IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SHIRE VIROPHARMA INCORPORATED,	)	
	)	
Plaintiff,	)	
	)	
v.	)	C.A. No. 18-_____
	)	
CSL BEHRING LLC and CSL BEHRING GmbH,	)	**JURY TRIAL DEMANDED**
	)	
	)	
Defendants.	)	

COMPLAINT

Plaintiff Shire ViroPharma Incorporated ("Shire"), by its undersigned attorneys, brings this action against defendants CSL Behring LLC and CSL Behring GmbH (collectively, "CSL" or "Defendants") and hereby alleges as follows:

NATURE OF THE ACTION

1. This action for patent infringement is brought pursuant to the patent laws of the United States, 35 U.S.C. § 1 *et seq.* Shire seeks judgment that Defendants are inducing, and will continue to induce others to infringe, and are contributorily infringing, and will continue to contributorily infringe, U.S. Patent No. 10,080,788 (the "'788 Patent"), attached hereto as Exhibit 1.

PARTIES

2. Plaintiff Shire ViroPharma Incorporated is a Delaware corporation, with a principal place of business located at 300 Shire Way, Lexington, MA 02421.

3. Shire is a global biotechnology company focused, *inter alia*, on serving people with rare diseases and other highly specialized conditions.

4. CSL Behring LLC is a Delaware limited liability company, with its principal place of business located at 1020 First Avenue, King of Prussia, PA 19406.

5. CSL Behring GmbH is a German company with its principal place of business at Emil-von-Behring-Strasse 76, Marburg, Hessen, 35041 Germany, and is a corporate affiliate of CSL Behring LLC.

6. Defendants are in the business of developing, manufacturing, and marketing, pharmaceutical drug products and biologics and selling them throughout the United States and the world.

JURISDICTION AND VENUE

7. This Court has subject matter jurisdiction over this action, pursuant to 28 U.S.C. §§ 1331 and 1338(a) because the action arises under the patent laws of the United States.

8. This Court has general personal jurisdiction over Defendants because CSL Behring LLC is incorporated in Delaware and because Defendants knowingly transact business in Delaware and, on information and belief, have engaged in infringing conduct in Delaware. CSL has also not objected to subject matter or personal jurisdiction in a currently-pending related action concerning the same infringing product, styled *Shire ViroPharma Incorporated v. CSL Behring LLC,* C.A. No. 17-00414-MSG.

9. Venue is proper in this Court pursuant to 28 U.S.C. §§ 1391(b), and 1400(b), because CSL Behring LLC resides in Delaware and is subject to personal jurisdiction in Delaware, and because Defendants transact business in Delaware and have committed acts of infringement in Delaware. CSL has also not objected to venue in a currently-pending related action concerning the same infringing product, styled *Shire ViroPharma Incorporated v. CSL Behring LLC*, C.A. No. 17-00414-MSG.

SHIRE'S '788 PATENT

10. Hereditary angioedema ("HAE") is a rare genetic disorder causing insufficient natural production of functional or adequate amounts of a protein called C1 esterase inhibitor. This protein is needed to help regulate several complex processes involved in immune system function (complement, contact system) and fibrinolytic system function (blood clotting, bleeding). The main function of C1 esterase inhibitor is to prevent the spontaneous activation of the complement system, which can cause local or systemic inflammation. Patients suffering from HAE experience symptoms including unpredictable, recurrent attacks of swelling commonly affecting the hands, feet, arms, legs, face, abdomen, tongue, genitals, and larynx.

11. HAE can be treated by administering to patients with the disorder a drug product containing a C1 esterase inhibitor in order to restore the levels of C1 esterase inhibitor to levels sufficient to prevent or reduce the frequency or severity of HAE attacks.

12. Shire, including through corporate affiliates, makes and sells products for the treatment of HAE, including CINRYZE, FIRAZYR, KALBITOR, and TAKHZYRO along with other products in development, including a product currently known as SHP616.

13. CINRYZE contains a human plasma-derived C1 esterase inhibitor as its active ingredient. CINRYZE is a C1 esterase inhibitor replacement therapy approved by the United States Food and Drug Administration (the "FDA") for routine prophylactic treatment of angioedema attacks in pediatric, adolescent, and adult patients with HAE. It is indicated for intravenous ("IV") administration at a concentration of 100 U/mL of human C1 esterase inhibitor. CINRYZE is sold by plaintiff Shire.

14. FIRAZYR is a peptide drug product approved for subcutaneous administration to treat acute attacks of HAE.

15. KALBITOR is a subcutaneously administered plasma kallikrein inhibitor indicated for treatment of acute attacks of HAE.

16. TAKHZYRO is a subcutaneously administered monoclonal antibody indicated for prophylactic treatment of HAE that the FDA approved for commercial marketing on August 23, 2018.

17. Shire and its affiliates are in the process of developing certain other products for the treatment of HAE, including a prophylactic C1 esterase inhibitor treatment to be administered subcutaneously rather than intravenously (known as SHP616).

18. On September 25, 2018, the United States Patent and Trademark Office lawfully issued the '788 Patent, entitled "C1-INH Compositions and Methods for the Prevention and Treatment of Disorders Associated With C1 Esterase Inhibitor Deficiency."

19. The claims of the '788 Patent are directed generally to a "method for prophylactic treatment of hereditary angioedema (HAE) . . . comprising subcutaneously administering . . . a composition comprising C1 esterase inhibitor, sodium citrate, and having a pH ranging from 6.5 – 8.0, wherein the C1 esterase inhibitor has a concentration of about 500 U/mL . . . ." The administration of the composition "increases the level of C1 esterase inhibitor in the blood of the subject to at least about 0.4 U/mL" and the "C1 esterase inhibitor comprises the amino acid sequence of residues 23 to 500 of SEQ ID NO: 1," which amino acid sequence is identified in the '788 Patent.

20. Shire is the assignee and owner of all rights, title, and interest in the '788 Patent, and has the right to sue for infringement.

DEFENDANTS' MARKETING AND SALE OF HAEGARDA

21. On or about July 25, 2017, Defendants began to sell in the United States a prophylactic C1 esterase inhibitor treatment for subcutaneous administration. Defendants market the new C1 esterase inhibitor product as "HAEGARDA." HAEGARDA received FDA approval on June 22, 2017.

DEFENDANTS' INFRINGING CONDUCT

22. Defendants' manufacture, importation, use, sale, and/or offer to sell HAEGARDA in the United States induces, and will continue to induce, others to infringe, and contributorily infringes, and will continue to contributorily infringe, either directly or under the doctrine of equivalents, one or more claims of Shire's '788 Patent, including at least claim 1.

23. Shire's '788 Patent claims a method for prophylactic treatment of hereditary angioedema (HAE) by subcutaneously administering a composition comprising a C1 esterase inhibitor, sodium citrate, and having a pH ranging from 6.5 – 8.0, wherein the C1 esterase inhibitor has a concentration of about 500 U/mL, and wherein the administration of the composition increases the level of C1 esterase inhibitor in the blood of the subject to at least about 0.4 U/mL, and wherein the C1 esterase inhibitor comprises the amino acid sequence of residues 23 to 500 of SEQ ID NO: 1, as disclosed in the patent.

24. The HAEGARDA product label, on its own and/or in combination with Defendants' website, press releases, studies, and other promotional materials, directs, instructs, encourages, recommends, and/or promotes that members of the public such as, *inter alia*, doctors, other medical professionals, and/or patients use, prescribe, administer, and/or provide HAEGARDA in a way that infringes the '788 Patent.

25. The FDA has described HAEGARDA as a treatment for HAE. For example, an FDA press release titled "FDA approves first subcutaneous C1 Esterase Inhibitor to treat rare genetic disease [HAE]" states "'[t]he approval of Haegarda provides a new treatment option for adolescents and adults with Hereditary Angioedema," said Peter Marks, M.D., Ph.D., director of FDA's Center for Biologics Evaluation and Research." Exhibit 2, FDA Press Release, FDA Approves First Subcutaneous C1 Esterase Inhibitor to Treat Rare Genetic Disease (June 22, 2017).

26. The HAEGARDA product label instructs that "HAEGARDA is a plasma-derived concentrate of C1 Esterase Inhibitor (Human) (C1-INH) indicated for routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in adolescent and adult patients." A true copy of the HAEGARDA Prescribing Information is attached hereto as Exhibit 3.

27. The HAEGARDA product label further instructs that HAEGARDA is "intended for self-administration after reconstitution at a dose of 60 International Units (IU) per kg body weight by subcutaneous (S.C.) injection twice weekly (every 3 or 4 days)." Exhibit 3 at p. 2 §2; *see also id.* at p. 4, §2.2 ("Attach the syringe containing the reconstituted HAEGARDA solution to a hypodermic needle or subcutaneous infusion set and administer by subcutaneous injection."); *id.* ("Inject in the abdominal area or other subcutaneous injection sites."); *id.* at p. 9, §11 ("HAEGARDA is a human plasma-derived, purified, pasteurized, lyophilized concentrate of C1-INH to be reconstituted for S.C. administration.").

28. The HAEGARDA product label further instructs that HAEGARDA is "a human plasma-derived, purified pasteurized, lyophilized concentrate of C1-INH to be reconstituted for S.C. administration." Exhibit 3 at p. 9, §11. The label further instructs that "[r]econstituted HAEGARDA has a concentration of 500 IU/mL C1-INH, 65 mg/mL total protein, 10 mg/mL

glycine, 8.5 mg/mL sodium chloride and 2.7 mg/mL sodium citrate." Exhibit 3 at p. 9, §11; *see also* Exhibit 4, Thelwell, C., et al., "An international collaborative study to establish the 1st WHO International Standards for C1-inhibitor, plasma and concentrate," World Health Organization Expert Committee on Biological Standardization, at pp. 2-3 (October 18-22, 2010) ("Diagnostic plasma samples and purified therapeutic products are currently assigned potency values relative to commercial or internal standards and 1 U is defined as the amount of C1-inh present in 1 ml of normal human plasma. It is therefore proposed that the IU is also defined in this way for continuity and consistency with current labelling practice."); Exhibit 5, International Patent Application Publication No. WO 2016/131958 (Aug. 25, 2016) at p. 7, lines 25-29 ("In general, U and IU are equivalent.").

29. As supported by the data disclosed in the '788 Patent, and in order for the composition to be sufficiently syringeable and pharmaceutically useful, HAEGARDA has a pH ranging from 6.5 – 8.0.

30. The HAEGARDA product label further instructs that administration of HAEGARDA increases the level of C1 esterase inhibitor in the blood of the subject to at least about 0.4 U/mL. Exhibit 3 at p. 11, §12.3 (Table 4 provides "the [pharmacokinetic parameters] of C1-INH following twice weekly subcutaneous 60 IU/kg dosing."); *see also* Exhibit 6, Longhurst, H. et al., "Prevention of Hereditary Angioedema Attacks with a Subcutaneous C1 Inhibitor." N. Engl. J. Med., 376(12):1131-1140 (2017); *see also* Exhibit 7, Zuraw, B.L., et al., "Phrase II study results of a replacement therapy for hereditary angioedema with subcutaneous C1-inhibitor concentrate," Allergy 70: 1319-1328, at 1326, Figure 2 (2015); Exhibit 8, CSL Ltd.'s Interim Earnings Presentation (confirming that CSL830 is another name for HAEGARDA). Accordingly, administration of HAEGARDA increases the level of C1 esterase

inhibitor in the blood of the subject to at least about 0.4 U/mL, which is 40% of 1 U/mL, the normal level of C1-INH in a typical person.

31. The HAEGARDA product label further instructs that "C1-INH is a soluble single-chain highly glycosylated protein containing 478 amino acid residues which belongs to the serine protease inhibitor (serpin) family." Exhibit 3 at p. 9, §11; *see also* Exhibit 9, Bock, et al., "Human C1 Inhibitor: Primary Structure, cDNA Cloning, and Chromosomal Localization," Biochemistry, 25(15): 4292-4301 (1986) (establishing the known sequence of human C1-INH, which is the same sequence as provided in the '788 Patent).

32. The publicly available information regarding HAEGARDA demonstrates that Defendants' marketing and sales of HAEGARDA in the United States actively induces others to infringe and/or contributorily infringes the '788 Patent. In particular, on information and belief, Defendants, through their ongoing marketing efforts, are actively inducing, and will continue to actively induce, physicians and/or other medical professional to prescribe and/or use HAEGARDA in accordance with its label and, thereby actively induce, and will continue to actively induce, infringement of the '788 Patent. Further, on information and belief, HAE patients have taken, and continue to take, HAEGARDA as prescribed for the prophylactic treatment of HAE and thereby have directly infringed, and continue to directly infringe the '788 Patent.

33. According to Paul Perreault, CEO of CSL, HAEGARDA had an "exceptionally strong" launch -- in fact, the "most successful chorionic [sic] drug launch in the United States in the past 5 years in a competitive market" -- and has "already achieved around a 50% market share of the HAE prophylactic market in the United States." *See* Exhibit 10, August 15, 2018 Full Year 2018 CSL Ltd Earnings Call Transcript. CSL expects to retain these newly acquired

patients. *Id.* ("[W]e're adding new patients. I think, even with competition, it doesn't mean that all new patients go to the competitor's product just because they launch. . . . So I feel pretty strongly that we'll be able to hold where we are in terms of where we are and the guidance is there for us to continue to go. And, I think, that when you look at the opportunity to meet over the next 5 years, is still in that range of specialty product portfolio that we talked about, which was guiding to somewhere between $750 million and $1 billion in the space. So very bullish on the product."); *see also* Exhibit 11, March 1, 2018 Half Year 2018 Earnings Presentation ("This has been a highly, highly successful launch, one of the most successful launches in the U.S. in the past 5 years of any product for chronic therapy. And so I think that, from that perspective, we were a bit surprised just because you had a competitor that stumbled as well as a very, very high demand for the product. But we're putting patients on as quickly as we can, and we want to make sure when a patient gets on HAEGARDA, they stay on HAEGARDA.")

34. Defendants have had actual knowledge of the '788 Patent no later than September 25, 2018, the date this complaint was filed and served on Defendants. In addition, the U.S. patent application which matured into the '788 Patent, and its file wrapper, have been published and publicly available since December 11, 2017.

35. On information and belief, CSL has been monitoring and has been aware of Shire's patents during their pendency before the USPTO. CSL has had knowledge of Shire's related patent, U.S. Patent 9,616,111, at least as of April 11, 2017. That related patent is the subject of currently pending, related litigation between Shire and CSL, styled *Shire ViroPharma Incorporated v. CSL Behring LLC,* C.A. No. 17-00414-MSG.

36. On information and belief, Defendants (a) had actual knowledge of the application leading to the '788 Patent prior to issuance of the patent; (b) have knowledge of the

acts of infringement that will occur and/or are occurring when the HAEGARDA product is administered; and (c) have the specific intent to cause direct infringement when the HAEGARDA product is administered. On information and belief, members of the public such as, *inter alia*, doctors, other medical professionals, and/or patients are and/or will use, prescribe, administer, and/or provide HAEGARDA in a way that directly infringes the '788 Patent.

37. Defendants have and continue to indirectly infringe one or more claims of the '788 Patent by actively inducing others to infringe the patent, and/or by contributory infringement.

COUNT I

(Infringement of U.S. Patent No. 10,080,788)

38. Shire re-alleges, and incorporates herein by reference, the allegations of the preceding paragraphs of this Complaint as if fully set forth herein.

39. On information and belief, Defendants, directly or through intermediaries, are making, importing, using, selling, and/or offering HAEGARDA for sale in the United States.

40. The '788 Patent is directly infringed, either literally or under the doctrine of equivalents, by the use, prescribing, administering, and/or providing of HAEGARDA by members of the public such as, *inter alia*, doctors, other medical professionals, and/or patients. Through its product label, website, press releases, and/or other promotional materials, Defendants instruct, direct, encourage, recommend, and/or promote members of the public such as, *inter alia*, doctors, other medical professionals, and/or patients to use, prescribe, administer, and/or provide HAEGARDA in a manner that infringes the '788 Patent. CSL has publicly touted the fact that doctors and other medical professionals have in fact prescribed, administered, and/or provided HAEGARDA to patients since HAEGARDA launched in July 2017.

41. Defendants are infringing, and will infringe, and/or are inducing, and/or will induce others to infringe, the '788 Patent, either literally or under the doctrine of equivalents, by making, importing, using, selling and/or offering for sale HAEGARDA for use in the methods claimed in the '788 Patent.

42. The use, prescribing, administering, and/or providing of HAEGARDA as instructed, directed, encouraged, recommended, and/or promoted by Defendants constitutes infringement of at least claim 1 of the '788 Patent. Defendants are currently, and/or will actively induce that infringement, with specific intent to induce and encourage such infringement, or at a minimum with willful blindness to the known risk of such infringement.

43. CSL Behring is selling or offering to sell within the United States and/or importing into the United States a component (namely, HAEGARDA) of the method claimed in the '788 Patent, knowing that component to be especially made or especially adapted for use in an infringement of the '788 Patent.

44. HAEGARDA has no substantial non-infringing use.

45. For at least the reasons cited herein, each and every element in at least claim 1 is infringed by Defendants.

46. Defendants have not obtained a license to the '788 Patent.

47. Unless Defendants are permanently enjoined by this Court from making, importing, using, selling, and/or offering for sale its HAEGARDA product for use in the methods claimed in the '788 Patent, Shire will be substantially and irreparably harmed by Defendants' infringing conduct.

48. Shire seeks damages in an amount adequate to compensate Shire for Defendants' infringement and a permanent injunction barring Defendants from inducing others to infringe and/or contributorily infringing Shire's '788 Patent.

JURY DEMAND

Shire hereby demands a jury trial pursuant to Fed. R. Civ. P. 38(b) of all issues so triable.

PRAYER FOR RELIEF

WHEREFORE, the plaintiffs respectfully request:

(a) That the Court determine that Defendants are inducing others to infringe and/or are contributorily infringing, one or more claims of United States Patent No. 10,080,788;

(b) That the Court enter a permanent injunction precluding Defendants, and all persons in active concert or participation with them, from making, importing, using, selling, or offering to sell in the United States a product that necessarily will be administered to patients in a way that infringes one or more claims of United States Patent No. 10,080,788;

(c) That the Court determine the amount of damage caused to Shire by Defendants' unlawful conduct and enter judgment for Shire in the amount of its damages, plus interest and the costs of this action;

(d) That the Court award Shire enhanced damages under 35 U.S.C. § 284 for Defendants' willful infringement of United States Patent No. 10,080,788;

(e) That the Court award Shire provisional remedies under 35 U.S.C. § 154(d);

(f) That the Court determine that this case is exceptional, within the meaning of 35 U.S.C. § 285, and order Defendants to pay Shire's reasonable attorneys' fees pursuant to 35 U.S.C. § 285; and

(g) That the Court grant such other and further relief as it deems appropriate.

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