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. 14-1370 (SLR)
UNIMARK REMEDIES LTD.,	)	
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 Unimark Remedies Ltd. ("Unimark"), 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, Unimark is a corporation organized and existing under the laws of India, having a principal place of business at Enterprise Center, 1st Floor, Orchid Lane, Nehru Road, Vile Parle (East), Mumbai 40099. On information and belief, Unimark, directly or through its agent, is in the business of, among other things, developing,

manufacturing, packaging, and selling active pharmaceutical ingredients and pharmaceutical products for the United States market.

NATURE OF THE ACTION

5. This is a civil action for infringement of U.S. Patent No. 7,361,676 ("the '676 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 Defendant Unimark by virtue of, *inter alia*, the fact that Unimark has 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, including Plaintiff Takeda, a Delaware corporation.

8. On information and belief, Unimark has submitted over forty type II drug master files ("DMF") to the U.S. Food and Drug Administration ("FDA"), providing information about Unimark's manufacture of various drug substances, including but not limited to DMF No. 25761 concerning "febuxostate [sic] as manufactured in Gujarat, India."

9. On information and belief, upon FDA approval of Unimark's Abbreviated New Drug Application ("ANDA") No. 205380, Unimark and/or its affiliates or agents will market and sell tablets containing 40 and 80 mg of febuxostat ("Unimark Generic Product") in Delaware and will derive substantial revenue therefrom.

10. On information and belief, upon FDA approval of Unimark's ANDA, Unimark and/or its affiliates or agents will market, offer for sale, and/or sell the Unimark

Generic Product with the reasonable expectation or knowledge and intent that such product will ultimately be purchased and used by consumers in this District.

11. Defendant Unimark was a party to another civil action filed in this District that arose under the Hatch-Waxman Act and the Patent Laws of the United States. *See Sanofi v. Unimark Remedies Ltd., et al.*, C.A. No. 14-876-RGA. Unimark filed its answer in that action on September 24, 2014. *Id.* at D.I. 10.

12. Alternatively, should the Court find that the above facts do not establish personal jurisdiction over Unimark in this action, this Court may exercise jurisdiction over Unimark pursuant to Fed. R. Civil P. 4(k)(2) because (a) Plaintiffs' claims arise under federal law; (b) Unimark is a foreign defendant not subject to personal jurisdiction in the courts of any state; and (c) Unimark has sufficient contacts with the United States as a whole, including but not limited to submitting ANDAs and DMFs 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 Unimark satisfies due process.

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

THE PATENTS-IN-SUIT

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

15. 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

16. 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®."

17. Pursuant to 21 U.S.C. § 355(b)(1), the '676 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.

18. Upon information and belief, Unimark submitted ANDA No. 205380 to the FDA under § 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(j)). Upon information and belief, Unimark's ANDA seeks FDA approval to engage in the commercial manufacture, use, sale, or offer for sale of the Unimark Generic Product prior to the expiration of the '676 patent.

19. Upon information and belief, pursuant to § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act, Unimark certified in ANDA No. 205380 that the claims of the '676 patent will not be infringed by the commercial manufacture, use, or sale of the Unimark Generic Product, and/or the claims of the '676 patent are invalid.

20. Plaintiffs received written notification of Unimark's ANDA and its accompanying § 505(j)(2)(A)(vii)(IV) certification by a letter ("Notice Letter"), dated September 23, 2014 and sent via Federal Express and certified U.S. mail.

21. Unimark's Notice Letter included an accompanying Offer of Confidential Access ("OCA") to certain Unimark confidential information regarding the Unimark Generic Product. Plaintiffs have negotiated with Unimark to obtain limited excerpts of Unimark's ANDA and received those excerpts on October 7, 2014.

22. Unimark's Notice Letter does not deny that the Unimark Generic Product contains polymorph A. The limited information relating to the Unimark Generic Product that has been provided to Plaintiffs to date does not demonstrate that the Unimark Generic Product does not and will not fall within the scope of any issued claim of the '676 patent.

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

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

25. Upon information and belief, pursuant to § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act, Unimark certified in ANDA No. 205380 that the sole claim of the '872 patent will not be infringed by the commercial manufacture, use, or sale of the Unimark Generic Product, and/or the claim of the '872 patent is invalid.

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

27. Unimark's Notice Letter does not refer to a certification with respect to U.S. Patent No. 5,614,520 ("the '520 patent"), and does not provide any detailed statement with regard to the '520 patent. Accordingly, upon information and belief, Unimark's ANDA No. 2053803 contains a "Paragraph III" certification with respect to the '520 patent pursuant to 21 U.S.C. § 5 05(j)(2)(A)(vii)(III). The expiration date of the '520 patent is March 25, 2019.

28. Unimark's Notice Letter does not refer to a certification with respect to U.S. Patent No. 6,225,474 ("the '474 patent"), and does not provide any detailed statement with

regard to the '474 patent. Accordingly, upon information and belief, Unimark's ANDA No. 205380 contains a "Paragraph III" certification with respect to the '474 patent pursuant to 21 U.S.C. § 5 05(j)(2)(A)(vii)(III). The expiration date of the '474 patent is June 18, 2019.

INFRINGEMENT BY UNIMARK OF U.S. PATENT NO. 7,361,676

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

30. Upon information and belief, Unimark's submission of ANDA No. 205380 to the FDA, including its § 505(j)(2)(A)(vii)(IV) certification, constitutes infringement of the '676 patent under 35 U.S.C. § 271(e)(2)(A).

31. Upon information and belief, the commercial manufacture, use, offer to sell, sale, or import of the Unimark Generic Product, if approved by the FDA prior to the expiration of the '676 patent, including any applicable exclusivities or extensions, would infringe the '676 patent under 35 U.S.C. § 271(a), (b), and/or (c).

32. 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 Unimark's ANDA No. 205380 be a date that is not earlier than the expiration of the term of the '676 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 '676 patent to which Plaintiffs are or become entitled.

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

34. Upon information and belief, Unimark was aware of the existence of the '676 patent, and was also aware that the filing of its ANDA and accompanying

§ 505(j)(2)(A)(vii)(IV) certification with respect to the '676 patent constituted an act of infringement of the '676 patent.

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

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

36. Upon information and belief, Unimark's submission of ANDA No. 205380 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).

37. 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.

38. 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.

39. 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.

40. 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.

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

42. The absence of the above-referenced contraindication in the prescribing information for Uloric® on Unimark'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.

43. 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 co-administering 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 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." Exhibits D, E and F.

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

45. 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.

46. Furthermore, the affirmative statements set forth in paragraph 43 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.

47. 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.

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

49. 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."

50. The affirmative statements set forth in paragraph 47 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.

51. Therefore, for the reasons alleged in paragraphs 37-50 and other reasons that may be subsequently developed, the commercial manufacture, use, offer to sell, sale, or import of the Unimark 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).

52. 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 Unimark's ANDA No. 205380 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.

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

54. Upon information and belief, Unimark 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 Unimark has infringed the '676 and '872 patents;

B. That, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of ANDA No. 205380 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 and '872 patents, including any applicable exclusivities or extensions;

C. That, Unimark, 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 Unimark Generic Product and any other product that infringes or induces or contributes to the infringement of one or more claims of the '676 and '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

Jack B. Blumenfeld (#1014)
Maryellen Noreika (#3208)
1201 North Market Street
P.O. Box 1347
Wilmington, DE 19899
(302) 658-9200
jblumenfeld@mnat.com
mnoreika@mnat.com

Attorneys for Takeda Pharmaceuticals U.S.A.

OF COUNSEL:

Bruce M. Wexler
Joseph M. O'Malley, Jr.
David M. Conca
Melanie R. Rupert
Jason T. Christiansen
PAUL HASTINGS LLP
75 East 55th Street
New York, NY 10022
(212) 318-6000

Attorneys for Teijin Limited and Teijin Pharma Limited

William F. Cavanaugh, Jr.
Zhiqiang Liu
PATTERSON BELKNAP WEBB & TYLER LLP
1133 Avenue of the Americas
New York, New York 10036
(212) 336-2000

Attorneys for Takeda Pharmaceuticals U.S.A., Inc.

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