IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

TEIJIN LIMITED, TEIJIN PHARMA LIMITED, and TAKEDA PHARMACEUTICALS U.S.A., INC.,	)	
Plaintiffs,	)	
v.	)	C.A. No. 14-854 (SLR)
PRINSTON PHARMACEUTICAL, INC.,	)	
Defendant.	)	

FIRST AMENDED 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") (collectively with Teijin, "Plaintiffs"), for their Complaint against Defendant Prinston Pharmaceutical, Inc. ("Prinston"), hereby allege as follows:

PARTIES

1. Plaintiff Teijin Ltd. is a Japanese corporation, having a principal place of business at 6-7, Minami-Hommachi 1-chome, Chuo-ku, Osaka 541-8587, 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, Prinston is a corporation organized and existing under the laws of Delaware, having a principal place of business at 2002 Eastpark Blvd., Cranbury, New Jersey 08512. On information and belief, Prinston, directly or through its subsidiaries, is in the business of, among other things, developing, manufacturing, packaging,

and selling generic versions of branded pharmaceutical products for the United States market, including in this judicial district and the State of Delaware, through its own systematic, continuous, constant and pervasive actions.

NATURE OF THE ACTION

5. This is a civil action for infringement of U.S. Patent No. 6,225,474 ("the '474 patent"), and 8,372,872 ("the '872 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

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

7. This Court has personal jurisdiction over Prinston in Delaware because, upon information and belief, Prinston is a Delaware corporation with a registered agent in Delaware, American Incorporators Ltd., which is located at 1013 Centre Road Suite 403-A, Wilmington, DE 19805, and has availed itself of the rights and benefits of Delaware law. Further, upon information and belief, Prinston regularly does business in Delaware and has engaged in a persistent course of conduct within Delaware by continuously and systematically placing goods into the stream of commerce for distribution throughout the United States, including Delaware, and/or by selling pharmaceutical products in Delaware, directly or through its subsidiaries.

8. This Court has personal jurisdiction over Defendant Prinston by virtue of, *inter alia*, the fact that Prinston has committed, or aided, abetted, contributed to, and/or participated in the commission of, the tortious act of patent infringement that has led to foreseeable harm and injury to Plaintiffs, including Plaintiff Takeda, a Delaware corporation.

Moreover, upon information and belief, Prinston has conducted business in Delaware, has derived substantial revenue therefrom, and has engaged in systematic, continuous, and pervasive contacts with the State of Delaware. This Court has personal jurisdiction over Prinston for the additional reasons set forth below and for other reasons that will be presented to the Court if jurisdiction is challenged.

9. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391 and 1400(b).

THE PATENTS-IN-SUIT

10. On May 1, 2001, the '474 patent, titled "Polymorphs of 2-(3-cyano-4-isobutyloxyphenyl)-4-methyl-5-thiazolecarboxylic acid and Method of Producing the Same," was duly and legally issued. A copy of the '474 patent is attached as Exhibit A. Teijin Ltd. is the owner of the '474 patent. Teijin Pharma Ltd. and Takeda hold exclusive licenses with respect to the '474 patent.

11. On February 12, 2013, the '872 patent, titled "Methods for Concomitant Treatment of Theophylline and Febuxostat," was issued. A copy of the '872 patent is attached as Exhibit B. Takeda is the owner of the '872 patent.

ACTS GIVING RISE TO THIS ACTION

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

13. Pursuant to 21 U.S.C. § 355(b)(1), the '474 patent is 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.

14. Upon information and belief, Prinston submitted ANDA No. 206266 ("Prinston's ANDA") to the FDA under § 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(j)). Upon information and belief, Prinston's ANDA seeks FDA approval to engage in the commercial manufacture, use, sale, or offer for sale of tablets containing 40 and 80 mg of febuxostat ("the Prinston Generic Product") prior to the expiration of the '474 patent.

15. Upon information and belief, pursuant to § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act, Prinston certified in ANDA No. 206266 that no valid claim of the '474 patent will be infringed by the commercial manufacture, use, or sale of the Prinston Generic Product.

16. Plaintiffs received written notification of Prinston's ANDA and its accompanying § 505(j)(2)(A)(vii)(IV) certification by a letter ("Notice Letter"), dated May 22, 2014 and sent via certified U.S. mail.

17. Prinston's Notice Letter fails to comply with the requirement of 21 U.S.C. § 355(j)(2)(B)(iv)(II) because, *inter alia*, although it does not deny the existence of polymorphic crystal forms of febuxostat in the Prinston Generic Product, it contains limited information about the polymorphic crystal form or forms of febuxostat that may be present in the Prinston Generic Product.

18. Prinston's Notice Letter included an accompanying Offer of Confidential Access ("original OCA") to certain Prinston confidential information regarding the Prinston Generic Product. Plaintiffs received Prinston's ANDA on June 26, 2015.

19. The limited information relating to the Prinston Generic Product that was provided in Prinston's Notice Letter and its ANDA do not demonstrate that the Prinston Generic

Product that Prinston is asking the FDA to approve for sale will not fall within the scope of any issued claim of the '474 patent.

20. Prinston's Notice Letter does not deny infringement of Claim 15 of the '474 patent, separate and apart from asserting invalidity.

21. Pursuant to 21 U.S.C. § 355(b)(1), the '872 patent is listed in the FDA's Orange Book as covering Uloric® or its use.

22. Upon information and belief, Prinston's ANDA seeks FDA approval to engage in the commercial manufacture, use, sale, or offer for sale of the Prinston Generic Product prior to the expiration of the '872 patent.

23. Upon information and belief, pursuant to § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act, Prinston certified in ANDA No. 206266 that no valid claim of the '872 patent will be infringed by the commercial manufacture, use, or sale of the Prinston Generic Product.

24. The limited information relating to the Prinston Generic Product that has been provided to Plaintiffs to date does not demonstrate that the Prinston Generic Product does not and will not fall within the scope of the sole issued claim of the '872 patent.

25. Upon information and belief, Prinston will manufacture the Prinston Generic Product and/or febuxostat and release the Prinston Generic Product for distribution in the United States.

26. Upon information and belief, Prinston will market and sell the Prinston Generic Product in the United States.

27. Upon information and belief, Prinston's ANDA No. 206266 contains a "Paragraph III" certification with respect to U.S. Patent No. 5,614,520 ("the '520 patent")

pursuant to 21 U.S.C. § 505(j)(2)(A)(vii)(III). The expiration date of the '520 patent is March 25, 2019.

INFRINGEMENT BY PRINSTON OF U.S. PATENT NO. 6,225,474

28. Plaintiffs re-allege paragraphs 1-27 as if fully set forth herein.

29. Upon information and belief, Prinston's submission of ANDA No. 206266 to the FDA, including its § 505(j)(2)(A)(vii)(IV) certification, constitutes infringement of the '474 patent under 35 U.S.C. § 271(e)(2)(A).

30. Upon information and belief, the commercial manufacture, use, offer to sell, sale, or import of the Prinston Generic Product, if approved by the FDA prior to the expiration of the '474 patent, including any applicable exclusivities or extensions, would infringe the '474 patent under 35 U.S.C. § 271.

31. Upon information and belief, Plaintiffs are entitled to the relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of the approval of Prinston's ANDA No. 206266 be a date that is not earlier than the expiration of the term of the '474 patent, including any extension granted by the USPTO pursuant to 35 U.S.C. §§ 154 or 156, or any later expiration of exclusivity for the '474 patent to which Plaintiffs are or become entitled.

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

33. Upon information and belief, Prinston was aware of the existence of the '474 patent and was aware that the filing of its ANDA and accompanying § 505(j)(2)(A)(vii)(IV) certification with respect to the '474 patent constituted an act of infringement of the '474 patent.

INFRINGEMENT BY PRINSTON OF U.S. PATENT NO. 8,372,872

34. Plaintiffs re-allege paragraphs 1-33 as if fully set forth herein.

35. Upon information and belief, Prinston's submission of ANDA No. 206266 to the FDA, including its § 505(j)(2)(A)(vii)(IV) certification, constitutes infringement of the '872 patent under 35 U.S.C. § 271(e)(2)(A).

36. 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®, Uniphyl®." Exhibit C.

37. 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 C.

38. Research leading to the '872 patent reveals that there is no need to contraindicate coadministration 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 further discloses that dose adjustment of theophylline is required when it is co-administered with alluprionol.

39. 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, and March 2013 are attached as Exhibits D, E and F, respectively.

40. Upon information and belief, Prinston's prescribing information provided with the Prinston Generic Product is expected to carry the same or substantially same contraindications as quoted in paragraph 39.

41. The absence of the above-referenced contraindication in the prescribing information for Uloric® on Prinston's prescribing information, aided by the fact that the use in such population previously was contraindicated, induces the practice of the invention of the '872 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.

42. 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 D, E and F.

43. Upon information and belief, Prinston's prescribing information provided with the Prinston Generic Product is expected to carry the same or substantially same affirmative statements as quoted in paragraph 42.

44. 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.

45. Furthermore, the affirmative statements set forth in paragraph 42 induce the practice of the invention of the '872 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.

46. 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 C, D, E and F.

47. Upon information and belief, Prinston's prescribing information provided with the Prinston Generic Product is expected to carry the same or substantially same dosage and administration statements as quoted in paragraph 46.

48. 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."

49. The affirmative statements set forth in paragraph 46 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.

50. Therefore, for the reasons alleged in paragraphs 36-49 and other reasons that may be subsequently developed, the commercial manufacture, use, offer to sell, sale, or import of the Prinston Generic Product, if approved by the FDA, prior to the expiration of the '872 patent, including any applicable exclusivities or extensions, would induce the infringement of the '872 patent under 35 U.S.C. § 271 (b).

51. Plaintiffs are entitled to relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of the approval of Prinston's ANDA No. 206266 be a date that is not earlier than the expiration of the patent term, including any extension granted or subsequently granted by the USPTO pursuant to 35 U.S.C. § 156 and/or § 154, or any later expiration of exclusivity for the '872 patent, to which Plaintiffs are or become entitled.

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

53. Upon information and belief, Prinston was aware of the existence of the '872 patent and was aware that the filing of its ANDA and certification with respect to the '872 patent constituted an act of infringement of that patent.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs pray for judgment as follows:

A. That Prinston has infringed the '474 patent, and the '872 patent;

B. That pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of ANDA No. 206266 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 '474 patent, and the '872 patent, including any applicable exclusivities or extensions;

C. That Prinston, its 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 the Prinston Generic Product and any other product that infringes or induces or contributes to the infringement of one or more claims of the '474 patent, and the '872 patent prior to its expiration, including any exclusivities or extensions;

D. That Plaintiffs be awarded the attorney 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.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

/s/ Maryellen Noreika

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