC 80 mg patients, reduction in serum uric acid levels to less than 6 mg/dL was noted by the Week 2 visit. Average serum uric acid levels were maintained at 6 mg/dL or below throughout treatment in 83% of these patients.

In all treatment groups, fewer patients with higher baseline serum urate levels (≥ 10 mg/dL) and/or tophi achieved the goal of lowering serum uric acid to less than 6 mg/dL at the final visit; however, a higher proportion achieved a serum uric acid less than 6 mg/dL with ULORIC 80 mg than with ULORIC 40 mg or allopurinol.

Study 1 evaluated efficacy in patients with mild to moderate renal impairment (i.e., baseline estimated Cl_{cr} less than 90 mL/min). The results in this sub-group of patients are shown in Table 4.

Table 4: Proportion of Patients with Serum Uric Acid Levels less than 6 mg/dL in Patients with Mild or Moderate Renal Impairment at Final Visit				
ULORIC 40 mg daily (N=479)	ULORIC 80 mg daily (N=503)	allopurinol* 300 mg daily (N=501)	Difference in Proportion (95% CI)	
			ULORIC 40 mg vs allopurinol	ULORIC 80 mg vs allopurinol
50%	72%	42%	7% (1%, 14%)	29% (23%, 35%)

*Allopurinol patients (n=145) with estimated $\text{Cl}_{\text{cr}} \geq 30$ mL/min and $\text{Cl}_{\text{cr}} \leq 59$ mL/min were dosed at 200 mg daily.

16 HOW SUPPLIED/STORAGE AND HANDLING

ULORIC 40 mg tablets are light green to green in color, round, debossed with "TAP" on one side and "40" on the other side and supplied as:

NDC Number	Size
64764-918-11	Hospital Unit Dose Pack of 100 Tablets
64764-918-30	Bottle of 30 Tablets
64764-918-90	Bottle of 90 Tablets
64764-918-18	Bottle of 500 Tablets

ULORIC 80 mg tablets are light green to green in color, teardrop shaped, debossed with "TAP" on one side and "80" on the other side and supplied as:

NDC Number	Size
64764-677-11	Hospital Unit Dose Pack of 100 Tablets
64764-677-30	Bottle of 30 Tablets
64764-677-13	Bottle of 100 Tablets
64764-677-19	Bottle of 1000 Tablets

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Patients should be advised of the potential benefits and risks of ULORIC. Patients should be informed about the potential for gout flares, elevated liver enzymes and adverse cardiovascular events after initiation of ULORIC therapy.

Concomitant prophylaxis with an NSAID or colchicine for gout flares should be considered.

Patients should be instructed to inform their healthcare professional if they develop a rash, chest pain, shortness of breath or neurologic symptoms suggesting a stroke. Some serious skin and allergic reactions such as rash, skin reddening, pain, swelling or blistering of lips, eyes or mouth, skin peeling and flu-like symptoms have been reported in patients taking ULORIC. Patients who had previous reactions to allopurinol may be at greater risk for these skin conditions [see *Warnings and Precautions (5.4)*].

Patients should be instructed to inform their healthcare professional of any other medications they are currently taking with ULORIC, including over-the-counter medications.

PATIENT INFORMATION
ULORIC (ü-lor-ik)
(febuxostat)
tablet for oral use

Read the Patient Information that comes with ULORIC before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is ULORIC?

ULORIC is a prescription medicine called a xanthine oxidase (XO) inhibitor used to lower blood uric acid levels in adults with gout.

It is not known if ULORIC is safe and effective in children under 18 years of age.

Who should not take ULORIC?

Do not take ULORIC if you:

- take azathioprine (Azasan, Imuran)
- take mercaptopurine (Purinethol, Purixan)

What should I tell my healthcare provider before taking ULORIC?

Before taking ULORIC tell your healthcare provider about all of your medical conditions, including if you:

- have liver or kidney problems.
- have a history of heart disease or stroke.
- are pregnant or plan to become pregnant. It is not known if ULORIC will harm your unborn baby. Talk with your healthcare provider if you are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. It is not known if ULORIC passes into your breast milk. You and your healthcare provider should decide if you should take ULORIC while breastfeeding.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ULORIC may affect the way other medicines work, and other medicines may affect how ULORIC works.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take ULORIC?

- Take ULORIC exactly as your healthcare provider tells you to take it.
- ULORIC can be taken with or without food.
- ULORIC can be taken with antacids.
- Your gout may get worse (flare) when you start taking ULORIC. Do not stop taking ULORIC even if you have a flare.
- Your healthcare provider may do certain tests while you take ULORIC.

What are the possible side effects of ULORIC?

ULORIC may cause serious side effects, including:

- **Gout Flares.** Gout flares can happen when you first start taking ULORIC. Your healthcare provider may give you other medicines to help prevent your gout flares.
- **Heart problems.** People who take ULORIC can have serious heart problems including heart attacks, strokes and heart-related deaths. It is not known that ULORIC caused these problems. Call your healthcare provider right away or get emergency medical help if you have any of the following symptoms:
 - chest pain
 - shortness of breath
 - dizziness
 - numbness or weakness on 1 side of your body
 - trouble talking
 - headache
- **Liver problems.** Liver problems can happen in people who take ULORIC. Your healthcare provider may do blood tests to check how well your liver is working before and during your treatment with ULORIC.

- **Severe skin and allergic reactions.** Serious skin and allergic reactions that may affect different parts of the body such as your liver, kidneys, heart or lungs, can happen in people who take ULORIC. Call your healthcare provider right away or get emergency medical help if you have any of the following symptoms:
 - rash
 - red and painful skin
 - severe skin blisters
 - peeling skin
 - sores around the lips, eyes or mouth
 - swollen face, lips, mouth, tongue or throat
 - flu-like symptoms

The most common side effects of ULORIC include:

- liver problems
- nausea
- gout flares
- joint pain
- rash

Tell your healthcare provider if you have any side effect that bothers you, or that does not go away.

These are not all of the possible side effects of ULORIC. For more information, ask your healthcare provider or pharmacist.

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

How should I store ULORIC?

- Store ULORIC at room temperature between 59°F to 86°F (15°C to 30°C).
- Keep ULORIC out of the light.

Keep ULORIC and all medicines out of the reach of children.

General information about the safe and effective use of ULORIC.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use ULORIC for a condition for which it was not prescribed. Do not give ULORIC to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about ULORIC that is written for health professionals.

What are the ingredients in ULORIC?

Active ingredient: febuxostat

Inactive ingredients: lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, sodium croscarmellose, silicon dioxide, magnesium stearate, and Opadry II, green

Distributed by:

Takeda Pharmaceuticals America, Inc.
Deerfield, IL 60015

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For more information, go to www.uloric.com or call 1-877-825-3327.

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

ULR015 R7

Revised: February 2018

EXHIBIT I

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ULORIC safely and effectively. See full prescribing information for ULORIC.

ULORIC (febuxostat) tablets, for oral use
Initial U.S. Approval: 2009

WARNING: CARDIOVASCULAR DEATH

See full prescribing information for complete boxed warning.

- Gout patients with established cardiovascular (CV) disease treated with ULORIC had a higher rate of CV death compared to those treated with allopurinol in a CV outcomes study. (5.1)
- Consider the risks and benefits of ULORIC when deciding to prescribe or continue patients on ULORIC. ULORIC should only be used in patients who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable. (1)

RECENT MAJOR CHANGES

Boxed Warning	2/2019
Indications and Usage	2/2019
Warnings and Precautions	
Cardiovascular Death (5.1)	2/2019

INDICATIONS AND USAGE

ULORIC is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in adult patients with gout who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable. (1)

For the safe and effective use of allopurinol, see allopurinol prescribing information.

Limitations of Use:

ULORIC is not recommended for the treatment of asymptomatic hyperuricemia. (1)

DOSAGE AND ADMINISTRATION

- Recommended ULORIC dosage is 40 mg or 80 mg once daily. The recommended starting dose is 40 mg once daily. For patients who do not achieve a serum uric acid (sUA) less than 6 mg/dL after 2 weeks, the recommended dosage is 80 mg once daily. (2.1)
- Can be administered without regard to food or antacid use. (2.1)
- Limit the dosage of ULORIC to 40 mg once daily in patients with severe renal impairment. (2.2, 8.6)

DOSAGE FORMS AND STRENGTHS

Tablet: 40 mg, 80 mg. (3)

CONTRAINDICATIONS

ULORIC is contraindicated in patients being treated with azathioprine or mercaptopurine. (4)

FULL PRESCRIBING INFORMATION: CONTENTS***WARNING: CARDIOVASCULAR DEATH****1 INDICATIONS AND USAGE****2 DOSAGE AND ADMINISTRATION**

- Recommended Dose
- Dosage Recommendations in Patients with Renal Impairment and Hepatic Impairment
- Uric Acid Level
- Recommended Prophylaxis for Gout Flares

3 DOSAGE FORMS AND STRENGTHS**4 CONTRAINDICATIONS****5 WARNINGS AND PRECAUTIONS**

- Cardiovascular Death
- Gout Flares
- Hepatic Effects
- Serious Skin Reactions

6 ADVERSE REACTIONS

- Clinical Trials Experience
- Postmarketing Experience

WARNINGS AND PRECAUTIONS

- Cardiovascular Death:** In a CV outcomes study, there was a higher rate of CV death in patients treated with ULORIC compared to allopurinol; in the same study ULORIC was non-inferior to allopurinol for the primary endpoint of major adverse cardiovascular events (MACE). Consider the risks and benefits of ULORIC when deciding to prescribe or continue patients on ULORIC. (1, 5.1)
- Gout Flares:** An increase in gout flares is frequently observed during initiation of anti-hyperuricemic agents, including ULORIC. If a gout flare occurs during treatment, ULORIC need not be discontinued. Prophylactic therapy (i.e., non-steroidal anti-inflammatory drug [NSAID] or colchicine upon initiation of treatment) may be beneficial for up to six months. (2.4, 5.2)
- Hepatic Effects:** Postmarketing reports of hepatic failure, sometimes fatal. Causality cannot be excluded. If liver injury is detected, promptly interrupt ULORIC and assess patient for probable cause, then treat cause if possible, to resolution or stabilization. Do not restart ULORIC if liver injury is confirmed and no alternate etiology can be found. (5.3)
- Serious Skin Reactions:** Postmarketing reports of serious skin and hypersensitivity reactions, including Stevens-Johnson Syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis (TEN) have been reported in patients taking ULORIC. Discontinue ULORIC if serious skin reactions are suspected. (5.4)

ADVERSE REACTIONS

Adverse reactions occurring in at least 1% of patients treated with ULORIC, and at least 0.5% greater than placebo, are liver function abnormalities, nausea, arthralgia, and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-877-TAKEDA-7 (1-877-825-3327) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Concomitant administration of ULORIC with XO substrate drugs, azathioprine or mercaptopurine could increase plasma concentrations of these drugs resulting in severe toxicity. (7)

USE IN SPECIFIC POPULATIONS

- No studies have been conducted in patients with severe hepatic impairment. Caution should be exercised in these patients. (8.7)
- No studies have been conducted in patients with secondary hyperuricemia (including patients being treated for Lesch-Nyhan syndrome or malignant disease, or in organ transplant recipients); therefore, ULORIC is not recommended for use in these patients. (8.8)

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

Revised: 2/2019

7 DRUG INTERACTIONS

- Xanthine Oxidase Substrate Drugs
- Cytotoxic Chemotherapy Drugs
- In Vivo Drug Interaction Studies

8 USE IN SPECIFIC POPULATIONS

- Pregnancy
- Lactation
- Pediatric Use
- Geriatric Use
- Renal Impairment
- Hepatic Impairment
- Secondary Hyperuricemia

10 OVERDOSAGE**11 DESCRIPTION****12 CLINICAL PHARMACOLOGY**

- Mechanism of Action
- Pharmacodynamics
- Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology

14 CLINICAL STUDIES

- 14.1 Management of Hyperuricemia in Gout
- 14.2 Cardiovascular Safety Study

16 HOW SUPPLIED/STORAGE AND HANDLING**17 PATIENT COUNSELING INFORMATION**

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

FULL PRESCRIBING INFORMATION**WARNING: CARDIOVASCULAR DEATH**

Gout patients with established cardiovascular (CV) disease treated with ULORIC had a higher rate of CV death compared to those treated with allopurinol in a CV outcomes study [see Warnings and Precautions (5.1)].

Consider the risks and benefits of ULORIC when deciding to prescribe or continue patients on ULORIC. ULORIC should only be used in patients who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable [see Indications and Usage (1)].

1 INDICATIONS AND USAGE

ULORIC is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in adult patients with gout who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable.

For the safe and effective use of allopurinol, see allopurinol prescribing information.

Limitations of Use:

ULORIC is not recommended for the treatment of asymptomatic hyperuricemia.

2 DOSAGE AND ADMINISTRATION**2.1 Recommended Dose**

The recommended ULORIC dosage is 40 mg or 80 mg once daily.

The recommended starting dosage of ULORIC is 40 mg once daily. For patients who do not achieve a serum uric acid (sUA) less than 6 mg/dL after two weeks, the recommended ULORIC dosage is 80 mg once daily.

ULORIC can be taken without regard to food or antacid use [see Clinical Pharmacology (12.3)].

2.2 Dosage Recommendations in Patients with Renal Impairment and Hepatic Impairment

No dose adjustment is necessary when administering ULORIC in patients with mild or moderate renal impairment.

The recommended dosage of ULORIC is limited to 40 mg once daily in patients with severe renal impairment [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].

No dose adjustment is necessary in patients with mild to moderate hepatic impairment [see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)].

2.3 Uric Acid Level

Testing for the target serum uric acid level of less than 6 mg/dL may be performed as early as two weeks after initiating ULORIC therapy.

2.4 Recommended Prophylaxis for Gout Flares

Gout flares may occur after initiation of ULORIC due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. Flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended upon initiation of ULORIC. Prophylactic therapy may be beneficial for up to six months [see *Clinical Studies (14.1)*].

If a gout flare occurs during ULORIC treatment, ULORIC need not be discontinued. The gout flare should be managed concurrently, as appropriate for the individual patient [see *Warnings and Precautions (5.2)*].

3 DOSAGE FORMS AND STRENGTHS

- 40 mg tablets, light green to green, round, debossed with “TAP” and “40”
- 80 mg tablets, light green to green, teardrop shaped, debossed with “TAP” and “80”

4 CONTRAINDICATIONS

ULORIC is contraindicated in patients being treated with azathioprine or mercaptopurine [see *Drug Interactions (7)*].

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Death

In a cardiovascular (CV) outcome study (ClinicalTrials.gov identifier NCT01101035), gout patients with established CV disease treated with ULORIC had a higher rate of CV death compared to those treated with allopurinol. The CV outcomes study in patients with gout (CARES) was a randomized, double-blinded, allopurinol-controlled, non-inferiority study conducted to evaluate the risk of major adverse cardiovascular events (MACE) in patients with gout who were treated with ULORIC. The study enrolled patients who had a history of major CV disease, cerebrovascular disease or diabetes mellitus with micro- and/or macrovascular disease. The primary endpoint was the time to first occurrence of MACE defined as the composite of CV death, nonfatal MI, nonfatal stroke, or unstable angina with urgent coronary revascularization. The study was designed to exclude a prespecified risk margin of 1.3 for the hazard ratio of MACE. Results showed that ULORIC was non-inferior to allopurinol for the primary endpoint of MACE [Hazard Ratio: 1.03, 95% Confidence Interval (CI): 0.89, 1.21]. However, there was a significant increase in CV deaths in patients treated with ULORIC (134 [1.5 per 100 patient-years]) compared to patients treated with allopurinol (100 [1.1 per 100 patient-years]) [Hazard Ratio: 1.34, 95% CI: 1.03, 1.73]. Sudden cardiac death was the most common cause of adjudicated CV deaths in the ULORIC group (83 of 3,098; 2.7%) as compared to the allopurinol group (56 of 3,092; 1.8%). ULORIC was similar to allopurinol for nonfatal MI, nonfatal stroke and unstable angina with urgent coronary revascularization [see *Clinical Studies (14.2)*].

Because of the increased risk of CV death, ULORIC should only be used in patients who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable [see *Indications and Usage(1)*].

Consider the risks and benefits of ULORIC when deciding to prescribe or continue patients on ULORIC [see *Indications and Usage (1)*]. Consider use of prophylactic low-dose aspirin therapy in patients with a history of CV disease. Physicians and patients should remain alert for the development of adverse CV event signs and symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

5.2 Gout Flares

After initiation of ULORIC, an increase in gout flares is frequently observed. This increase is due to reduction in serum uric acid levels, resulting in mobilization of urate from tissue deposits.

In order to prevent gout flares when ULORIC is initiated, concurrent prophylactic treatment with an NSAID or colchicine is recommended [see *Dosage and Administration* (2.4)].

5.3 Hepatic Effects

There have been postmarketing reports of fatal and nonfatal hepatic failure in patients taking ULORIC, although the reports contain insufficient information necessary to establish the probable cause. During randomized controlled studies, transaminase elevations greater than three times the upper limit of normal (ULN) were observed (AST: 2%, 2%, and ALT: 3%, 2% in ULORIC and allopurinol-treated patients, respectively). No dose-effect relationship for these transaminase elevations was noted [see *Clinical Pharmacology* (12.3)].

Obtain a liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) as a baseline before initiating ULORIC.

Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. In this clinical context, if the patient is found to have abnormal liver tests (ALT greater than three times the upper limit of the reference range), ULORIC treatment should be interrupted and investigation done to establish the probable cause. ULORIC should not be restarted in these patients without another explanation for the liver test abnormalities.

Patients who have serum ALT greater than three times the reference range with serum total bilirubin greater than two times the reference range without alternative etiologies are at risk for severe drug-induced liver injury and should not be restarted on ULORIC. For patients with lesser elevations of serum ALT or bilirubin and with an alternate probable cause, treatment with ULORIC can be used with caution.

5.4 Serious Skin Reactions

Postmarketing reports of serious skin and hypersensitivity reactions, including Stevens-Johnson Syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis (TEN) have been reported in patients taking ULORIC. Discontinue ULORIC if serious skin reactions are suspected [see *Patient Counseling Information* (17)]. Many of these patients had reported previous similar skin reactions to allopurinol. ULORIC should be used with caution in these patients.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the prescribing information:

- Cardiovascular Death [see *Warnings and Precautions* (5.1)]
- Hepatic Effects [see *Warnings and Precautions* (5.3)]
- Serious Skin Reactions [see *Warnings and Precautions* (5.4)]

6.1 Clinical Trials Experience

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

In Phase 2 and 3 clinical studies, a total of 2757 patients with hyperuricemia and gout were treated with ULORIC 40 mg or 80 mg daily. For ULORIC 40 mg, 559 patients were treated for ≥6 months. For ULORIC 80 mg, 1377 patients were treated for ≥6 months, 674 patients were treated for ≥1 year and 515 patients were treated for ≥2 years. In the CARES study, a total of 3098 patients

were treated with ULORIC 40 mg or 80 mg daily; of these, 2155 patients were treated for ≥ 1 year and 1539 were treated for ≥ 2 years [see *Clinical Studies* (14.2)].

Most Common Adverse Reactions

In three randomized, controlled clinical studies (Studies 1, 2 and 3), which were six to 12 months in duration, the following adverse reactions were reported by the treating physician as related to study drug. Table 1 summarizes adverse reactions reported at a rate of at least 1% in ULORIC treatment groups and at least 0.5% greater than placebo.

Table 1: Adverse Reactions Occurring in $\geq 1\%$ of Patients Treated with ULORIC and at Least 0.5% Greater than Seen in Patients Receiving Placebo in Controlled Studies

Adverse Reactions	Placebo	ULORIC		allopurinol*
	(N=134)	40 mg daily (N=757)	80 mg daily (N=1279)	(N=1277)
Liver Function Abnormalities	0.7%	6.6%	4.6%	4.2%
Nausea	0.7%	1.1%	1.3%	0.8%
Arthralgia	0%	1.1%	0.7%	0.7%
Rash	0.7%	0.5%	1.6%	1.6%

* Of the patients who received allopurinol, 10 received 100 mg, 145 received 200 mg, and 1122 received 300 mg, based on level of renal impairment.

The most common adverse reaction leading to discontinuation from therapy was liver function abnormalities in 1.8% of ULORIC 40 mg, 1.2% of ULORIC 80 mg, and in 0.9% of patients treated with allopurinol.

In addition to the adverse reactions presented in Table 1, dizziness was reported in more than 1% of patients treated with ULORIC although not at a rate more than 0.5% greater than placebo.

In the CARES study, liver function abnormalities and diarrhea were reported in more than 1% of patients treated with ULORIC, although not at a rate more than 0.5% greater than allopurinol.

Less Common Adverse Reactions

In clinical studies the following adverse reactions occurred in less than 1% of patients and in more than one subject treated with doses ranging from 40 mg to 240 mg of ULORIC. This list also includes adverse reactions (less than 1% of patients) associated with organ systems from Warnings and Precautions.

Blood and Lymphatic System Disorders: anemia, idiopathic thrombocytopenic purpura, leukocytosis/leukopenia, neutropenia, pancytopenia, splenomegaly, thrombocytopenia.

Cardiac Disorders: angina pectoris, atrial fibrillation/flutter, cardiac murmur, ECG abnormal, palpitations, sinus bradycardia, tachycardia.

Ear and Labyrinth Disorders: deafness, tinnitus, vertigo.

Eye Disorders: vision blurred.

Gastrointestinal Disorders: abdominal distention, abdominal pain, constipation, dry mouth, dyspepsia, flatulence, frequent stools, gastritis, gastroesophageal reflux disease, gastrointestinal discomfort, gingival pain, haematemesis, hyperchlorhydria, hematochezia, mouth ulceration, pancreatitis, peptic ulcer, vomiting.

General Disorders and Administration Site Conditions: asthenia, chest pain/discomfort, edema, fatigue, feeling abnormal, gait disturbance, influenza-like symptoms, mass, pain, thirst.

Hepatobiliary Disorders: cholelithiasis/cholecystitis, hepatic steatosis, hepatitis, hepatomegaly.

Immune System Disorder: hypersensitivity.

Infections and Infestations: herpes zoster.

Procedural Complications: contusion.

Metabolism and Nutrition Disorders: anorexia, appetite decreased/increased, dehydration, diabetes mellitus, hypercholesterolemia, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypokalemia, weight decreased/increased.

Musculoskeletal and Connective Tissue Disorders: arthritis, joint stiffness, joint swelling, muscle spasms/twitching/tightness/weakness, musculoskeletal pain/stiffness, myalgia.

Nervous System Disorders: altered taste, balance disorder, cerebrovascular accident, Guillain-Barré syndrome, headache, hemiparesis, hypoesthesia, hyposmia, lacunar infarction, lethargy, mental impairment, migraine, paresthesia, somnolence, transient ischemic attack, tremor.

Psychiatric Disorders: agitation, anxiety, depression, insomnia, irritability, libido decreased, nervousness, panic attack, personality change.

Renal and Urinary Disorders: hematuria, nephrolithiasis, pollakiuria, proteinuria, renal failure, renal insufficiency, urgency, incontinence.

Reproductive System and Breast Changes: breast pain, erectile dysfunction, gynecomastia.

Respiratory, Thoracic and Mediastinal Disorders: bronchitis, cough, dyspnea, epistaxis, nasal dryness, paranasal sinus hypersecretion, pharyngeal edema, respiratory tract congestion, sneezing, throat irritation, upper respiratory tract infection.

Skin and Subcutaneous Tissue Disorders: alopecia, angio-edema, dermatitis, dermographism, ecchymosis, eczema, hair color changes, hair growth abnormal, hyperhidrosis, peeling skin, petechiae, photosensitivity, pruritus, purpura, skin discoloration/alteration/pigmentation, skin lesion, skin odor abnormal, urticaria.

Vascular Disorders: flushing, hot flush, hypertension, hypotension.

Laboratory Parameters: activated partial thromboplastin time prolonged, creatine increased, bicarbonate decreased, sodium increased, EEG abnormal, glucose increased, cholesterol increased, triglycerides increased, amylase increased, potassium increased, TSH increased, platelet count decreased, hematocrit decreased, hemoglobin decreased, MCV increased, RBC decreased, creatinine increased, blood urea increased, BUN/creatinine ratio increased, creatine phosphokinase (CPK) increased, alkaline phosphatase increased, LDH increased, PSA increased, urine output increased/decreased, lymphocyte count decreased, neutrophil count decreased, WBC increased/decreased, coagulation test abnormal, low density lipoprotein (LDL) increased, prothrombin time prolonged, urinary casts, urine positive for white blood cells and protein.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of ULORIC. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: agranulocytosis, eosinophilia.

Hepatobiliary Disorders: hepatic failure (some fatal), jaundice, serious cases of abnormal liver function test results, liver disorder.

Immune System Disorders: anaphylaxis, anaphylactic reaction.

Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis.

Psychiatric Disorders: psychotic behavior including aggressive thoughts.

Renal and Urinary Disorders: tubulointerstitial nephritis.

Skin and Subcutaneous Tissue Disorders: generalized rash, Stevens-Johnson Syndrome, hypersensitivity skin reactions, erythema multiforme, drug reaction with eosinophilia and systemic symptoms, toxic epidermal necrolysis.

7 DRUG INTERACTIONS

7.1 Xanthine Oxidase Substrate Drugs

ULORIC is an XO inhibitor. Based on a drug interaction study in healthy patients, febuxostat altered the metabolism of theophylline (a substrate of XO) in humans [see *Clinical Pharmacology (12.3)*]. Therefore, use with caution when coadministering ULORIC with theophylline.

Drug interaction studies of ULORIC with other drugs that are metabolized by XO (e.g., mercaptopurine and azathioprine) have not been conducted. Inhibition of XO by ULORIC may cause increased plasma concentrations of these drugs leading to toxicity [see *Clinical Pharmacology (12.3)*]. ULORIC is contraindicated in patients being treated with azathioprine or mercaptopurine [see *Contraindications (4)*].

7.2 Cytotoxic Chemotherapy Drugs

Drug interaction studies of ULORIC with cytotoxic chemotherapy have not been conducted. No data are available regarding the safety of ULORIC during cytotoxic chemotherapy.

7.3 *In Vivo* Drug Interaction Studies

Based on drug interaction studies in healthy patients, ULORIC does not have clinically significant interactions with colchicine, naproxen, indomethacin, hydrochlorothiazide, warfarin or desipramine [see *Clinical Pharmacology (12.3)*]. Therefore, ULORIC may be used concomitantly with these medications.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited available data with ULORIC use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes. No adverse developmental effects were observed in embryo-fetal development studies with oral administration of febuxostat to pregnant rats and rabbits during organogenesis at doses that produced maternal exposures up to 40 and 51 times, respectively, the exposure at the maximum recommended human dose (MRHD). No adverse developmental effects were observed in a pre- and postnatal development study with administration of febuxostat to pregnant rats from organogenesis through lactation at an exposure approximately 11 times the MRHD (see *Data*).

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

Data

Animal Data

In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation Days 7 – 17, febuxostat was not teratogenic and did not affect fetal development or survival at exposures up to approximately 40 times the MRHD (on an AUC basis at maternal oral

doses up to 48 mg/kg/day). In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation Days 6 – 18, febuxostat was not teratogenic and did not affect fetal development at exposures up to approximately 51 times the MRHD (on an AUC basis at maternal oral doses up to 48 mg/kg/day).

In a pre- and postnatal development study in pregnant female rats dosed orally from gestation Day 7 through lactation Day 20, febuxostat had no effects on delivery or growth and development of offspring at a dose approximately 11 times the MRHD (on an AUC basis at a maternal oral dose of 12 mg/kg/day). However, increased neonatal mortality and a reduction in neonatal body weight gain were observed in the presence of maternal toxicity at a dose approximately 40 times the MRHD (on an AUC basis at a maternal oral dose of 48 mg/kg/day).

Febuxostat crossed the placental barrier following oral administration to pregnant rats and was detected in fetal tissues.

8.2 Lactation

Risk Summary

There are no data on the presence of febuxostat in human milk, the effects on the breastfed infant, or the effects on milk production. Febuxostat is present in rat milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ULORIC and any potential adverse effects on the breastfed child from ULORIC or from the underlying maternal condition.

Data

Animal Data

Orally administered febuxostat was detected in the milk of lactating rats at up to approximately 7 times the plasma concentration.

8.4 Pediatric Use

Safety and effectiveness of ULORIC in pediatric patients have not been established.

8.5 Geriatric Use

No dose adjustment is necessary in elderly patients. Of the total number of patients in Studies 1, 2, and 3 (clinical studies of ULORIC in the treatment of gout) [see *Clinical Studies (14.1)*], 16% were 65 and over, while 4% were 75 and over. Comparing patients in different age groups, no clinically significant differences in safety or effectiveness were observed but greater sensitivity of some older individuals cannot be ruled out. The C_{max} and AUC_{24} of febuxostat following multiple oral doses of ULORIC in geriatric patients (≥ 65 years) were similar to those in younger patients (18 to 40 years) [see *Clinical Pharmacology (12.3)*].

8.6 Renal Impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment (Cl_{cr} 30 to 89 mL/min). For patients with severe renal impairment (Cl_{cr} 15 to 29 mL/min), the recommended dosage of ULORIC is limited to 40 mg once daily [see *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

No dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh Class A or B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C); therefore, caution should be exercised in these patients [see *Clinical Pharmacology (12.3)*].

8.8 Secondary Hyperuricemia

No studies have been conducted in patients with secondary hyperuricemia (including organ transplant recipients); ULORIC is not recommended for use in patients whom the rate of urate

formation is greatly increased (e.g., malignant disease and its treatment, Lesch-Nyhan syndrome). The concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract.

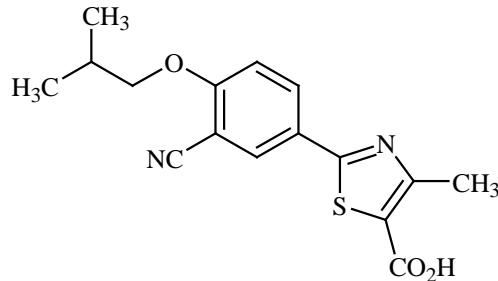
10 OVERDOSAGE

ULORIC was studied in healthy patients in doses up to 300 mg daily for seven days without evidence of dose-limiting toxicities. No overdose of ULORIC was reported in clinical studies. Patients should be managed by symptomatic and supportive care should there be an overdose.

11 DESCRIPTION

ULORIC (febuxostat) is a xanthine oxidase inhibitor. The active ingredient in ULORIC is 2-[3-cyano-4-(2-methylpropoxy) phenyl]-4-methylthiazole-5-carboxylic acid, with a molecular weight of 316.38. The empirical formula is C₁₆H₁₆N₂O₃S.

The chemical structure is:



Febuxostat is a non-hygroscopic, white crystalline powder that is freely soluble in dimethylformamide; soluble in dimethylsulfoxide; sparingly soluble in ethanol; slightly soluble in methanol and acetonitrile; and practically insoluble in water. The melting range is 205°C to 208°C.

ULORIC tablets for oral use contain the active ingredient, febuxostat, and are available in two dosage strengths, 40 mg and 80 mg. Inactive ingredients include lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, sodium croscarmellose, silicon dioxide and magnesium stearate. ULORIC tablets are coated with Opadry II, green.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ULORIC, a xanthine oxidase inhibitor, achieves its therapeutic effect by decreasing serum uric acid. ULORIC is not expected to inhibit other enzymes involved in purine and pyrimidine synthesis and metabolism at therapeutic concentrations.

12.2 Pharmacodynamics

Effect on Uric Acid and Xanthine Concentrations

In healthy patients, ULORIC resulted in a dose dependent decrease in 24 hour mean serum uric acid concentrations and an increase in 24 hour mean serum xanthine concentrations. In addition, there was a decrease in the total daily urinary uric acid excretion. Also, there was an increase in total daily urinary xanthine excretion. Percent reduction in 24 hour mean serum uric acid concentrations was between 40% and 55% at the exposure levels of 40 mg and 80 mg daily doses.

Effect on Cardiac Repolarization

The effect of ULORIC on cardiac repolarization as assessed by the QTc interval was evaluated in normal healthy patients and in patients with gout. ULORIC in doses up to 300 mg daily (3.75 times the maximum recommended daily dosage), at steady-state, did not demonstrate an effect on the QTc interval.

12.3 Pharmacokinetics

In healthy patients, maximum plasma concentrations (C_{max}) and AUC of febuxostat increased in a dose proportional manner following single and multiple doses of 10 mg (0.25 times the lowest recommended dosage) to 120 mg (1.5 times the maximum recommended dosage). There is no accumulation when therapeutic doses are administered every 24 hours. Febuxostat has an apparent mean terminal elimination half-life ($t_{1/2}$) of approximately 5 to 8 hours. Febuxostat pharmacokinetic parameters for patients with hyperuricemia and gout estimated by population pharmacokinetic analyses were similar to those estimated in healthy patients.

Absorption

The absorption of radiolabeled febuxostat following oral dose administration was estimated to be at least 49% (based on total radioactivity recovered in urine). Maximum plasma concentrations of febuxostat occurred between 1 and 1.5 hours postdose. After multiple oral 40 mg and 80 mg once daily doses, C_{max} is approximately 1.6 ± 0.6 mcg/mL (N=30), and 2.6 ± 1.7 mcg/mL (N=227), respectively. Absolute bioavailability of the febuxostat tablet has not been studied.

Following multiple 80 mg once daily doses with a high fat meal, there was a 49% decrease in C_{max} and an 18% decrease in AUC, respectively. However, no clinically significant change in the percent decrease in serum uric acid concentration was observed (58% fed vs 51% fasting). Thus, ULORIC may be taken without regard to food.

Concomitant ingestion of an antacid containing magnesium hydroxide and aluminum hydroxide with an 80 mg single dose of ULORIC has been shown to delay absorption of febuxostat (approximately one hour) and to cause a 31% decrease in C_{max} and a 15% decrease in AUC ∞ . As AUC rather than C_{max} was related to drug effect, change observed in AUC was not considered clinically significant. Therefore, ULORIC may be taken without regard to antacid use.

Distribution

The mean apparent steady state volume of distribution (V_{ss}/F) of febuxostat was approximately 50 L (CV ~40%). The plasma protein binding of febuxostat is approximately 99.2% (primarily to albumin), and is constant over the concentration range achieved with 40 mg and 80 mg doses.

Metabolism

Febuxostat is extensively metabolized by both conjugation via uridine diphosphate glucuronosyltransferase (UGT) enzymes including UGT1A1, UGT1A3, UGT1A9, and UGT2B7 and oxidation via cytochrome P450 (CYP) enzymes including CYP1A2, 2C8 and 2C9 and non-P450 enzymes. The relative contribution of each enzyme isoform in the metabolism of febuxostat is not clear. The oxidation of the isobutyl side chain leads to the formation of four pharmacologically active hydroxy metabolites, all of which occur in plasma of humans at a much lower extent than febuxostat.

In urine and feces, acyl glucuronide metabolites of febuxostat (~35% of the dose), and oxidative metabolites, 67M-1 (~10% of the dose), 67M-2 (~11% of the dose), and 67M-4, a secondary metabolite from 67M-1 (~14% of the dose), appeared to be the major metabolites of febuxostat *in vivo*.

Elimination

Febuxostat is eliminated by both hepatic and renal pathways. Following an 80 mg oral dose of ^{14}C -labeled febuxostat, approximately 49% of the dose was recovered in the urine as unchanged febuxostat (3%), the acyl glucuronide of the drug (30%), its known oxidative metabolites and their conjugates (13%), and other unknown metabolites (3%). In addition to the urinary excretion, approximately 45% of the dose was recovered in the feces as the unchanged febuxostat (12%), the acyl glucuronide of the drug (1%), its known oxidative metabolites and their conjugates (25%), and other unknown metabolites (7%).

The apparent mean terminal elimination half-life ($t_{1/2}$) of febuxostat was approximately 5 to 8 hours.

Specific Populations

Geriatic Patients

The C_{max} and AUC of febuxostat and its metabolites following multiple oral doses of ULORIC in geriatric patients (≥ 65 years) were similar to those in younger patients (18 to 40 years). In addition, the percent decrease in serum uric acid concentration was similar between elderly and younger patients. No dose adjustment is necessary in geriatric patients [see *Use in Specific Populations* (8.5)].

Patients with Renal Impairment

In a dedicated phase I pharmacokinetics study, following multiple 80 mg doses of ULORIC in healthy patients with mild (Cl_{cr} 50 to 80 mL/min), moderate (Cl_{cr} 30 to 49 mL/min) or severe renal impairment (Cl_{cr} 10 to 29 mL/min), the C_{max} of febuxostat did not change relative to patients with normal renal function (Cl_{cr} greater than 80 mL/min). AUC and half-life of febuxostat increased in patients with renal impairment in comparison to patients with normal renal function, but values were similar among three renal impairment groups. Mean febuxostat AUC values were up to 1.8 times higher in patients with renal impairment compared to those with normal renal function. Mean C_{max} and AUC values for three active metabolites increased up to two and four-fold, respectively. However, the percent decrease in serum uric acid concentration for patients with renal impairment was comparable to those with normal renal function (58% in normal renal function group and 55% in the severe renal function group).

Based on population pharmacokinetic analysis, following multiple 40 mg or 80 mg doses of ULORIC, the mean oral clearance (CL/F) values of febuxostat in patients with gout and mild ($n=334$), moderate ($n=232$) or severe ($n=34$) renal impairment were decreased by 14%, 34%, and 48%, respectively, compared to patients with normal ($n=89$) renal function. The corresponding median AUC values of febuxostat at steady-state in patients with renal impairment were increased by 18%, 49%, and 96% after 40 mg dose, and 7%, 45% and 98% after 80 mg dose, respectively, compared to patients with normal renal function.

ULORIC has not been studied in end stage renal impairment patients who are on dialysis.

Patients with Hepatic Impairment

Following multiple 80 mg doses of ULORIC in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, an average of 20% to 30% increase was observed for both C_{max} and AUC_{24} (total and unbound) in hepatic impairment groups compared to patients with normal hepatic function. In addition, the percent decrease in serum uric acid concentration was comparable between different hepatic groups (62% in healthy group, 49% in mild hepatic impairment group, and 48% in moderate hepatic impairment group). No dose adjustment is necessary in patients with mild or moderate hepatic impairment. No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C); caution should be exercised in those patients [see *Use in Specific Populations* (8.7)].

Male and Female Patients

Following multiple oral doses of ULORIC, the C_{max} and AUC_{24} of febuxostat were 30% and 14% higher in females than in males, respectively. However, weight-corrected C_{max} and AUC were similar between the genders. In addition, the percent decrease in serum uric acid concentrations was similar between genders. No dose adjustment is necessary based on gender.

Racial Groups

No specific pharmacokinetic study was conducted to investigate the effects of race.

Drug Interaction Studies

Effect of ULORIC on Other Drugs

Xanthine Oxidase Substrate Drugs-Azathioprine, Mercaptopurine, and Theophylline

Febuxostat is an XO inhibitor. A drug-drug interaction study evaluating the effect of ULORIC upon the pharmacokinetics of theophylline (an XO substrate) in healthy patients showed that coadministration of febuxostat with theophylline resulted in an approximately 400-fold increase in the amount of 1-methylxanthine, one of the major metabolites of theophylline, excreted in the urine. Since the long-term safety of exposure to 1-methylxanthine in humans is unknown, use with caution when coadministering febuxostat with theophylline.

Drug interaction studies of ULORIC with other drugs that are metabolized by XO (e.g., mercaptopurine and azathioprine) have not been conducted. Inhibition of XO by ULORIC may cause increased plasma concentrations of these drugs leading to toxicity. ULORIC is contraindicated in patients being treated with azathioprine or mercaptopurine [see *Contraindications (4)* and *Drug Interactions (7)*].

Azathioprine and mercaptopurine undergo metabolism via three major metabolic pathways, one of which is mediated by XO. Although ULORIC drug interaction studies with azathioprine and mercaptopurine have not been conducted, concomitant administration of allopurinol [a xanthine oxidase inhibitor] with azathioprine or mercaptopurine has been reported to substantially increase plasma concentrations of these drugs. Because ULORIC is a xanthine oxidase inhibitor, it could inhibit the XO-mediated metabolism of azathioprine and mercaptopurine leading to increased plasma concentrations of azathioprine or mercaptopurine that could result in severe toxicity.

P450 Substrate Drugs

In vitro studies have shown that febuxostat does not inhibit P450 enzymes CYP1A2, 2C9, 2C19, 2D6, or 3A4 and it also does not induce CYP1A2, 2B6, 2C9, 2C19, or 3A4 at clinically relevant concentrations. As such, pharmacokinetic interactions between ULORIC and drugs metabolized by these CYP enzymes are unlikely.

Effect of Other Drugs on ULORIC

Febuxostat is metabolized by conjugation and oxidation via multiple metabolizing enzymes. The relative contribution of each enzyme isoform is not clear. Drug interactions between ULORIC and a drug that inhibits or induces one particular enzyme isoform is in general not expected.

In Vivo Drug Interaction Studies

Theophylline

No dose adjustment is necessary for theophylline when coadministered with ULORIC. Administration of ULORIC (80 mg once daily) with theophylline resulted in an increase of 6% in C_{max} and 6.5% in AUC of theophylline. These changes were not considered statistically significant. However, the study also showed an approximately 400-fold increase in the amount of 1-methylxanthine (one of the major theophylline metabolites) excreted in urine as a result of XO inhibition by ULORIC. The safety of long-term exposure to 1-methylxanthine has not been evaluated. This should be taken into consideration when deciding to coadminister ULORIC and theophylline.

Colchicine

No dose adjustment is necessary for either ULORIC or colchicine when the two drugs are coadministered. Administration of ULORIC (40 mg once daily) with colchicine (0.6 mg twice daily) resulted in an increase of 12% in C_{max} and 7% in AUC_{24} of febuxostat. In addition, administration of colchicine (0.6 mg twice daily) with ULORIC (120 mg daily) resulted in a less than 11% change in C_{max} or AUC of colchicine for both AM and PM doses. These changes were not considered clinically significant.

Naproxen

No dose adjustment is necessary for ULORIC or naproxen when the two drugs are coadministered. Administration of ULORIC (80 mg once daily) with naproxen (500 mg twice daily) resulted in a 28% increase in C_{max} and a 40% increase in AUC of febuxostat. The increases were not considered clinically significant. In addition, there were no significant changes in the C_{max} or AUC of naproxen (less than 2%).

Indomethacin

No dose adjustment is necessary for either ULORIC or indomethacin when these two drugs are coadministered. Administration of ULORIC (80 mg once daily) with indomethacin (50 mg twice daily) did not result in any significant changes in C_{max} or AUC of febuxostat or indomethacin (less than 7%).

Hydrochlorothiazide

No dose adjustment is necessary for ULORIC when coadministered with hydrochlorothiazide. Administration of ULORIC (80 mg) with hydrochlorothiazide (50 mg) did not result in any clinically significant changes in C_{max} or AUC of febuxostat (less than 4%), and serum uric acid concentrations were not substantially affected.

Warfarin

No dose adjustment is necessary for warfarin when coadministered with ULORIC. Administration of ULORIC (80 mg once daily) with warfarin had no effect on the pharmacokinetics of warfarin in healthy patients. INR and Factor VII activity were also not affected by the coadministration of ULORIC.

Desipramine

Coadministration of drugs that are CYP2D6 substrates (such as desipramine) with ULORIC are not expected to require dose adjustment. Febuxostat was shown to be a weak inhibitor of CYP2D6 *in vitro* and *in vivo*. Administration of ULORIC (120 mg once daily) with desipramine (25 mg) resulted in an increase in C_{max} (16%) and AUC (22%) of desipramine, which was associated with a 17% decrease in the 2-hydroxydesipramine to desipramine metabolic ratio (based on AUC).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two year carcinogenicity studies were conducted in F344 rats and B6C3F1 mice. Increased transitional cell papilloma and carcinoma of the urinary bladder was observed at 24 mg/kg (25 times the MRHD on an AUC basis and 18.75 mg/kg (12.5 times the MRHD on an AUC basis) in male rats and female mice, respectively. The urinary bladder neoplasms were secondary to calculus formation in the kidney and urinary bladder.

Febuxostat showed a positive clastogenic response in a chromosomal aberration assay in a Chinese hamster lung fibroblast cell line with and without metabolic activation *in vitro*. Febuxostat was negative in the following genotoxicity assays: the *in vitro* Ames assay, *in vitro* chromosomal aberration assay in human peripheral lymphocytes, the L5178Y mouse lymphoma cell line assay, the *in vivo* mouse micronucleus assay, and the rat unscheduled DNA synthesis assay.

Fertility and reproductive performance were unaffected in male or female rats that received febuxostat at oral doses up to 48 mg/kg/day (approximately 31 and 40 times the MRHD on an AUC basis in males and females respectively).

13.2 Animal Toxicology

A 12 month toxicity study in beagle dogs showed deposition of xanthine crystals and calculi in kidneys at 15 mg/kg (approximately 4 times the MRHD on an AUC basis). A similar effect of calculus formation was noted in rats in a six month study due to deposition of xanthine crystals at

48 mg/kg (approximately 31 and 40 times the MRHD on an AUC basis in males and females respectively).

14 CLINICAL STUDIES

A serum uric acid level of less than 6 mg/dL is the goal of antihyperuricemic therapy and has been established as appropriate for the treatment of gout.

14.1 Management of Hyperuricemia in Gout

The efficacy of ULORIC was demonstrated in three randomized, double-blind, controlled trials in patients with hyperuricemia and gout. Hyperuricemia was defined as a baseline serum uric acid level ≥ 8 mg/dL.

Study 1 (ClinicalTrials.gov identifier NCT00430248) randomized patients to: ULORIC 40 mg daily, ULORIC 80 mg daily, or allopurinol (300 mg daily for patients with estimated creatinine clearance (Cl_{cr}) ≥ 60 mL/min or 200 mg daily for patients with estimated $Cl_{cr} \geq 30$ mL/min and ≤ 59 mL/min). The duration of Study 1 was six months.

Study 2 (ClinicalTrials.gov identifier NCT00174915) randomized patients to: placebo, ULORIC 80 mg daily, ULORIC 120 mg daily, ULORIC 240 mg daily or allopurinol (300 mg daily for patients with a baseline serum creatinine ≤ 1.5 mg/dL or 100 mg daily for patients with a baseline serum creatinine greater than 1.5 mg/dL and ≤ 2 mg/dL). The duration of Study 2 was six months.

Study 3 (ClinicalTrials.gov identifier NCT00102440), a one year study, randomized patients to: ULORIC 80 mg daily, ULORIC 120 mg daily, or allopurinol 300 mg daily. Patients who completed Study 2 and Study 3 were eligible to enroll in a Phase 3 long-term extension study in which patients received treatment with ULORIC for over three years.

In all three studies, patients received naproxen 250 mg twice daily or colchicine 0.6 mg once or twice daily for gout flare prophylaxis. In Study 1 the duration of prophylaxis was six months; in Study 2 and Study 3 the duration of prophylaxis was eight weeks.

The efficacy of ULORIC was also evaluated in a four week dose ranging study which randomized patients to: placebo, ULORIC 40 mg daily, ULORIC 80 mg daily, or ULORIC 120 mg daily. Patients who completed this study were eligible to enroll in a long-term extension study in which patients received treatment with ULORIC for up to five years.

Patients in these studies were representative of the patient population for which ULORIC use is intended. Table 2 summarizes the demographics and baseline characteristics for the patients enrolled in the studies.

Table 2: Patient Demographics and Baseline Characteristics in Study 1, Study 2, and Study 3

Male	95%
Race: Caucasian	80%
	10%
Ethnicity: Hispanic or Latino	7%
Alcohol User	67%
Mild to Moderate Renal Insufficiency (percent with estimated Cl_{cr} less than 90 mL/min)	59%
History of Hypertension	49%

History of Hyperlipidemia	38%
BMI $\geq 30 \text{ kg/m}^2$	63%
Mean BMI	33 kg/m ²
Baseline sUA $\geq 10 \text{ mg/dL}$	36%
Mean baseline sUA	9.7 mg/dL
Experienced a gout flare in previous year	85%

Serum Uric Acid Level less than 6 mg/dL at Final Visit

ULORIC 80 mg was superior to allopurinol in lowering serum uric acid to less than 6 mg/dL at the final visit. ULORIC 40 mg daily, although not superior to allopurinol, was effective in lowering serum uric acid to less than 6 mg/dL at the final visit (*Table 3*).

Table 3: Proportion of Patients with Serum Uric Acid Levels less than 6 mg/dL at Final Visit

Study*	ULORIC 40 mg daily	ULORIC 80 mg daily	allopurinol	Placebo	Difference in Proportion (95% CI)	
					ULORIC 40 mg vs allopurinol	ULORIC 80 mg vs allopurinol
Study 1 (6 months) (N=2268)	45%	67%	42%		3% (-2%, 8%)	25% (20%, 30%)
Study 2 (6 months) (N=643)		72%	39%	1%		33% (26%, 42%)
Study 3 (12 months) (N=491)		74%	36%			38% (30%, 46%)

* Randomization was balanced between treatment groups, except in Study 2 in which twice as many patients were randomized to each of the active treatment groups compared to placebo.

In 76% of ULORIC 80 mg patients, reduction in serum uric acid levels to less than 6 mg/dL was noted by the Week 2 visit. Average serum uric acid levels were maintained at 6 mg/dL or below throughout treatment in 83% of these patients.

In all treatment groups, fewer patients with higher baseline serum urate levels ($\geq 10 \text{ mg/dL}$) and/or tophi achieved the goal of lowering serum uric acid to less than 6 mg/dL at the final visit; however, a higher proportion achieved a serum uric acid less than 6 mg/dL with ULORIC 80 mg than with ULORIC 40 mg or allopurinol.

Study 1 evaluated efficacy in patients with mild to moderate renal impairment (i.e., baseline estimated Cl_{cr} less than 90 mL/min). The results in this subgroup of patients are shown in Table 4.

Table 4: Proportion of Patients with Serum Uric Acid Levels less than 6 mg/dL in Patients with Mild or Moderate Renal Impairment at Final Visit

	ULORIC 40 mg daily (N=479)	ULORIC 80 mg daily (N=503)	allopurinol* 300 mg daily (N=501)	Difference in Proportion (95% CI)	
				ULORIC 40 mg vs allopurinol	ULORIC 80 mg vs allopurinol
	50%	72%	42%	7% (1%, 14%)	29% (23%, 35%)

* Allopurinol patients (n=145) with estimated $\text{Cl}_{\text{Cr}} \geq 30 \text{ mL/min}$ and $\text{Cl}_{\text{Cr}} \leq 59 \text{ mL/min}$ were dosed at 200 mg daily.

14.2 Cardiovascular Safety Study

A randomized, double-blind, allopurinol-controlled CV outcomes study (CARES) was conducted to evaluate the CV risk of ULORIC. The study compared the risk of MACE between patients treated with ULORIC (N=3098) and allopurinol-treated patients (N=3092). The primary endpoint was the time to first occurrence of a MACE defined as the composite of CV death, nonfatal MI, nonfatal stroke, or unstable angina with urgent coronary revascularization. The study was designed to exclude a prespecified risk margin of 1.3 for the hazard ratio of MACE. An independent committee conducted a blinded evaluation of serious CV adverse events according to predefined criteria (adjudication) for determination of MACE. The study was event driven and patients were followed until a sufficient number of primary outcome events accrued. The median on-study follow-up time was 2.6 years.

Patients randomized to ULORIC initially received 40 mg once daily which was increased to 80 mg once daily, if their sUA was $\geq 6 \text{ mg/dL}$ at Week 2. For patients randomized to allopurinol, those who had normal renal function or mild renal impairment (estimated creatinine clearance (eCl_{Cr}) ≥ 60 to $< 90 \text{ mL/minute}$) initially received 300 mg once daily with 100 mg/day dose increments monthly until either sUA $< 6 \text{ mg/dL}$ or an allopurinol dosage of 600 mg once daily was achieved; those who had moderate renal impairment ($\text{eCl}_{\text{Cr}} \geq 30$ to $< 60 \text{ mL/minute}$) initially received 200 mg once daily with 100 mg/day dose increments monthly until either a sUA $< 6 \text{ mg/dL}$ or an allopurinol dosage of 400 mg once daily was achieved.

The mean age of the population was 65 years (range: 44 to 93 years). Most patients were male (84%) and Caucasian (69%). Patients had a diagnosis of gout for approximately 12 years, a mean baseline sUA of 8.7 mg/dL, and 90% had experienced at least one gout flare in the past year. CV history included MI (39%), hospitalization for unstable angina (28%), cardiac revascularization (37%), and stroke (14%). The most prevalent comorbid conditions were hypertension (92%), hyperlipidemia (87%), diabetes mellitus (55%), diabetes mellitus with micro- or macrovascular disease (39%), and renal impairment [92% with an eCl_{Cr} 30 to 89 mL/minute]. The use of CV disease medication was balanced across treatment groups. Baseline CV disease medications included: ACE inhibitors or ARBs (70%), lipid modifying agents (74%), aspirin (62%), beta-blockers (59%), calcium channel blockers (26%), and nonaspirin antiplatelet medications (31%).

Table 5 shows the study results for the primary MACE composite endpoint and its individual components. For the composite primary endpoint, the ULORIC group was non-inferior compared with the allopurinol group. The rates of nonfatal MI, stroke, and unstable angina with urgent coronary revascularization were similar. There was a higher rate of CV deaths in patients treated with ULORIC (134 CV deaths; 1.5 per 100 PY) than in allopurinol-treated patients (100 CV deaths; 1.1 per 100 PY). Sudden cardiac death was the most common cause of adjudicated CV deaths in the ULORIC group (83

of 3,098; 2.7%) as compared to the allopurinol group (56 of 3,092; 1.8%). The biological plausibility of CV death associated with ULORIC is unclear.

All-cause mortality was higher in the ULORIC group (243 deaths [7.8%]; 2.6 per 100 PY) than the allopurinol group (199 deaths [6.4%]; 2.2 per 100 PY) [Hazard Ratio: 1.22, 95% CI: 1.01, 1.47], due to a higher rate of CV deaths.

Table 5: Patients with MACE in CARES (Cardiovascular Outcomes Study in Patients with Gout)

	ULORIC N=3098		Allopurinol N=3092		Hazard Ratio
	Number of Patients with Event (%)	Rate per 100 PY*	Number of Patients with Event (%)	Rate per 100 PY*	95% CI
Composite of primary endpoint MACE	335 (10.8)	3.8	321 (10.4)	3.7	1.03 (0.89, 1.21)
Cardiovascular Death	134 (4.3)	1.5	100 (3.2)	1.1	1.34 (1.03, 1.73)
Nonfatal MI	111 (3.6)	1.2	118 (3.8)	1.3	0.93 (0.72, 1.21)
Nonfatal stroke	71 (2.3)	0.8	70 (2.3)	0.8	1.01 (0.73, 1.41)
Unstable angina with urgent coronary revascularization	49 (1.6)	0.5	56 (1.8)	0.6	0.86 (0.59, 1.26)

* Patient Years (PY)

16 HOW SUPPLIED/STORAGE AND HANDLING

ULORIC 40 mg tablets are light green to green in color, round, debossed with "TAP" on one side and "40" on the other side and supplied as:

NDC Number	Size
64764-918-11	Hospital Unit Dose Pack of 100 Tablets
64764-918-30	Bottle of 30 Tablets
64764-918-90	Bottle of 90 Tablets
64764-918-18	Bottle of 500 Tablets

ULORIC 80 mg tablets are light green to green in color, teardrop shaped, debossed with "TAP" on one side and "80" on the other side and supplied as:

NDC Number	Size
64764-677-11	Hospital Unit Dose Pack of 100 Tablets
64764-677-30	Bottle of 30 Tablets
64764-677-13	Bottle of 100 Tablets
64764-677-19	Bottle of 1000 Tablets

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

CV Death

Inform patients that gout patients with established CV disease treated with ULORIC had a higher rate of CV death compared to those treated with allopurinol in a CV outcomes study. Inform all patients of the higher rate of CV death with ULORIC compared to allopurinol. Instruct all patients (those with and without CV disease) to be alert for the development of signs and symptoms of CV events [see *Warnings and Precautions (5.1)*].

Gout Flares

Inform patients that after initiation of ULORIC there was an increased frequency of gout flares. Instruct patients that it is recommended to initiate and continue gout prophylaxis therapy for six months while taking ULORIC [see *Warnings and Precautions (5.2)*].

Hepatic Effects

Inform patients that hepatic effects have occurred in patients treated with ULORIC and instruct them to inform their healthcare provider if they experience liver injury symptoms [see *Warnings and Precautions (5.3)*].

Serious Skin Reactions

Inform patients that serious skin and hypersensitivity reactions have occurred in patients treated with ULORIC. Instruct patients to discontinue ULORIC if they develop symptoms of these reactions [see *Warnings and Precautions (5.4)*].

MEDICATION GUIDE
ULORIC (ü-lor-ik)
(febuxostat)
tablets, for oral use

Read the Medication Guide that comes with ULORIC before you start taking it and each time you get a refill. There may be new information. The Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information that I should know about ULORIC?

ULORIC may cause serious side effects, including:

Heart -related deaths.

Call your doctor or get emergency medical help right away if you have any of the following symptoms, especially if they are new, worse, or worry you:

- chest pain
- shortness of breath or trouble breathing
- dizziness, fainting or feeling lightheaded
- rapid or irregular heartbeat
- numbness or weakness in one side of your body
- slurring of speech
- sudden blurry vision or sudden severe headache

What is ULORIC?

ULORIC is a prescription medicine called a xanthine oxidase (XO) inhibitor used to lower blood uric acid levels in adult patients with gout when allopurinol has not worked well enough or when allopurinol is not right for you. ULORIC is not for use in people who do not have symptoms of high blood uric acid levels.

It is not known if ULORIC is safe and effective in children.

Who should not take ULORIC?

Do not take ULORIC if you:

- take azathioprine (Azasan, Imuran)
- take mercaptopurine (Purinethol, Purixan)

What should I tell my doctor before taking ULORIC?

Before taking ULORIC tell your doctor about all of your medical conditions, including if you:

- have taken allopurinol and what happened to you while you were taking it.
- have a history of heart disease or stroke.
- have liver or kidney problems.
- are pregnant or plan to become pregnant. It is not known if ULORIC will harm your unborn baby. Talk with your doctor if you are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. It is not known if ULORIC passes into your breast milk. You and your doctor should decide if you should take ULORIC while breastfeeding.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ULORIC may affect the way other medicines work, and other medicines may affect how ULORIC works.

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

How should I take ULORIC?

- Take ULORIC exactly as your doctor tells you to take it.
- ULORIC can be taken with or without food.
- ULORIC can be taken with antacids.
- Your gout may get worse (flare) when you start taking ULORIC. **Do not stop taking ULORIC because you have a flare.**

Your doctor may do certain tests while you take ULORIC.

What are the possible side effects of ULORIC?

ULORIC may cause serious side effects, including:

- **Heart problems.** See “**What is the most important information I should know about ULORIC?**”.
- **Gout Flares.** Gout flares can happen when you start taking ULORIC. Your doctor may give you other medicines to help prevent your gout flares.
- **Liver problems.** Liver problems can happen in people who take ULORIC. Your doctor may do blood tests to check how well your liver is working before and during your treatment with ULORIC. Tell your doctor if you get any of the following signs or symptoms of liver problems:
 - fatigue
 - loss of appetite for several days or longer
 - pain, aching, or tenderness on the right side
 - dark or “tea-colored” urine
 - your skin or the white part of your eyes turns yellow (jaundice)

of your stomach-area

- **Severe skin and allergic reactions.** Serious skin and allergic reactions that may affect different parts of the body such as your liver, kidneys, heart or lungs, can happen in people who take ULORIC. Call your doctor right away or get emergency medical help if you have any of the following symptoms:
 - rash
 - red and painful skin
 - severe skin blisters
 - peeling skin
 - sores around the lips, eyes or mouth
 - swollen face, lips, mouth, tongue or throat
 - flu-like symptoms

The most common side effects of ULORIC include:

- abnormal liver function tests
- joint pain
- nausea
- rash

These are not all of the possible side effects of ULORIC.

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

How should I store ULORIC?

- Store ULORIC at room temperature.
- Keep ULORIC out of the light.

Keep ULORIC and all medicines out of the reach of children.

General information about the safe and effective use of ULORIC.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ULORIC for a condition for which it was not prescribed. Do not give ULORIC to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your doctor or pharmacist for information about ULORIC that is written for health professionals.

What are the ingredients in ULORIC?

Active ingredient: febuxostat

Inactive ingredients: lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, sodium croscarmellose, silicon dioxide, magnesium stearate, and Opadry II, green

Distributed by:

Takeda Pharmaceuticals America, Inc.

Deerfield, IL 60015

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For more information, go to www.ULORIC.com or call 1-877-TAKEDA (1-877-825-3327).

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