IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GLAXOSMITHKLINE LLC, SMITHKLINE BEECHAM (CORK) LIMITED Plaintiffs, v. GLENMARK PHARMACEUTICALSINC., USA Defendant.	CIVIL ACTION NO. 14-877-LPS-CJB DEMAND FOR JURY TRIAL

SECOND AMENDED COMPLAINT FOR PATENT INFRINGEMENT

For their Second Amended Complaint against Defendant Glenmark Pharmaceuticals Inc., USA ("Glenmark"), Plaintiffs GlaxoSmithKline LLC ("GSK") and SmithKline Beecham (Cork) Limited ("SB Cork"), by their attorneys, allege as follows:

NATURE OF THE ACTION

1. This is an action for infringement of United States Patent No. RE40,000 relating to the use of carvedilol in decreasing mortality caused by congestive heart failure in a patient.

THE PARTIES

2. Plaintiff GSK is a company organized and existing under the laws of the State of Delaware, with a principal place of business at 5 Crescent Drive, Philadelphia, PA 19112.

3. Plaintiff SB Cork is a corporation organized and existing under the laws of Ireland, having its principal office at Currabinny, Carrigaline, County Cork, Ireland.

4. On information and belief, Defendant Glenmark Generics Inc., USA, formerly known as Glenmark Pharmaceuticals Inc., USA, is a corporation organized and existing under

the laws of the State of Delaware, having a principal place of business at 750 Corporate Drive, Mahwah, NJ 07430.

JURISDICTION AND VENUE

5. This is an action for patent infringement arising under the patent laws of the United States, 35 U.S.C. §§ 100 et seq. This Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338(a).

6. This Court has personal jurisdiction over Glenmark. Glenmark is a corporation organized and existing under the laws of the State of Delaware, has systematic and continuous contacts with this judicial district, and has committed acts of patent infringement giving rise to this action within this judicial district, including placing carvedilol 3.125 mg, 6.25 mg, 12.5 mg and 25 mg tablets into the stream of commerce for infringing use under circumstances such that Glenmark reasonably should have anticipated being subject to suit in this judicial district. The Court also has personal jurisdiction over Glenmark because the acts of patent infringement are aimed at this judicial district and/or have effect in this judicial district, including harm and injury to Plaintiffs, who manufacture drug products covered by United States Patent No. RE40,000 for sale and use throughout the United States, including the State of Delaware.

7. Venue is proper in this District under 28 U.S.C. §§ 1391(b) and (c) and 1400(b).

BACKGROUND

A. Carvedilol, Sold Under The Tradename COREG®, Decreases Mortality For Congestive Heart Failure Patients

8. Carvedilol belongs to a class of chemical compounds known as beta-blockers, which are drugs that may be used to treat patients with high blood pressure. On March 31, 1993, after conducting hypertension clinical trials with carvedilol, GSK filed a New Drug Application ("NDA") No. 20-297 on carvedilol tablets for management of essential hypertension. On

September 14, 1995, GSK received approval from the Food and Drug Administration ("FDA") to market carvedilol tablets in the United States for management of hypertension. However, in view of the crowded hypertensive treatment market as well as the results from clinical studies showing that long-term administration of carvedilol tablets decreased the risk of mortality in patients suffering from congestive heart failure, GSK did not immediately launch carvedilol tablets in the United States, but worked towards seeking the FDA's approval to market carvedilol tablets for a new indication: treatment of chronic heart failure ("CHF"), sometimes referred to as congestive heart failure.

9. As its name suggests, CHF is a chronic clinical condition (*i.e.*, it requires long-term treatment) that occurs when the diseased heart has a reduced ability to pump blood and is unable to deliver sufficient oxygen to meet the body's needs and is associated with substantial mortality. Ex. H at 1. According to Centers for Disease Control and Prevention, about 5.1 million people in the United States have CHF, and about half of people who develop CHF die within 5 years of diagnosis. *See* http://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_heart_failure.htm.

10. CHF is the end stage of the cardiovascular disease continuum—a chain of events precipitated by several cardiovascular risk factors (e.g., diabetes, hypertension, and obesity), which, if left untreated, will lead to end stage heart failure and death. Ex. H at 3. In hypertension patients, for example, high blood pressure forces the patient's heart to work harder than necessary to pump blood to the rest of the body. This causes the left ventricle to thicken or stiffen. These changes limit the ventricle's ability to pump blood. And, over time, this strain on the heart is very likely to cause the patient to develop CHF and die. *Id.* at 3.

11. In general, there are two types of heart failure: systolic left ventricular dysfunction ("LVD") and heart failure with preserved left ventricular function (diastolic heart failure). *Id*. at 1. Systolic LVD occurs when the muscle in the heart's left ventricle does not contract with enough force, so less oxygen-rich blood is pumped throughout the body. *Id*. Diastolic heart failure occurs when the heart contracts normally, but the ventricles do not relax properly or are stiff, and less blood enters the heart during normal filling. *Id*.

12. The patient's ejection fraction can be used to measure how well their heart pumps with each beat to determine the level of LVD. *Id*. at 1-2. Ejection fraction is usually expressed as a percentage of the total amount of blood in the left ventricle pumped out with each beat. *Id*. A normal ejection fraction ranges from 55% to 70%. *Id*. A reduced ejection fraction may confirm a diagnosis of CHF. *Id*. And an ejection fraction of less than 35% increases the risk of irregular heartbeats that can cause sudden cardiac arrest and sudden cardiac death. *Id*.

13. Symptoms of CHF include: shortness of breath or difficulty breathing with exercise, at rest, or when lying flat in bed; a dry, hacking cough or wheezing; swollen ankles, legs, and abdomen and weight gain; need to urinate while resting at night; tiredness (fatigue) and weakness during exercise or activities; dizziness, confusion, difficulty concentrating or fainting; rapid or irregular heartbeats (palpitations); and feeling of fullness (bloating) in the stomach, loss of appetite, or nausea. *Id*. at 1.

14. Starting in the late 1980's, GSK researchers, in collaboration with researchers from Boehringer Mannheim, explored the possibility of using carvedilol to treat CHF. At the time of GSK researchers' endeavor, beta-blockers were clinically contraindicated for CHF. Despite this conventional wisdom, starting in or around 1988, GSK researchers conducted carefully designed clinical studies to evaluate the effects of carvedilol on CHF patients.

15. In or around 1992, after initial results from the pilot studies were analyzed, GSK researchers started designing a large-scale, double-blind, placebo-controlled, stratified clinical trial program, which became known as the US Carvedilol Heart Failure Study. The study was later published in the May 23, 1996 issue of the New England Journal of Medicine, entitled "The Effect of Carvedilol on Morbidity and Mortality in Patients with Chronic Heart Failure." A true and correct copy of the article is attached as Exhibit A.

16. According to the study protocol, after a run-in period, patients randomized to receive carvedilol were intended to be treated for "an additional 6 months" or "an additional 12 months" depending on the severity of their CHF. *See* Ex. A at 1350.

17. Randomization for the US Carvedilol Heart Failure Study began on or about April 29, 1993. On February 3, 1995, the study was stopped early on the recommendation of the independent Data and Safety Monitoring Board ("DSMB") based on the finding of a significant beneficial effect of carvedilol on survival—an effect that exceeded all conventional boundaries used to stop clinical trials. *Id.* At the time of the study's early termination, 1094 patients were randomly assigned to double-blind treatment, with 696 patients receiving carvedilol. Due to the early termination, the duration of therapy ranged from 1 day to 15.1 months (median, 6.5 months). *See id.*

18. Around the same time, GSK also sponsored another large scale, double-blind, placebo-controlled clinical trial program in Australia and New Zealand, known as the Australia/New Zealand Heart Failure Trial. The study was later published in the February 8, 1997 issue of the Lancet, entitled "Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease." A true and correct copy of the article is attached as Exhibit B.

19. According to the study protocol, after a 2-5-week dose titration period, patients were maintained on either carvedilol or placebo, "with clinical assessments at 5 weeks and 3 months, then every 3 months for a minimum of 15 months and an average of 19 months." Ex. B at 376 ("Design and study treatment"). 415 patients were randomly assigned to double-blind treatment, with 207 patients receiving carvedilol. *Id.* The investigators reported that "[t]here was an overall reduction in events resulting in death or hospital admission, and a year of treatment with carvedilol resulted in the avoidance of one such serious event among every 12-13 [] of these patients with chronic stable heart failure." *Id.* at 375.

20. In or about November 1995, GSK submitted a supplement to NDA No. 20-297 (S-001) to seek approval for the use of carvedilol tablets as treatment for CHF, including reducing the risk of mortality in CHF patients.

21. On May 29, 1997, the FDA approved GSK's carvedilol tablets for the treatment of mild to moderate CHF of ischemic or cardiomyopathic origin, in conjunction with digitalis, diuretics, and ACE inhibitor, to reduce the progression of disease as evidenced by cardiovasular death, cardiovascular hospitalization, or the need to adjust other CHF medications. Carvedilol was the first beta-blocker ever approved by the FDA for the treatment of CHF.

22. After FDA approval, GSK began marketing and selling carvedilol 3.125 mg, 6.25 mg, 12.5 mg and 25 mg tablets in the United States under the COREG® registered mark, promoting only the CHF indication.

23. After the US Carvedilol Heart Failure Study was published, the study was criticized by many scientists, who continued to express skepticism on the effect of beta-blockers on survival in CHF patients.

24. In response, GSK sponsored another large-scale, prospective, randomized, double-blind, placebo-controlled trial of the effect of carvedilol on the survival of patients with severe CHF, known as the Carvedilol Prospective Randomized Cumulative Survival Study, or the "COPERNICUS" study. The study was later reported in the May 31, 2001 issue of the New England Journal of Medicine, entitled "Effect of Carvedilol on Survival in Severe Chronic Heart Failure." A true and correct copy of the article is attached as Exhibit C.

25. According to the study protocol, after an upward titration period, patients were to be maintained on either carvedilol or placebo and were "evaluated every two months until the end of the study." Ex. C at 1652 ("Study Design"). Randomization began on or about October 28, 1997. The study was again stopped early on March 20, 2000, on the recommendation of an independent DSMB based on the finding of significant beneficial effect of carvedilol on survival that exceeded the pre-specified interim monitoring boundaries. *Id.* at 1653. At the time of the early termination of the trial, 2289 patients had been assigned to treatment groups, with 1156 patients to the carvedilol group. *Id.* The mean duration of follow-up was 10.4 months. *Id.*

26. In or about February 2001, GSK submitted another supplement to NDA No. 20-297 (S-007) to seek approval for the use of COREG® for severe CHF as well.

27. On November 1, 2001, the FDA approved GSK's carvedilol tablets for the treatment of mild-to-severe CHF of ischemic or cardiomyopathic origin, usually in addition to diuretics, ACE inhibitors and digitalis, to increase survival and, also, to reduce the risk of hospitalization.

28. There were, however, patients with CHF, or that were likely to develop CHF, that could not receive COREG® because they recently experienced a myocardial infarction (i.e., a

heart attack) and COREG® was not approved for use following a recent heart attack due, at least in part, to concerns about worsening the patient's condition. Ex. I at 14-16

29. To expand the use of COREG® to these patients, two additional studies were conducted—the Carvedilol Heart Attack Pilot Study (CHAPS), which supported the ability of COREG® to reduce the risk of death in post-infarction patients, and the CAPRICORN study. The CAPRICORN study focused specifically on patients with left ventricular ejection fractions $\leq$ 40% who had recently suffered a heart attack. All of these patients likely had CHF. Ex. H (explaining that a heart attack can cause CHF and that an ejection fraction of less than 40% may confirm a diagnosis of CHF). Indeed, 47% of them were already showing symptoms of CHF. Ex. F at Section 14.2. And the patients not showing symptoms shortly after the heart attack would likely develop symptoms of CHF. Ex. H at 3.

30. According to the CAPRICORN study protocol, after an upward titration period, patients were to be maintained on either carvedilol or placebo and were evaluated every three to four months until the end of the study. Ex. I at 45. When the trial was terminated, 1959 patients had been assigned to treatment groups, with 975 patients to the carvedilol group. *Id*. at 52. The mean duration of follow-up was 15 months. *Id*. Patients in the carvedilol group experienced significantly lower rates of cardiovascular-caused mortality. Ex. F at Section 14.2.

31. On March 27, 2003, COREG® received approval for another indication: treatment of LVD following myocardial infarction "to reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of $\leq$ 40% (with or without symptomatic heart failure)." Ex. F at Section 1.2.

32. Despite the multiple approved indications, GSK has marketed COREG® in the United States only for the CHF indication. Hypertensive treatment is a crowded market in which many treatment options are available. According to the 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults ("Guideline"), a report commissioned by the U.S. Department of Health and Services (a true and correct copy attached hereto as Exhibit D), the Panel appointed to the Eighth Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8) recommended the following four classes of drugs for initial antihypertensive treatment: (1) thiazide-type diuretic, (2) calcium channel blocker (CCB), (3) angiotensin-converting enzyme inhibitor (ACEI) (general non-black population), or (4) angiotensin receptor blocker (ARB) (general non-black population). Ex. D at 511 (Recommendations 6 and 7). The Guideline specifically stated that the "panel did not recommend β-blockers for the initial treatment of hypertension because in one study use of beta blockers resulted in a higher rate of the primary composite outcome of cardiovascular death, myocardial infarction, or stroke compared to use of an ARB," and did not recommend dual α_1 + β-blocking agents such as carvedilol because there were no randomized controlled trials of good or fair quality comparing this class to the 4 recommended classes. *See id.* at 513.

33. Compared to the number of patients suffering from CHF, a much smaller population of patients suffer from LVD following a heart attack. Patients with LVD after a heart attack may also have signs of CHF, and many will eventually develop CHF.

34. Therefore, upon information and belief, the vast majority of the carvedilol tablets are prescribed or administered long term (extending for more than six months unless terminated by unintended adverse events) to patients with CHF to increase survival and to reduce the risk of

hospitalization; uses of carvedilol tablets for the other two indications, namely treatment of hypertension and left ventricular dysfunction after myocardial infarction, are not substantial.

B. GSK Listed The Patent-in-Suit, And Its Predecessor, In The FDA's Orange Book As Covering Coreg®

35. U.S. Patent Application No. 08/483,635, entitled "Method of Treatment for Decreasing Mortality Resulting from Congestive Heart Failure," was filed on June 7, 1995, and issued as U.S. Patent No. 5,760,069 ("the '069 patent") on June 2, 1998.

36. On November 25, 2003, the then-owner of the '069 patent instituted a reissue proceeding for the '069 patent before the Patent Office. On January 8, 2008, United States Patent No. RE40,000 ("the '000 patent"), entitled "Method of Treatment for Decreasing Mortality Resulting from Congestive Heart Failure," was duly and legally reissued from the '069 patent. The '000 patent concludes with nine method claims directed to methods of decreasing mortality caused by CHF in a patient in need thereof by administering carvedilol in a manner recited in the claims. A true and correct copy of the '000 patent is attached as Exhibit E.

37. SB Cork owns the entire right, title, and interest in the '000 patent by assignment.

38. GSK is an exclusive licensee of the '000 patent.

39. In conjunction with NDA No. 20-297, GSK submitted patent information relating to COREG®. In or about July 1998, the FDA published the original '069 patent in its list of "Approved Drug Products with Therapeutic Equivalence Evaluations," commonly referred to as the "Orange Book," which provides notice concerning patents covering FDA-approved drugs. The '069 patent had a patent term that would expire on June 7, 2015.

40. In February 2008, after the issuance of the '000 reissue patent, GSK submitted patent information regarding the '000 patent and requested the withdrawal of the '069 patent from the Orange Book. The '069 patent was de-listed from the Orange Book on or about

February 7, 2008. The ’000 patent was listed in the Orange Book on or about February 12, 2008, with patent use code U-233, “decreasing mortality caused by congestive heart failure.” Like the original ’069 patent, the ’000 patent expires on June 7, 2015. The ’000 patent is the only patent currently listed in the Orange Book for COREG®.

41. Methods of using COREG® (carvedilol) 3.125 mg, 6.25 mg, 12.5 mg and 25 mg tablets for treating patients with CHF as provided in the COREG® label are covered by at least one claim of the ’000 patent. A true and correct copy of the COREG® label is attached as Exhibit F.

C. Acts Giving Rise to This Action

42. The Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the “Hatch-Waxman Act,” amended the Federal Food, Drug, and Cosmetic Act (“FDCA”) and governs approvals of generic drugs. Under Section 505(j) of the amended FDCA, codified at 21 U.S.C. § 355(j), companies wishing to bring a generic version of a branded prescription drug to market can submit an Abbreviated New Drug Application (“ANDA”) to the FDA.

43. The ANDA process allows the generic drug company to avoid the expensive clinical trials required of an NDA holder to demonstrate a drug’s safety and effectiveness by relying on the original NDA submission for that purpose. This process results in an enormous cost and time savings to the generic drug company. Reliance on the innovator company’s data and the ability to “free ride” on the innovator company’s development saves the generic drug company millions of dollars and years in development and clinical research costs.

44. The Hatch-Waxman Act also contains provisions meant to balance the competing interests of innovator and generic drug companies. When seeking ANDA approval, the generic

applicant must consult the Orange Book and make certain certifications with respect to each patent listed for the branded drug. The generic applicant can certify that no patent information appears in the Orange Book ("Paragraph I certification"); that the listed patent has already expired ("Paragraph II certification"); that the applicant will not market the generic version before the date on which the patent will expire ("Paragraph III certification"); or that the patent is invalid or will not be infringed by the manufacture, use, or sale of the drug for which the ANDA is submitted ("Paragraph IV certification"). 21 U.S.C. § 355(j)(2)(A)(vii)(I)-(IV). When a Paragraph IV certification is made, the generic applicant must also provide notice of the certification to the innovator company, who can choose to enforce its patents in federal court.

45. When the listed patent is a method-of-use patent, like the '000 patent, the generic applicant can attempt to seek FDA approval to label its drug only for uses not covered by the patent, in which case a statement is submitted under 21 U.S.C. § 355(j)(2)(A)(viii), commonly known as a "Section viii carve-out," in place of a patent certification. "A section viii statement 'indicates that a patent poses no bar to approval of an ANDA because the applicant seeks to market the drug for a use other than the one encompassed by the patent.'" *AstraZeneca Pharm. LP v. Apotex Corp.*, No. 10-338, 2010 WL 5376310, at *2 (D. Del. Dec. 22, 2010) (citation omitted). If approved, the FDA will require the generic company to duplicate only the portions of the branded drug's label not protected by the applicable method-of-use patent, as identified in the patent use code.

46. For an Orange Book-listed method-of-use patent that has not expired, whether to make a Paragraph III or Paragraph IV certification or a Section viii statement is a calculated business decision the generic applicant makes after evaluating the associated commercial risks.

47. On information and belief, on or about April 7, 2006, Glenmark submitted an ANDA No. 78-251 for generic copies of COREG® (carvedilol) 3.125 mg, 6.25 mg, 12.5 mg and 25 mg tablets under section 505(j) of the FDCA.

48. As an ANDA filer, Glenmark was required to provide certifications addressing each of the patents listed in the Orange Book for COREG®, which at the time of Glenmark's submission included the '069 patent as well as U.S. Patent No. 4,503,067 ("the '067 patent"), a compound patent for carvedilol and exclusively licensed to GSK. On information and belief, Glenmark did not submit a Paragraph IV certification with respect to either the '069 patent or the '067 patent.

49. On information and belief, the FDA granted final approval on or about September 5, 2007, when the '067 patent expired, for Glenmark's ANDA No. 78-251 with a Section viii carve-out, *i.e.*, without those portions of the label relating to the CHF indication. On information and belief, Glenmark launched its generic COREG® tablets in the United States shortly after receiving final approval.

50. While Glenmark removed some portions of the COREG® label, Glenmark's Section viii carve-out label still instructed and encouraged administering Glenmark's generic carvedilol tablets long term (extending for more than six months unless terminated by unintended adverse events) to decrease a risk of mortality caused by CHF. For example, like the COREG® label, Glenmark's Section viii carve-out label states that carvedilol tablets "are indicated to ***reduce cardiovascular mortality in clinically stable patients*** who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of ≤ 40% (***with*** or without ***symptomatic heart failure***)." Ex. J at Section 1.2 (emphasis added). Glenmark's Section viii carve-out label also indicates that a significant portion of these patients

already have symptoms of CHF. *See id.* at Section 14.2 ("CAPRICORN was a double-blind study comparing carvedilol and placebo in 1,959 patients with a recent myocardial infarction (within 21 days) and left ventricular ejection fraction of ≤ 40%, ***with (47%)*** or without ***symptoms of heart failure***.") (emphasis added); *see also id*. at Section 5.4 ("Worsening ***heart failure*** or fluid retention may occur during up-titration of carvedilol."), Section 17.1 ("***Patients with heart failure*** should consult their physician if they experience signs or ***symptoms of worsening heart failure*** such as weight gain or increasing shortness of breath.") (emphasis added). And, as explained above, to the extent any of these patients do not have CHF, they will likely develop it.

51. On information and belief, in at least about August 2009, Glenmark revised its label for generic carvedilol 3.125 mg, 6.25 mg, 12.5 mg, and 25 mg tablets to expressly include the CHF indication. A true and correct copy of Glenmark's revised label, as filed by Glenmark in this action (D.I. 12-1, at pp. 8-9), is attached as Exhibit G.

52. At least between about August 2009 and about August 2010, Glenmark's generic labels for all strengths were identical to GSK's COREG® labeling and list "mild to severe chronic heart failure" as one of the approved indications and include safety and efficacy information relating to the CHF indication that instructs and encourages administering Glenmark's generic carvedilol tablets long term (extending for more than six months unless terminated by unintended adverse events) to decrease a risk of mortality caused by CHF. For example, like the COREG® label, Glenmark's generic label stated that carvedilol tablets "are indicated for the treatment of mild-to-severe chronic heart failure of ischemic or cardiomyopathic origin, usually in addition to diuretics, ACE inhibitors, and digitalis, to increase survival and, also, to reduce the risk of hospitalization."

53. The FDA regulations on the labeling requirements for prescription drugs require an identification in the Dosage and Administration section of "[t]he usual duration of treatment when treatment duration should be limited." 21 C.F.R. § 201.57(c)(3)(F). Glenmark's full and Section viii carve-out labels do not identify a limitation on treatment duration for the CHF indication.

54. In sections 17.1 and 17.2 of the full and Section viii carve-out labels, Glenmark cautions patients not to stop taking carvedilol without consulting their doctors. For example, the labels states: "Patients should not interrupt or discontinue using carvedilol tablets without a physician's advice"; "**Do not stop taking carvedilol tablets and do not change the amount of carvedilol tablets you take without talking to your doctor**"; "**It is important for you to take your medicine every day as directed by your doctor. If you stop taking carvedilol tablets suddenly, you could have chest pain and/or a heart attack.**" Ex. G at §§ 17.1, 17.2 (emphasis in original).

55. Like the COREG® label, Glenmark's full label also includes a "CLINICAL STUDIES" section describing efficacy data from the clinical trials. All the treatment durations mentioned in this section of the label that are associated with efficacy are greater than 6 months. *See, e.g., id.* at § 14.1 ("*Slowing Progression of Heart Failure*: . . . Heart failure progression was reduced, during an average follow-up of 7 months, by 48% (p = 0.008)." "In the Australia-New Zealand study, death and total hospitalizations were reduced by about 25% over 18 to 24 months." "The [COPERNICUS] trial was stopped after a median follow-up of 10 months because of an observed 35% reduction in mortality (from 19.7% per patient year on placebo to 12.8% on carvedilol, hazard ratio 0.65, 95% CI 0.52 to 0.81, p = 0.0014, adjusted).").

56. Consistent with the intended long-term use of carvedilol, for a maintenance period extending for more than six months unless terminated by unintended adverse events, the safety data reported in the "ADVERSE REACTIONS"/"Clinical Studies Experience" section of Glenmark's full label were gathered from placebo-controlled trials where the "[m]edian study medication exposure was 6.3 months . . . in the trials of mild-to-moderate heart failure, and 10.4 months in the trial of severe heart failure patients." *See id.* at § 6.1. The label also advises physicians and patients that "[i]n the COMET trial, 1,511 patients with mild-to-moderate heart failure were treated with carvedilol for up to 5.9 years (mean 4.8 years)." *Id.* In total, "[c]arvedilol has been evaluated for safety in heart failure in more than 4,500 patients worldwide of whom more than 2,100 participated in placebo-controlled clinical trials. Approximately 60% of the total treated population in placebo-controlled clinical trials received carvedilol for at least 6 months and 30% received carvedilol for at least 12 months." *Id.* The remaining about 40% of the patients enrolled in the carvedilol treatment groups were intended to be administered with the carvedilol for at least 6 months but received carvedilol for less than 6 months due to multiple reasons, including the early termination of the trials by the DSMB, death, and other adverse events. *See* Exs. A-C.

57. GSK did not receive and has not received any notice from Glenmark relating to Glenmark's August 2009 labeling change or any other supplement relating to Glenmark's ANDA No. 78-251.

58. Glenmark did not supplement its ANDA No. 78-251 to seek approval from the FDA of the labeling change.

59. On information and belief, Glenmark offered to sell and sold its generic copies of COREG® tablets with a label that included the CHF indication in the United States at least

between about August 2009 and about August 2010, with knowledge of the '000 patent and its predecessor '069 patent, and with an intent to actively induce infringement of the '000 patent.

60. Glenmark's strategic submission of a Section viii statement attempting to carve out the patented and primary use of its generic carvedilol and its subsequent use of the full COREG® label with the CHF indication show that despite its representation to the FDA to the contrary in its Section viii statement, Glenmark always intended its generic carvedilol tablets be used for the CHF indication.

61. In addition, even prior to its labeling change, Glenmark caused its generic carvedilol 3.125 mg, 6.25 mg, 12.5 mg and 25 mg tablets to be listed in the Orange Book with a therapeutic equivalence rating of "AB," which indicates that its generic copies are considered therapeutically equivalent to COREG® on all indications approved for the generic drug. On information and belief, since the approval of its ANDA No. 78-251, Glenmark has actively promoted on its website and other marketing materials the "AB" rating of its generic carvedilol tablets and marketed them as therapeutically equivalent to and fully substitutable for GSK's COREG® tablets indicated for treatment of CHF.

62. For example, Glenmark's September 10, 2007 press release announcing the approval of its generic carvedilol tablets states, "Glenmark Pharmaceuticals Ltd. [Glenmark], a research-based pharmaceutical company, headquartered in Mumbai (India), has received final approval from the U.S. Food and Drug Administration for marketing the first generic version of Coreg (Carvedilol). … Coreg is a widely used medication that is FDA approved to treat high blood pressure, mild to severe ***chronic heart failure*** and left ventricular dysfunction following a heart attack." Ex. K. Glenmark's press release also stated, "Coreg was the 30th top selling brand name by retail dollars in 2006. Carvedilol sales was approximately US$1.6 billion, for the 12-

month period ending March 31, 2007…." *Id*. Those sales, of course, included sales used to treat patients with CHF symptoms.

63. On information and belief, Glenmark registered its generic carvedilol tablets with data aggregators (e.g., Red Book) as AB-rated to Coreg®. Glenmark's website has identified Glenmark's carvedilol tablets as "AB" rated to Coreg® tablets. And when a user of Glenmark's website requests the prescribing information for Glenmark's carvedilol tablets the website asks the user whether they are a physician.

64. Although the Orange Book states explicitly that an AB rating is limited to what is on the generic's approved label, *see* http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf, at vii ("Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling."), Glenmark never informed the public that its generic carvedilol was not approved by the FDA for the CHF indication when it touted its generic copy as AB-rated and fully substitutable for COREG®.

65. On information and belief, Glenmark knew that when an AB-rated generic drug is available, many states and/or third party payers of prescription drugs (*e.g.*, health insurance plans, Medicare and Medicaid programs) have adopted policies to encourage or require the substitution of the AB-rated generic drugs for the branded drugs, regardless of whether the generic drug label includes all the indications contained in the branded drug label. Glenmark also knew that unless informed otherwise, the market would assume that, like most AB-rated generic drugs, Glenmark's generic carvedilol tablets were labeled identically to COREG® and included the CHF indication. As a result, by promoting its generic carvedilol tablets as AB-rated

and fully substitutable for COREG® without informing the market that its generic carvedilol tablets were not approved for the CHF indication, Glenmark knew and intended that its generic carvedilol tablets would be substituted for COREG® for patients prescribed the drug for treatment of CHF resulting in the direct infringement of the ’000 patent.

COUNT I

(Inducement of Infringement)

66. Plaintiffs restate and reallege Paragraphs 1-65 of this Complaint as if fully set forth herein.

67. On information and belief, Glenmark has been and is actively inducing others to infringe the ’000 patent in this District and elsewhere in the United States by making, offering to sell, selling, importing and otherwise promoting and distributing carvedilol 3.125 mg, 6.25 mg, 12.5 mg and 25 mg tablets for long-term treatment (extending for more than six months unless terminated by unintended adverse events) of patients to decrease the risk of mortality caused by CHF.

68. On information and belief, healthcare providers administering and/or patients using Glenmark’s generic version of COREG® tablets within the United States do so for long-term treatment (extending for more than six months unless terminated by unintended adverse events) to decrease a risk of mortality caused by CHF, and thus directly infringe at least one claim of the ’000 patent.

69. On information and belief, Glenmark possessed specific intent to encourage direct infringement of the ’000 patent. On information and belief, Glenmark knew about the original ’069 patent at least as of April 7, 2006, when it submitted ANDA No. 78-251 and the requisite certification concerning the ’069 patent. Until it was replaced by the reissued ’000 patent, the

’069 patent had a patent term until June 7, 2015. On information and belief, Glenmark also knew about the reissued ’000 patent before performing the activities referenced in Paragraph 67 of this Complaint.

70. Alternatively, Glenmark subjectively believed that there was a high probability that the use of carvedilol tablets for long-term treatment (extending for more than six months unless terminated by unintended adverse events) of patients to decrease a risk of mortality caused by CHF was protected by a valid patent, and that the activities referenced in Paragraph 67 of this Complaint would actively induce infringement of the patent, but took deliberate steps to avoid confirming these facts, and therefore willfully blinded itself to the infringing nature of its sales of generic copies of COREG®.

71. On information and belief, Glenmark knew that the administration or use of its generic version of COREG® would be for long-term treatment of patients to decrease the risk of mortality cause by CHF and would thus extend for more than six months unless terminated by unintended adverse events, and so would be an act of direct infringement of the ’000 patent, and that the activities referenced in Paragraph 67 of this Complaint would actively induce direct infringement of the ’000 patent. On information and belief, despite such knowledge, Glenmark has been and is actively inducing the infringement of the ’000 patent by others.

72. On information and belief, Glenmark acted despite an objectively high likelihood that its actions constituted infringement of a valid patent. On information and belief, Glenmark actually knew, or it was so obvious that Glenmark should have known, that its actions constituted infringement of a valid patent. Glenmark’s infringement is therefore willful.

73. On information and belief, Glenmark will continue to induce the infringement of the ’000 patent unless and until it is enjoined by the Court.

74. As a result of Glenmark's inducement of infringement of the '000 patent, Plaintiffs have suffered damages, including lost profits.

COUNT II

(Contributory Infringement)

75. Plaintiffs restate and reallege Paragraphs 1-74 of this Complaint as if fully set forth herein.

76. On information and belief, Glenmark has been and is contributing to the infringement of the '000 patent in this District and elsewhere in the United States by making, offering to sell, selling, importing and otherwise promoting and distributing carvedilol 3.125 mg, 6.25 mg, 12.5 mg and 25 mg tablets for long-term treatment (extending for more than six months unless terminated by unintended adverse events) of patients with CHF to decrease the risk of mortality caused by CHF.

77. On information and belief, healthcare providers administering and/or patients using Glenmark's generic version of COREG® tablets within the United States for the CHF indication do so for long-term treatment extending for more than six months unless terminated by unintended adverse events, and thus directly infringe at least one claim of the '000 patent.

78. On information and belief, carvedilol tablets are not a staple article or commodity of commerce suitable for substantial non-infringing use. On information and belief, the vast majority of the carvedilol tablets are prescribed or administered long term (extending for more than six months unless terminated by unintended adverse events) to patients with CHF to increase survival and to reduce the risk of hospitalization; uses of carvedilol tablets for the other two indications, namely treatment of hypertension and left ventricular dysfunction after myocardial infarction, are not substantial.

79. On information and belief, Glenmark knew about the original ’069 patent at least as of April 7, 2006, when it submitted ANDA No. 78-251 and the requisite certification concerning the ’069 patent. Until it was replaced by the reissued ’000 patent, the ’069 patent had a patent term until June 7, 2015. On information and belief, Glenmark also knew about the reissued ’000 patent before performing the activities referenced in Paragraph 76 of this Complaint, and knew that those activities infringed the ’000 patent.

80. Alternatively, Glenmark subjectively believed that there was a high probability that the use of carvedilol tablets for the CHF indication was protected by a valid patent, and that the activities referenced in Paragraph 76 of this Complaint would contribute to the infringement of the patent, but took deliberate steps to avoid confirming these facts, and therefore willfully blinded itself to the infringing nature of its sales of generic copies of COREG®.

81. On information and belief, Glenmark knew that its generic COREG® tablets were especially made or especially adapted for administration by a healthcare provider or use by a patient for long-term treatment (extending for more than six months unless terminated by unintended adverse events) to decrease a risk of mortality caused by CHF in a manner that would infringe the ’000 patent, and that its generic COREG® tablets were not a staple article or commodity of commerce suitable for substantial non-infringing use.

82. On information and belief, Glenmark acted despite an objectively high likelihood that its actions constituted infringement of a valid patent. On information and belief, Glenmark actually knew, or it was so obvious that Glenmark should have known, that its actions constituted infringement of a valid patent. Glenmark’s infringement is therefore willful.

83. On information and belief, Glenmark will continue to contribute to the infringement of the ’000 patent unless and until it is enjoined by the Court.

84. As a result of Glenmark's contributory infringement of the '000 patent, Plaintiffs have suffered damages, including lost profits.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request for the following relief:

(1) Enter judgment that Glenmark has induced the infringement of the '000 patent by making, selling, offering to sell and importing generic carvedilol tablets in or into the United States;

(2) Enter judgment that Glenmark has contributed to the infringement of the '000 patent by making, selling, offering to sell and importing generic carvedilol tablets in or into the United States;

(3) Award Plaintiffs damages in an amount sufficient to compensate them for Glenmark's infringement of the '000 patent, together with prejudgment and post-judgment interest and costs under 35 U.S.C. § 284;

(4) Find that Glenmark's infringement has been willful, and treble the damages awarded to Plaintiffs under 35 U.S.C. § 284;

(5) Declare this case to be exceptional under 35 U.S.C. § 285 and award Plaintiffs their attorney fees, expenses, and costs incurred in this action;

(6) Perform an accounting of Glenmark's infringing activities through trial and judgment, and

(7) Award Plaintiffs such other and further relief as this Court deems just and proper.

DEMAND FOR JURY TRIAL

Plaintiffs demand a jury trial on all issues so triable.

FISH & RICHARDSON P.C.

By: */s/ Martina Tyreus Hufnal*

Martina Tyreus Hufnal (#4771)
222 Delaware Avenue, 17th Floor
Wilmington, DE 19801
(302) 652-5070 (Main)
hufnal@fr.com

W. Chad Shear (#5711)
Craig Countryman
Robert M. Yeh
Ryan O'Connor
12390 El Camino Real
San Diego, CA 92130
(858) 678-5070 (Main)
shear@fr.com; countryman@fr.com;
ryeh@fr.com; oconnor@fr.com

Limin Zheng
500 Arguello Street, Suite 500
Redwood City, CA 94063
(650) 839-5070 (Main)
zheng@fr.com

Attorneys for Plaintiffs GlaxoSmithKline and SmithKline Beecham (Cork) Limited

Dated: September 22, 2014