No. 18-1976, -2023

United States Court of Appeals for the Federal Circuit

GLAXOSMITHKLINE LLC AND SMITHKLINE BEECHAM (CORK) LIMITED,
Plaintiffs-Appellants,

v.

TEVA PHARMACEUTICALS USA, INC.,
Defendant-Cross-Appellant,

APPEALS FROM THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF DELAWARE, CASE NO. 14-CV-878-LPS-CJB, DISTRICT JUDGE LEONARD P. STARK

GSK'S OPENING BRIEF

Juanita R. Brooks
Jonathan E. Singer
Michael A. Amon
Craig E. Countryman
Fish & Richardson P.C.
12390 El Camino Real
San Diego, CA 92130
(858) 678-5070
brooks@fr.com;
singer@fr.com;
amon@fr.com;
countryman@fr.com

Michael J. Kane
William R. Woodford
Elizabeth M. Flanagan
Fish & Richardson P.C.
3200 RBC Plaza
60 South Sixth Street
Minneapolis, MN 55402
(612) 335-5070
kane@fr.com;
woodford@fr.com;
betsy.flanagan@fr.com

Douglas E. McCann
Fish & Richardson P.C.
222 Delaware Avenue
17th Floor, P.O. Box 1114
Wilmington, DE 19801
(302) 652-5070
dmccann@fr.com

July 16, 2018

CERTIFICATE OF INTEREST

1. The full name of every party represented by me is: GlaxoSmithKline LLC and SmithKline Beecham (Cork) Ltd.

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is: N/A.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party represented by me are: GlaxoSmithKline plc.

4. The names of all law firms and the partners or associates that appeared for the party now represented by me in the trial court or agency or are expected to appear in this Court are: Fish & Richardson P.C.: Juanita R. Brooks, Jonathan E. Singer, Craig E. Countryman, Michael A. Amon, Douglas E. McCann, Elizabeth M. Flanagan, Michael J. Kane, William R. Woodford, John Farrell, Phillip Goter, Jeremy Anderson, Robert M. Yeh, Ryan O'Connor, Jeremy Saks, W. Chad Shear, Limin Zheng*, Santosh Coutinho*. * = No longer with firm.

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal: *GlaxoSmithKline LLC, et al. v. Glenmark Pharmaceuticals Inc., USA, et al.*, Case No. 14-cv-877-LPS-CJB (D. Del.).

Dated: July 16, 2018

/s/ Craig E. Countryman
Craig E. Countryman

TABLE OF CONTENTS

Page

TABLE OF CONTENTS (continued)

Page

TABLE OF AUTHORITIES

Page(s)

Cases

Statutes

Other Authorities

STATEMENT OF RELATED CASES

No prior appeal from this case has been before this or any other appellate court, nor is there any other currently pending appeal from this proceeding.

One other district court case may be impacted by the outcome in this appeal—*GlaxoSmithKline LLC, et al. v. Glenmark Pharmaceuticals Inc., USA, et al.*, Case No. 14-cv-877-LPS-CJB (D. Del.). That case involves the same patent at issue here; the parties have requested a stay pending the outcome of these proceedings.

STATEMENT OF JURISDICTION

This is an appeal from a final judgment of non-infringement from a district court entered on April 25, 2018. (Appx29–30.) GSK timely filed its notice of appeal on May 14, 2018, and Teva timely filed a conditional cross-appeal on May 25, 2018, both within the 30-day deadline set by Federal Rule of Appellate Procedure 4(a)(1)(A). (Appx12110–12113.) This Court thus has jurisdiction over both appeals under 28 U.S.C. § 1295(a)(1).

STATEMENT OF THE ISSUE

Whether substantial evidence supports the jury's verdict that Teva willfully induced infringement of GSK's patented method of treating congestive heart failure where:

a. Teva encouraged the infringing use in promotional materials communicated to doctors, such as product catalogs, product reference guides, press releases, and product information on its website, including by advertising that its product should be used just like GSK's Coreg® product;

b. Teva provided instructions for the infringing use on the labels it distributed with its generic drug product and encouraged doctors to read the labels;

c. GSK's expert testified that Teva's promotional materials and labels caused him and other physicians to use Teva's product just like Coreg® to treat congestive heart failure in an infringing manner; and

d. Teva intended to induce physicians to prescribe its generic carvedilol in an infringing manner.

INTRODUCTION

This case is about Teva's willful infringement of GSK's patent on a revolutionary method of treating heart failure. GSK defied conventional wisdom by treating heart failure with carvedilol—a drug that doctors thought would kill heart failure patients. It turned out the opposite was true. Carvedilol was so effective (it reduced the risk of death by over 65%) that clinical trials were halted so patients on placebo could immediately take carvedilol. GSK's new approach changed the standard of care and guidelines for heart failure.

Before launching a generic copy of GSK's Coreg® carvedilol product, Teva promoted it as a complete substitute for Coreg®, including its use for treating heart failure—the patented use. Teva continued that promotion after launch through its product catalogs, product reference guides, website, and drug labeling. Although Teva's original label included a subset of the information on treating heart failure (but still enough to infringe), Teva eventually replaced this "partial" label with a "full" label that contained everything on GSK's Coreg® label. Teva admitted that it intended for doctors to prescribe its generic carvedilol in an infringing manner. And Teva's efforts were successful—it ultimately captured half the market for generic carvedilol. At trial, GSK's expert cardiologist testified that Teva's promotional materials and labels caused him and other doctors to infringe GSK's patent. The jury credited this testimony and GSK's other evidence and found that Teva willfully induced infringement during both the "partial" and "full" label periods.

After trial, however, the district court set aside the jury's infringement finding. In doing so, the court improperly reweighed the evidence—giving little or no weight to GSK's evidence while crediting Teva's. This error alone warrants reversal.

The court further erred by holding that Teva's encouragement of the patented use was insufficient because GSK had already educated doctors about how to use Coreg® before Teva launched its generic product. Precedent permits a jury to infer inducement where, as here, the defendant communicates promotional materials encouraging the infringing use to direct infringers. Teva encouraged the infringing use, in part, by telling doctors to use its drug just like Coreg®. So the fact that doctors' prior experience influenced how they used Teva's product reinforces liability, because Teva relied on that prior experience to encourage infringement.

The district court's approach, if allowed to stand, will have broad implications, particularly for pharmaceuticals. In nearly every case, the innovator promotes a drug's patented use and establishes a standard of care before generic entry. If those activities absolve the generic from inducement, method patents will have little value, and innovators will have no incentive to invest in new uses for existing drugs. It will also allow generics to bypass the Hatch-Waxman framework, because generics will simply launch and use the innovator's prior work as a non-infringement defense. Moreover, if an inducer can avoid liability by simply offering evidence that a factor outside its activities may have also influenced infringement, proving inducement will be impossible. The judgment should be reversed.

STATEMENT OF THE FACTS

I. GSK's Patented Invention: A New Treatment Method that Prolongs the Lives of Heart Failure Patients.

A. GSK's Inventors Defy Conventional Wisdom by Administering a Beta-Blocker (Carvedilol) to Treat Heart Failure.

GSK's U.S. Patent RE40,000 claims an unexpected breakthrough in the treatment of congestive heart failure. Heart failure stems from the left ventricle's inability to pump enough blood to the body's organs. (Appx10359–10360; Appx10601–10604; Appx11519.) The heart's ability to pump blood is often measured by the "ejection fraction," which is the percentage of blood pumped out of the left ventricle each time it contracts. A heart with a normal ejection fraction pumps out 55% to 70%, while a heart in failure typically pumps out less than 40%. (*Id.*) Heart failure causes a range of symptoms, including fatigue, shortness of breath, and, eventually, the inability to exert oneself physically. (*Id.*) Prior treatments sometimes improved patients' symptoms but did not extend patients' lives, making heart failure "a death sentence" with "more grave mortality than most cancers." (Appx10361–10362.) Half of heart failure patients died within five years of their diagnosis. (*Id.*) This left a "clear need for additional pharmacotherapy to improve quality of life and life expectancy." (Appx3408–3410 at Appx3409.)

GSK's inventors devised a new heart failure treatment that defied the conventional wisdom and prolonged many thousands of lives. When GSK's inventors began work with carvedilol, the prevailing view was not to give a beta-

blocker like carvedilol to a heart failure patient. (*See, e.g.,* Appx10357–10364; Appx11267, Appx11279; Appx6372; Appx4298; Appx11393–11395.) Beta-blockers were "contraindicated" because skilled artisans were worried that administering "a standard dose" would decrease heart rate and worsen the heart's pumping function, exacerbating the problem from which heart failure patients suffer. (Appx10357–10358; Appx11687.)

Despite significant positive preclinical work, including thousands of experiments resulting in numerous publications, GSK's inventors had to fight for permission to even attempt a clinical trial because of carvedilol's contraindication. (*See* Appx11272-11279.) They were only able to do so after agreeing to establish a Data Safety and Monitoring Board to watch how patients were progressing—a departure from the usual practice of blinded clinical trials. (Appx11280, Appx11286–11287; Appx10436–10438, Appx10371–10372; Appx44 at 6:15–35, Appx2996–3002 at Appx2997.) When inventor Robert Ruffolo learned that the Board had halted the trial, he feared the worst, thinking "oh my God, it killed people, just like everybody said, and it's my fault." (Appx11282.)

But to Dr. Ruffolo's great relief, and to the great benefit of many heart failure patients and their loved ones, the trial wasn't stopped because someone died. (Appx11282, Appx10372–10373.) Quite the opposite. Carvedilol was so effective in reducing the risk of death "that it was no longer ethical" to continue administering placebo and denying some patients the benefit of the treatment. (*Id.*) As a

subsequent *New England Journal of Medicine* article reported, treating heart failure patients with the inventors' method of administering carvedilol resulted in a "reduction in risk" of death of "65 percent." (Appx2996.) The inventors were "really shocked" by their own success, and, "to have this effect be as large as it was, was completely unexpected." (Appx10374.) These results, the culmination of over 10 years' work, led the FDA to approve carvedilol as the first-ever beta-blocker for heart failure in 1997, changing the standard of care. (Appx10376–10379, Appx10383–10385; Appx6422; Appx3055.) GSK sold carvedilol for heart failure and other uses under the Coreg® name.

B. GSK Obtains FDA Approval for an Additional Group of Heart Failure Patients—Those Also Suffering from "Post-MI LVD."

GSK's research efforts didn't stop after Coreg®'s initial approval for heart failure. Heart failure is a broad disease that includes a wide spectrum of patients—some in the early stages with few symptoms and others in the later stages with severe problems. (Appx10378–10383.) GSK ran additional clinical trials so that patients at both ends of the spectrum could be treated with carvedilol. (*Id.*)

One of the disputes at issue in this appeal involves the category of patients on the earlier end of the heart failure spectrum. These patients have recently suffered a heart attack (*i.e.*, a "myocardial infarction" (MI)) and their hearts have trouble pumping blood (*i.e.*, "left ventricular dysfunction" (LVD) where the ejection fraction was 40% or below). (Appx10381–10382; Appx11963.) Some of these "post-MI

LVD" patients already have the symptoms of heart failure, while others don't have them yet. (Appx10381–10382, Appx10602–10605; Appx11520.) But, in either case, these patients have "an early form of heart failure," because "the left ventricle cannot pump out and keep a normal ejection fraction." (Appx10603.) Indeed, Teva's expert agreed that "a patient who has a left ventricular ejection fraction of less than or equal to 40 percent with symptomatic heart failure would [be] diagnosed as suffering from congestive heart failure." (Appx11226.)

GSK obtained FDA approval to sell Coreg® for this "post-MI LVD" indication in 2003. It then added indication 1.2 to the Coreg® label, which addressed reducing the risk of death in post-MI LVD patients that have a left ventricular ejection fraction of 40% or less "with or without symptomatic heart failure." (Appx7665.) GSK's label thus instructed doctors to give certain post-MI LVD patients Coreg® to treat heart failure. Moreover, when seeking approval for the post-MI LVD indication, GSK explained that LVD and heart failure "are part of a single disease continuum," (Appx11965), and that the "post-MI LVD" indication addressed "the beginning of the heart failure continuum." (Appx11963 *see also* Appx11968–11969.) GSK also noted that about half of post-MI LVD patients in the clinical trial also had symptoms of congestive heart failure. (*See* Appx11964.)

C. GSK's Patent Claims Its Breakthrough Method of Administering Carvedilol to Reduce the Risk of Mortality from Heart Failure.

GSK sought patent protection in 1995 for its breakthrough heart failure treatment to protect the hundreds of millions of dollars it had invested. (Appx4294; Appx10501–10505; Appx10349–10350; Appx10791–10793; Appx11971–11984.) GSK's patent originally issued in 1998 as U.S. Patent No. 5,760,069. But, as discussed more below, Teva sent GSK a paragraph IV letter in 2003 alleging the '069 patent was invalid. (Appx3003–3019.) GSK responded by seeking a reissue patent with narrower claims more focused on its invention. (Appx31–45.) GSK's reissue patent, RE40,000, issued in January 2008, and several of its claims are at issue here. (*Id.*)

For example, Claim 1 of the '000 patent recites a method of reducing the risk of death from heart failure by administering "maintenance dosages" of carvedilol for a period greater than 6 months in conjunction with one of several other drugs:

> 1. A method of decreasing mortality caused by congestive heart failure in a patient in need thereof which comprises
>
> > administering a therapeutically acceptable amount of carvedilol in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of an angiotensin converting enzyme inhibitor (ACE), a diuretic, and digoxin,
> >
> > wherein the administering comprises administering to said patient daily maintenance dosages for a maintenance period to decrease a risk of mortality caused by congestive heart failure, and said maintenance period is greater than six months.

(Appx45 at 8:30–40.) A doctor performs the claimed method by administering carvedilol in the recited manner. (Appx120–124; Appx134–135.) GSK also asserted

dependent claims 2–3 and 6–9, which include more detail about dosing, other drugs administered with carvedilol, and the patient's particular class of heart failure.

The broad claim language covers administering carvedilol to any heart-failure patient to reduce the risk of death caused by congestive heart failure. (Appx88–132; Appx133–139.) It does not exclude treating heart-failure patients that may also suffer from additional conditions. Nevertheless, as discussed further below, the district court's JMOL order erroneously set aside the jury's finding that the treatment of post-MI LVD patients suffering from heart failure infringes—a finding that was well supported by the testimony of GSK's expert cardiologist. (Appx14-15 n.9.)

II. Teva's Infringement: Teva Intentionally Promotes Use of Its Generic Carvedilol in an Infringing Manner.

Because GSK's patent claims cover treatment methods performed by doctors, the key issue is whether Teva induced doctors to infringe (*i.e.*, to use its product to reduce the risk of death from heart failure as claimed in GSK's patent). A jury found that Teva did, so we review here the facts in the light most favorable to that verdict.

Years before launching its generic carvedilol product, Teva declared its intent for doctors to administer its product to treat heart failure and planned to instruct them to do so. For example, Teva filed its Abbreviated New Drug Application for carvedilol in March 2002, seeking approval to sell the product for all uses, including heart failure. (Appx10443, Appx10447.) Teva certified that it wouldn't begin selling the product until 2007, after patents on the carvedilol molecule expired. But Teva

contended that GSK's '069 patent for treating heart failure with carvedilol was invalid rather than agreeing not to sell until it expired in 2015. (Appx3005–3009; Appx5463; Appx10529–10530; Appx10890.) Teva's initial proposed labeling instructed doctors to use the product to treat heart failure. (Appx10456–10457; Appx10447; Appx10968–10969.) And, after Coreg® was approved for post-MI LVD in 2003, Teva also added that indication to its label, and thus further instructed treating heart failure in that set of heart failure patients. (*See, e.g.,* Appx5508; Appx10622–10631.)

Teva obtained tentative approval of its generic carvedilol in 2004 and immediately encouraged doctors to use it just like Coreg® to treat heart failure. Teva trumpeted in a press release that its "Carvedilol Tablets are the AB-rated generic equivalent of GlaxoSmithKline's Coreg® Tablets and are indicated for treatment of heart failure." (Appx6347.) GSK's expert cardiologist, who saw the press release when it issued, explained that it communicated to doctors that they should use Teva's generic carvedilol product to treat heart failure patients:

> Q. So the fact that it says here, carvedilol tablets are the AB rated generic equivalent of GlaxoSmithKline's Coreg tablets and are indicated for the treatment of heart failure, what did that tell you, as a physician, as to whether or not you could or should prescribe generic carvedilol for the treatment of heart failure?
>
> A. It indicates that we should be able to prescribe generic carvedilol for heart failure.

(Appx11659; *see also* Appx11656.) The press release also referenced GSK's total Coreg® sales, which included heart failure sales and showed that Teva planned to

capture sales for the patented use. (*Id.*; Appx6347.) This press release remains on Teva's website to this day, and it was there throughout the entire period of infringement. *See, e.g.,* https://bit.ly/2L2EtD7 (last visited July 16, 2018).

As that launch date drew near, Teva refined its regulatory strategy but still ensured that its drug labeling instructed the infringing heart failure use. (Appx10969, Appx10534–10536; Appx6176–6182.) Teva initially thought it would have the benefit of a "first-filer" 180-exclusivity against other generics. *See* 21 U.S.C. § 355(j)(5)(B)(v). This turned out to be wrong—other generic companies devised a way to launch immediately by purporting to make a "section viii" carveout, where they removed some of the heart failure information from the product's label. (Appx6175; Appx10449–10451; Appx10477; 21 U.S.C. § 355(j)(2)(A)(viii).) But this wasn't a true section viii carveout: the label still included the post-MI LVD indication, instructing doctors to use the product to infringe. (Appx5506–5530; Appx10622–10631.)

The public was aware of Teva's intent to capture the treatment of all heart failure patients. For example, a customer asked Teva if the other generics' section viii carveouts meant that Teva's product, which was still proposed for all the same uses as Coreg®, would be the only "correct" generic to dispense to heart failure patients. (Appx6175.) Teva never responded. Instead, Teva switched course and, like the other generics, removed only ***some*** of the heart failure language from its "partial" label, without telling doctors it was doing so. (Appx10458, Appx10488, Appx10491.) Yet Teva's label still encouraged doctors to use its product to reduce the risk of death

caused by heart failure in post-MI LVD patients with symptoms of heart failure:

> Carvedilol is 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 ≤ 40%*** (***with*** or without ***symptomatic heart failure***).

(Appx5508 (emphases added); *see also* Appx10622–10623, Appx10602–10606, Appx10673, Appx10682; Appx10381–10383.) Teva's partial label also still included language warning of the risk of "worsening heart failure" when patients first use its product, (Appx5510), and included data from GSK's clinical studies that showed carvedilol reduced the risk of death in post-MI LVD patients with heart failure. (Appx5523–5524.) And, as GSK's expert explained, Teva's partial label also still instructed doctors to use the product in a manner that meets the other limitations of claim 1 of the '000 patient—*i.e.*, with one of the other listed drugs and for greater than 6 months. (Appx10622–10631; Appx5506–5530.)

Despite removing some of the heart failure language from its partial label, Teva still expected to capture sales from all heart failure patients upon launch, including those without post-MI LVD. Teva's Director of New Products admitted as much:

> Q. So is it the expectation of Teva that when you carve out a particular indication, that Teva will still get sales of that drug for that indication once it's launched its product?
>
> A. It's a legal strategy, not a commercial strategy.
>
> Q. But as a commercial person, ***is it your expectation that Teva will get sales for the carved out indication?***
>
> ***A. Yes.***

***

Q. ***Teva was aware in 2007*** that its drug was being prescribed by physicians, its ***carvedilol*** generic, was being ***prescribed by physicians for treatment of congestive heart failure***?

A. Okay, ***yes***.

(Appx10488, Appx10491.) Likewise, Teva's Senior Director of Regulatory Affairs admitted that its carvedilol product could be substituted for any use of Coreg®, including treating heart failure. (Appx10453.)

Teva also communicated to doctors that its "partial label" carvedilol product should be used to treat all congestive heart failure patients. For example, Teva issued a press release when it launched the partial label product in 2007 that said it was selling a "Generic version of GlaxoSmithKline's cardiovascular agent Coreg®." (Appx6353.) GSK's expert testified that the phrase "cardiovascular agent" told him and other doctors that they should use the product to treat heart failure:

Q. Can you tell the jury what Teva is telling you and your colleagues here in their 2007 press release?

A. Right. So here in 2007, Teva is telling doctors right in the title that they have approval and actual shipment of generic Coreg tablets, that the FDA granted final approval of Teva's generic version of GSK's cardiovascular drug, Coreg.

Q. Now, what did that tell you, Dr. McCullough, and your colleagues, as a physician about what Teva's generic carvedilol, what indications it could be used for?

A. It could be used for ***all the indications***.

Q. Would that include heart failure in your mind?

A. Sure.

Q. Well, I don't see the words "heart failure" in this particular press release. What made you think that Teva's generic carvedilol had been approved for the treatment of congestive heart failure.

A. The use of the term "cardiovascular agent."

(Appx11659–11660; *see also* Appx10672, Appx11655–11657, Appx11238–11241.) And, as with its 2004 press release, the 2007 press release included Coreg®'s total revenue, which shows that Teva intended to capture the entire market, including heart failure. (Appx6353; Appx10643–10644.) In fact, Teva included heart failure revenue despite an employee explicitly questioning whether it was right to do so. (Appx6173–Appx6174; Appx10972–10974.) Teva has kept the 2007 press release on its website to this day, and, as with the prior press release, it was on the website throughout the infringement period. *See, e.g.,* https://bit.ly/2m7FS0s (last visited July 16, 2018).

Teva's subsequent marketing materials built upon those press releases and reinforced that its generic product should be used exactly like GSK's product, including for the infringing use. Teva's product catalogs stated its generic was "AB"-rated and juxtaposed it next to "Coreg®," as shown in the example below:

PRODUCT NAME	DESCRIPTION	IMPRINT	TEE*	NDC NUMBER	SIZE	UNIT OF SALE	MASTER CASE	BRAND
Carvedilol Tablets								Coreg® Tablets
3.125 mg	Elliptical-shaped, White	93/51	AB	0093-0051-01	100	12	144	
6.25 mg	Elliptical-shaped, White	93/135	AB	0093-0135-01	100	12	120	
12.5 mg	Elliptical-shaped, White	93/7295	AB	0093-7295-01	100	12	120	
25 mg	Elliptical-shaped, White	93/7296	AB	0093-7296-01	100	12	120	

(Appx6221; *see also* Appx6270; Appx6072; Appx6324; Appx6185; Appx10543–10545,

Appx10634, Appx10685.) Teva's website has made that same comparison since 2007. (Appx10991–10992; Appx4245–4246.) Teva's product guide is even more explicit, referring to Coreg® as the "Brand Equivalent" of Teva's product. (Appx6185.)

GSK's cardiologist expert confirmed these materials communicated to doctors, such as himself, that the products were "therapeutically interchangeable." (Appx10634–10636.) Likewise, GSK's regulatory expert explained that, according to the FDA, such direct comparisons—where the generic not only refers to an "AB" rating but also invokes the name of the branded drug (Coreg®)—communicate that both products are approved for all the same uses. (Appx10544–10545, Appx10582–10583.) Even Teva's expert admitted doctors' prescribed generic carvedilol just like Coreg® because they thought the two were "therapeutically interchangeable." (Appx11176; *see also* Appx11168.) Doctors receive Teva's catalogs and guides and visit its website, so they would have reviewed this information. (Appx11664–11665.)

In 2011, Teva's instructions to doctors about using the product for the infringing use of treating heart failure became even more explicit. Teva amended its label to add back all the information about heart failure that it had previously removed. (Appx5531–5553; Appx5554–5559; Appx10569–10572.) Teva's "full" label thus now told doctors to use the product for all types of congestive heart failure, just as its other promotional materials had done for years:

1.1 Heart Failure

Carvedilol tablets are indicated for the treatment of mild-to-severe chronic

> heart failure of ischemeric or cardiomyopathic origin, usually in addition to diuretics, ACE inhibitors, and digitalis, to increase survival and, also, to reduce the risk of hospitalization.

(Appx5532.) Likewise, Teva's 2012 and 2013 Monthly Prescribing References, which are communicated to "Healthcare Professional[s]," instructed that its product should be used for "Mild to severe heart failure (HF) to increase survival," as well as "[t]o reduce cardiovascular mortality" in post-MI LVD patients, including those with symptomatic heart failure. (Appx6194, Appx6200; *see also* Appx6203, Appx6208; Appx10608–10612.) GSK's expert cardiologist confirmed that doctors receive these materials "on a regular basis." (Appx10607–10608.)

Teva asked the jury to disregard its promotional materials and labels at trial by arguing that doctors didn't read any of that information. But GSK's expert testified that doctors do read generic labels and that he personally had read Teva's label outside of his work on this case. (Appx10608–10612; Appx11661–11662.) Indeed, Teva's other documents told doctors that they should read the label. For example, Teva's Monthly Prescribing References instructs that "[t]he clinician must be familiar with the full product labeling provided by the manufacturer or distributor of the drug, of every product he or she prescribes, as well as the relevant medical literature." (Appx6196, Appx6205.) It also says that Teva offers "high-quality educational tools to serve as convenient, authoritative references in daily use" that are "organized into therapeutic sections to make it simple to find the information you need quickly," and are designed to be "a trusted tool in your clinical armamentarium." (Appx6194; *see*

also Appx6203.) Teva's References go on, in a section titled "Important Information for Readers," to say that, "if any questions arise" about the information it contains, doctors should "verify it against the labeling or by contacting the company marketing the drug." (Appx6196; *see also* Appx6205.) Teva also directs doctors to visit its website. (Appx6202.) And, as noted, GSK's expert cardiologist testified that doctors do read Teva's press releases, product catalogs, and other materials. (Appx10607–10610; Appx11655, Appx11664.) Even Teva's expert acknowledged that doctors read press releases. (Appx11238–11241.)

The jury also heard direct evidence that Teva's activities caused doctors to prescribe generic carvedilol to treat heart failure. GSK's expert testified that he and other doctors are "completely reliant" on information they receive from a generic company like Teva in deciding how to use its product:

> Q. So do you or do you not rely on the information that you get from the generic as to whether or not they are truly a generic equivalent of the original brand?
>
> A. Yes, we're completely reliant on what they provide to us.

(Appx11661–11662.) Moreover, he testified that Teva's press releases and other marketing materials led him to believe that its generic carvedilol was approved for all the same uses that Coreg® had been approved for, including treating heart failure:

> Q. Now, rather than reinvent the wheel, the last time you testified, we introduced, through you, some Teva product brochures, that MPR for the physician, and it ranged, basically we introduced a bunch of Teva information that ranged from 2008 to 2013 showing that Teva represented their carvedilol . . . tablet was the generic equivalent of

> Coreg and was AB rated. Based on what Teva said in 2004 and 2007, any time after that, 2008, 9, 10, 11, up to 2013, did you ever come to believe that Teva's generic carvedilol had not been approved for the treatment of heart failure?
>
> A. No, I never knew it.

(Appx11661.) GSK's expert also testified that, had he known Teva's product was not approved for use in treating heart failure during the "partial label" period, he would not have prescribed it generally for the infringing use:

> Q. And, Dr. McCullough, ha[d] you known that Teva had not been approved – I'm sorry – Teva's generic carvedilol had not been approved for the use in congestive heart failure, would you have used it anyway to treat congestive heart failure?
>
> A. No, I wouldn't have.
>
> Q. Why not?
>
> A. Because even though the drug is the same, the difference is the package insert and the label which is missing too much information.

(Appx11660–11661.) As it turned out, however, GSK's expert believed Teva's product was a "complete replacement" that was approved for all the same uses as Coreg® because of Teva's press releases and other promotional materials:

> Q. Now, before you started administering generic carvedilol to your patients, whether you wrote it as Coreg or not, did you read Teva's generic label?
>
> A. No, I didn't.
>
> Q. Why not?
>
> A. I just assume[d] they were the same.

> Q. What made you assume that?
>
> A. Well, we had lots of information as we had gone over [*i.e.,* Teva's promotional materials] that indicated that, you know, it was a complete replacement. That in fact the two, the drug was the same and all the information regarding it was the same.

(Appx11662–11663.) He did later read Teva's label to answer patient questions. (*Id.*)

Finally, the jury heard evidence that doctors directly infringed by prescribing Teva's product. Both sides' experts testified they had prescribed generic carvedilol to treat heart failure. (Appx11662–11663; Appx10631; Appx11177.) The evidence also showed that Teva captured as much as half the generic carvedilol market. (Appx6771.) In addition, a survey showed a significant percentage of carvedilol prescriptions were infringing (*i.e.*, to reduce the risk of death from heart failure and used with ACE inhibitors or diuretics and as part of a treatment method lasting longer than 6 months). (Appx10727, Appx10736.) GSK's damages expert calculated that Teva's infringement caused GSK to lose profits of $477 million. (Appx10816.)

III. The Proceedings Below: The District Court Sets Aside the Jury's Finding that Teva Induced Infringement.

Having heard the evidence of Teva's conduct during a 7-day trial, and having shown diligence by requesting a magnifying glass to help it review the trial exhibits, the jury found that Teva induced infringement during the "partial" label period (January 8, 2008–April 30, 2011) and the "full" label period (May 1, 2011–June 7, 2015). (Appx204–213.) The jury also found that Teva's infringement was willful, that the '000 patent was not invalid, and that Teva was liable for $235.51 million. (*Id.*)

The district court instructed the jury on inducement and specifically charged that it could not find liability unless "Teva's alleged inducement, as opposed to other factors, actually caused the physicians to directly infringe." (Appx173.) The court's jury instructions further elaborated that "[t]his means that Teva cannot be liable for induced infringement where GSK does not show that Teva successfully communicated with and induced a third-party infringer and that the communication was the cause of the direct infringement by the third-party infringer." (*Id.*) The jury's verdict thus reflected its determination that Teva communicated its labels and promotional materials to doctors and that those materials caused their infringement.

The district court, however, set aside the jury's findings on inducement and, in doing so, substituted its own view of the evidence. (Appx1–27.) For example, the court did not address the testimony from GSK's cardiologist expert that Teva's promotional materials (*e.g.*, press releases, product guides, etc.) caused him to administer Teva's product to treat heart failure and concluded, instead, that he was not induced because he "did not read Teva's label" when the product first launched. (Appx13–14, *citing* Appx11659–11663.) The court noted that GSK's expert was also influenced by other sources, such as GSK's marketing before Teva's launch and standard guidelines for treating heart failure. (Appx14, *citing* Appx10666–10669, Appx10676–10678.) Having begun with those general observations, the Court divided its analysis into two parts—one for the "partial" (or "skinny") label period, and another for the "full" label period.

For the "partial" label period, the court noted Teva had "omitted from its label" some of the heart failure language and that GSK's expert "would not prescribe generic carvedilol for CHF if it was not an approved use on the label." (Appx14–15, *citing* Appx11660–11661.) But the court did not mention the expert's further testimony that Teva's other promotional materials had led him to believe that Teva's product ***was*** approved to treat heart failure and thus caused him to infringe. The court also inexplicably set aside the jury's factual finding that the "post-MI LVD language in [Teva's partial] label caused or even encouraged direct infringement," (Appx15–16 & n.9), even though the label says the product should be used to "reduce cardiovascular mortality" in patients "with … symptomatic heart failure," (Appx5508) and even though GSK's expert testified that the partial label instructed doctors to use the product in a way that met every other claim limitation. (Appx10622–10631.)

The court also dismissed Teva's marketing materials comparing its AB-rated partial label product to Coreg® without mentioning GSK's cardiologist expert testimony that this communicated that the products were therapeutically interchangeable. Nor did the court discuss GSK's regulatory expert who testified that the FDA views such a comparison as implying that the generic is approved for all the same uses as the branded drug. (Appx16–17.) The court also did not address either of Teva's press releases about its product, much less GSK's expert testimony that cardiologists would have seen those releases and inferred from them that Teva's partial-label product was approved to treat heart failure.

Instead, the court noted that, after Teva launched its product, "doctors continued prescribing carvedilol (be it Coreg® or a generic) in the same manner as they had prior to the generics' entrance," and "relied on guidelines and research, as well as their own experience in addition to GSK marketing." (Appx18–19.) The court thus concluded "there was no reasonable basis for the jury to have found that anything Teva did – including selling generic carvedilol, giving it a "skinny" label, and all aspects of how Teva marketed its carvedilol – caused even a single doctor to prescribe carvedilol for the treatment of" heart failure. (Appx19-20.) But this ignored the fact that Teva caused infringement by telling doctors to use its product like Coreg® and thus capitalized on that pre-existing knowledge to encourage infringement. Finally, the court criticized GSK for supposedly presenting "no direct evidence" of inducement, (Appx20), even though GSK did present direct evidence from its expert, and even though circumstantial evidence alone would be sufficient.

With respect to the "full label" period, the court's analysis was brief. (Appx22–24.) The court barely acknowledged GSK's evidence that Teva's full label, which contains the language reproduced above at pp. 14–15, now even more explicitly instructed doctors to use the product to infringe and that Teva's other materials told doctors to read its label. (Appx22.) Instead, the court again blamed GSK for doctors' direct infringement when administering Teva's generic carvedilol because "physicians were already prescribing generic carvedilol to treat CHF [congestive heart failure]" when Teva changed its label to add more language on heart failure. (Appx23.)

SUMMARY OF THE ARGUMENT

The district court's JMOL should be reversed because the jury's inducement finding was supported by substantial evidence. This Court has repeatedly held that a jury may infer a defendant's actions caused others to infringe where the defendant intentionally encourages the infringing use. The jury here was thus presented with a quintessential question of fact—whether Teva's promotional materials and labels encourage the infringing use. It found that they do, and that finding was well supported. Teva's promotional materials (*e.g.*, press releases, catalogs, and website) encouraged infringement by communicating that its generic should be used just like Coreg® and touting its use to "treat heart failure." Teva's labels also encouraged use of the product to treat heart failure throughout the relevant period. The jury also had another independent basis on which to find causation—direct evidence from GSK's expert cardiologist that Teva's acts caused him to infringe. Any one of these standing alone could sustain the jury's verdict, and, taken together, they are certainly sufficient.

In concluding otherwise, the district court erred by ignoring (or giving little weight) to evidence that the jury credited (*e.g.*, Teva's press releases and the expert testimony about how Teva's promotional materials would be interpreted) and re-analyzing other issues that were within the jury's province (*e.g.*, whether Teva's partial label encouraged infringement). The court compounded that error by analyzing causation in a manner inconsistent with the statute, precedent, and common law. The JMOL should thus be reversed and the jury's verdict reinstated.

STANDARD OF REVIEW

This Court reviews a district court's grant of judgment as a matter of law *de novo*. *Callaway Golf Co. v. Acushnet Co.*, 576 F.3d 1331, 1339 (Fed. Cir. 2009). "Infringement is a question of fact, reviewed for substantial evidence when tried to a jury." *Lucent Techs., Inc. v. Gateway, Inc.*, 580 F.3d 1301, 1309 (Fed. Cir. 2009).

A "court may grant judgment as a matter of law contrary to the verdict only if the record is critically deficient of the minimum quantum of evidence to sustain the verdict." *Acumed LLC v. Advanced Surgical Servs., Inc.*, 561 F.3d 199, 211 (3d Cir. 2009)). JMOL should be granted "sparingly" and "only if, viewing the evidence in the light most favorable to the nonmovant and giving it the advantage of every fair and reasonable inference, there is insufficient evidence from which a jury reasonably could find liability." *Marra v. Philadelphia Hous. Auth.*, 497 F.3d 286, 300 (3d Cir. 2007). "In performing this narrow inquiry, we must refrain from weighing the evidence, determining the credibility of witnesses, or substituting our own version of the facts for that of the jury." *Id.*

ARGUMENT

I. The Jury's Inducement Finding Was Supported by Substantial Evidence.

The district court's grant of JMOL should be reversed. This Court has repeatedly held that a jury may infer that the defendant induced (caused) infringement where, as here, the defendant intentionally promotes the infringing use and communicates that message to the direct infringers. The jury's factual finding that Teva did promote the infringing use and thus induced infringement through both the "partial" and "full" label periods was supported by Teva's promotional materials and labels, and by expert testimony. The district court was wrong to set aside that finding by reweighing evidence (including expert credibility), and its analysis of causation was simply incorrect. Moreover, substantial evidence supported the jury's finding that the other elements of inducement were met as well.

A. The Jury's Causation Finding Was Supported by Substantial Evidence.

1. Precedent Permits the Jury to Find Causation Based on Teva's Intentional Encouragement of the Infringing Use.

"Whoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b). A defendant is liable if (1) "a third party directly infringed the asserted claims," (2) the defendant "induced those infringing acts," and (3) the defendant "knew the acts it induced constituted infringement." *Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc.*, 843 F.3d 1315, 1332 (Fed. Cir. 2016). The term "induce" means "[t]o lean on; to influence; to prevail upon; to move by

persuasion." *Global-Tech Appliances, Inc. v. SEB S.A.*, 553 U.S. 754, 760 (2011). As a result, the second element requires "successful communication between the alleged inducer and the third-party direct infringer," such that the defendant's conduct "led to direct infringement." *Power Integrations*, 843 F.3d at 1331. "The inducement may be proven via circumstantial evidence." *Id.* "Circumstantial evidence is not only sufficient, but may also be more certain, satisfying and persuasive than direct evidence." *Moleculon Research Corp. v. CBS, Inc.*, 793 F.3d 1261, 1272 (Fed. Cir. 1986).

This Court has repeatedly held that a jury may infer that a defendant has actually induced infringement—*i.e.*, that its actions have "led to direct infringement" by third parties—where the defendant has intentionally promoted infringement. "[I]f an entity offers a product with the object of promoting its use to infringe, as shown by clear expression or other affirmative steps taken to foster infringement, it is then liable for the resulting acts of infringement by third parties." *DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1305-06 (Fed. Cir. 2006) (en banc in relevant part). The Supreme Court described the rule similarly when extending patent law's inducement standard into copyright. *See Metro-Goldwyn-Meyer Studios Inc. v. Grokster, Ltd.*, 545 U.S. 913, 936–37 (2005) ("[O]ne who distributes a device with the object of promoting its use to infringe copyright, as shown by clear expression or other affirmative steps taken to foster infringement, is liable for the resulting acts of infringement by third parties."). "The classic instance of inducement is by advertisement or solicitation that broadcasts a message designed to stimulate others to commit violations." *Id.* at 937.

Applying that principle, this Court has "affirmed induced infringement verdicts based on circumstantial evidence of inducement (*e.g.*, advertisements, user manuals) directed to a class of direct infringers (*e.g.*, customers, end users) without requiring hard proof that any individual third-party direct infringer was actually persuaded to infringe by that material." *Power Integrations*, 843 F.3d at 1335. A patent owner need only show that the defendant promoted the infringing use in materials that were successfully communicated to customers. *See, e.g.*, *id.* at 1332–35 (holding the defendant's "affirmative acts to induce third parties to import its products into the United States" were enough to allow a jury to infer the defendant "had induced its customers" to "infringe as a class"); *Ericsson, Inc. v. D-Link Sys., Inc.*, 773 F.3d 1201, 1220, 1222 (Fed. Cir. 2014) (affirming jury's induced infringement verdict where defendant advertised compliance with an infringing standard); *Lucent Techs., Inc. v. Gateway, Inc.*, 580 F.3d 1301, 1323 (Fed. Cir. 2009) (affirming jury's inducement finding based on expert testimony that the defendant's "documentation encouraged users to use the infringing tool"); *Arthrocare Corp. v. Smith & Nephew, Inc.*, 406 F.3d 1365, 1377 (Fed. Cir. 2005) (affirming jury's induced infringement verdict where defendant distributed "sales literature" and "manuals" that instructed how to use product in infringing manner); *Mentor H/S, Inc. v. Medical Device Alliance, Inc.*, 244 F. 3d 1365, 1379 (Fed. Cir. 2001) (reversing JMOL of no inducement where there was substantial evidence the defendant "sold the [accused] device with the intention that doctors would use it to perform the patented method"); *Moleculon*, 793 F.2d at 1272

(affirming jury verdict of inducement based on dissemination of "instruction sheets" and "solution books" teaching the infringing use of the accused puzzle); *see also Grokster*, 545 U.S. at 937–40 (permitting copyright inducement claim to go to the jury based on intentional advertisement of the infringing use); *Toshiba Corp. v. Imation Corp.*, 681 F.3d 1358, 1365 (Fed. Cir. 2012) ("Appellees designed the DVDs to be used in an infringing way and instructed users to use them in the infringing way by finalizing the DVDs or using the disc-at-once mode. This is sufficient to preclude summary judgment.").

Likewise, this Court has repeatedly affirmed inducement findings in Hatch-Waxman cases that occur before a generic company launches its product where, as here, the defendant's label or other promotional materials intentionally instruct the infringing use. *See, e.g.*, *Vanda Pharms. Inc. v. West-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1130 (Fed. Cir. 2018) ("The district court made factual findings that the proposed label 'recommends' that physicians perform the claimed steps, and its analysis of the proposed label to assess potential direct infringement by physicians was proper under our precedent.") (internal cite omitted); *Sanofi v. Watson Labs. Inc.*, 875 F.3d 636, 646 (Fed. Cir. 2017) ("The evidence in this case supports the finding of intentional encouragement of infringing use and, therefore, of inducement."); *Eli Lilly & Co. v. Teva Parental Medicines Inc.*, 845 F.3d 1357, 1369 (Fed. Cir. 2017) ("[E]vidence that the product labeling that Defendants seek would inevitably lead some physicians to infringe establishes the requisite intent for inducement."); *AstraZeneca LP v. Apotex,*

Inc., 633 F.3d 1042, 1059 (Fed. Cir. 2010) ("[L]iability for active inducement may be found where evidence goes beyond a product's characteristics or the knowledge that it may be put to infringing uses, and shows statements or actions directed to promoting infringement.").

2. The Jury Could Properly Find that Teva Caused Infringement During the Partial Label Period.

The jury's inducement finding for the partial-label period was supported by sufficient evidence given the precedent just discussed. Teva actively and intentionally promoted its partial-label generic product for the infringing use—*i.e.*, treatment of heart failure in the manner claimed—through various channels, including (1) through press releases, product guides, and its website, and (2) through a partial label that instructed and encouraged the infringing use. Either category of evidence alone would be sufficient to find causation, as a defendant's successful communication of any instruction to infringe is circumstantial evidence that third parties followed those instructions. When these categories of promotion are taken together, they are certainly sufficient to support the jury verdict. GSK also submitted a third category of evidence—direct evidence—that goes beyond that required in the prior cases: GSK's cardiologist expert testified that he used Teva's product for the infringing use based on Teva's promotion of that use through its press releases and product guides. The district court's JMOL would have to be reversed based on any one of the categories of evidence and cannot stand given the combination of all three.

a. Teva's Press Releases, Product Guides, and Website Encouraged the Infringing Use.

Teva actively encouraged doctors, through its promotional materials, to prescribe its partial label generic carvedilol just as doctors prescribed Coreg®—for the infringing use. For example, Teva widely distributed its 2004 and 2007 press releases to doctors, both of which announced the approval of its product and touted the infringing use. The 2004 press release said the product was "for the treatment of heart failure" (the patented use), was "the AB-rated equivalent of [GSK's] Coreg®," and that Teva had already received tentative approval. (Appx6347.) It also said it expected final approval in 2007. (*Id.*) Teva's 2007 press release described its approved product as a generic version of GSK's "cardiovascular agent" Coreg®. (Appx6353.) GSK's expert explained, without contradiction, that doctors would understand this language to mean that the product could and should be used to treat heart failure. (Appx11659–11660.) Indeed, both press releases referenced Coreg®'s full revenue, including revenue from heart failure sales, which was the "main use" of Coreg® at the time. (Appx6347; Appx6353; Appx10643–10644.) That confirmed how GSK's expert interpreted the press releases—*i.e.,* as teaching the infringing use. Moreover, Teva kept these press releases on its website throughout the infringement period (2008–2015) and continues to do so today. *See, e.g.,* https://bit.ly/2L2EtD7; https://bit.ly/2m7FS0s.

Having laid this foundation, Teva continued to promote its partial label product as a Coreg®-equivalent for the infringing use in its product guides and advertisements. For example, Teva's product catalogs and website not only referred to its product as "AB-rated" but they directly compared it to GSK's Coreg® products and called it the "Brand Equivalent." (Appx6221; Appx6185; Appx6270; Appx6072; Appx6324; Appx10543–10545, Appx10634, Appx10685; Appx4245–4246; Appx10991–10992.) The jury could properly conclude from these direct comparisons that Teva was marketing its product for the infringing use of treating heart failure. GSK's regulatory expert testified that such marketing conveys that the generic may be used in the same manner as the branded product. (Appx10544–10545, Appx10582–10583.) GSK's cardiologist expert likewise testified that the comparison would lead doctors to treat the generic as "therapeutically interchangeable" with GSK's product, *i.e.*, that it could be used in exactly the same manner, including to treat heart failure. (Appx10634–10636.) Even Teva's expert acknowledged that the reason he prescribed generic carvedilol in the same way he prescribed Coreg was because he viewed them as "therapeutically interchangeable." (Appx11176.) The jury was entitled to conclude that Teva's acts gave doctors the impression the products were interchangeable, leading them to infringe. And the jury's decision to do so was particularly reasonable given that Teva had already encouraged physicians to use the product to treat heart failure in its press releases—press releases that were on its website throughout the infringement period.

These materials promoting the infringing use are precisely the type of evidence that this Court has held would allow a jury to infer that the defendant's acts led to (caused) third-party infringement. *See, e.g.*, *Power Integrations*, 843 F.3d at 1332–35; *Ericsson*, 773 F.3d at 1220, 1222; *Toshiba*, 681 F.3d at 1365; *Lucent*, 580 F.3d at 1323; *Arthrocare*, 406 F.3d at 1377; *Mentor H/S*, 244 F. 3d at 1379; *Moleculon*, 793 F.2d at 1272. For example, in *Power Integrations*, advertisements promoting that a product complied with United States energy standards were sufficient for a jury to infer that the defendant promoted the infringing use (*i.e.*, importing the product into the United States). *See* 843 F.3d at 1333. Likewise, in *Ericsson*, a defendant's advertisements promoting that its products complied with an industry standard were sufficient to show inducement where use of the standard was found to infringe. *See* 773 F.3d at 1222; *see also Power Integrations*, 843 F.3d at 1335 (characterizing *Ericsson* in this manner). Neither case required that a defendant provide a list of detailed instructions explaining how to directly infringe. For example, the *Power Integrations* defendant did not expressly say "bring your products to the United States," nor did the *Ericsson* defendant say "use multiple types of feedback responses," which was the infringing functionality there. But both found that a jury could reasonably conclude that what the defendant did say was enough to encourage infringement.

The same is true here. Teva's message to doctors in its product guides and on its website was that they could use its product just like GSK's Coreg®. This communication alone was sufficient to encourage doctors to infringe, because they

would use its generic for all the uses for which Coreg® was approved, including treating heart failure. Teva knew this and the jury agreed. This scenario is just like the *Ericsson* defendant instructing its customers to use the standard, knowing that if they did so, they would infringe. In fact, Teva went much further than the *Ericsson* and *Power Integrations* defendants, because one of its press releases explicitly told doctors to use the product to "treat heart failure" (the infringing use), and it kept that press release on its website throughout the infringement period.

Moreover, the jury properly concluded that Teva successfully communicated these materials describing the infringing use to doctors and that doctors actually read them. For example, GSK's cardiologist expert testified that he read Teva's press releases, and that doctors receive Teva's catalogs, visit its website, and read its other guides. (Appx11664–11665, Appx11656; Appx10607–10610.) Even Teva's cardiologist expert admitted that he had seen the press releases. (Appx11238–11241.) Given the jury's implicit findings that the promotional materials instructed the infringing use and that doctors received and read them, this Court's precedent bars setting aside its factual finding of causation.

b. Teva's Partial Label Encouraged the Infringing Use.

The second independent category of evidence showing that Teva promoted infringement is Teva's partial label itself. GSK's cardiologist expert explained in detail that the partial label instructed doctors to perform each step of the claimed method on post-MI LVD patients with heart failure. (Appx10622-10631; Appx5506–5530.)

For example, the label said the drug should be used to "reduce cardiovascular mortality" in patients with "symptomatic heart failure," (Appx5508), identified the therapeutically effective amount to be used, (Appx5506), instructed use of the drug with ACE inhibitors and diuretics, (Appx5508, Appx5523), and pointed to clinical studies showing the administration of maintenance dosages for over 6 months. (Appx5508, Appx5524.) Teva's cardiologist expert likewise admitted that some of the post-MI LVD patients referenced on the label have heart failure—he agreed that "a patient who has a left ventricular ejection fraction of less than or equal to 40 percent with symptomatic heart failure would [be] diagnosed as suffering from congestive heart failure." (Appx11226.) Moreover, Teva told doctors to read the label, and GSK's expert testified that doctors (including himself) read generic labels. (Appx10608–10612; Appx11661–11662; Appx6196, Appx6205.) The jury thus had ample evidence to conclude that Teva's partial label was a successful communication to doctors that encouraged the infringing use, making it alone sufficient to support the inducement verdict under *Power Integrations* and the other cases cited above.

Teva's partial label is also the type of instruction that this Court has repeatedly held is sufficient, all by itself, to establish inducement in Hatch-Waxman cases. *See, e.g.*, *Vanda*, 887 F.3d at 1130; *Sanofi*, 875 F.3d at 646; *Eli Lilly*, 845 F.3d at 1369; *see also AstraZeneca*, 633 F.3d at 1056. Those cases deal with a situation where although the generic has not yet launched its product, the Court has enjoined the generic launch by concluding that a label instructing the infringing use would cause doctors to infringe if

the product was sold. *Id.* That same rationale applies directly in this post-launch case: GSK's cardiologist expert testified that doctors do read generic drug labels, and Teva's marketing materials encouraged doctors to read the label. (Appx10608–10612; Appx11661–11662; Appx6196, Appx6205.) The jury could thus properly conclude that those intentional instructions to infringe actually caused at least some doctors to follow them post-launch and infringe, just as this Court has previously said that they would in the pre-launch context. If a drug label that instructs the infringing use can justify an injunction barring any sale of the product pre-launch, it is surely enough to justify a damages award on only the infringing uses post-launch.

c. GSK's Expert Presented Direct Evidence that Teva Induced Him to Infringe.

The circumstantial evidence of causation discussed above was more than adequate to the support the jury's verdict. But GSK presented even more: direct evidence from its expert that Teva's behavior caused him and other physicians to infringe. (Appx11659–11663.) He testified that doctors are "completely reliant" on the information generic drug companies provide them and that Teva's marketing materials—including the press releases, product catalogs, and website—caused him to think its partial label product was approved to treat congestive heart failure, just like Coreg®. (Appx11661–11662.) Teva's marketing materials led him to believe its product was a "complete replacement" for Coreg® and thus caused him to administer it for the infringing use—treating heart failure. (Appx11662–11663.) The jury

reasonably credited this testimony and found that Teva's behavior caused him and other doctors to infringe.

d. Teva's Intent to Infringe Further Reinforced the Jury's Finding of Causation.

The jury's finding that Teva's acts caused infringement was all the more reasonable given that this was Teva's expectation and intent all along. Teva's witnesses admitted that Teva expected to sell its product to treat heart failure, the infringing use. (Appx10488, Appx10491, Appx10453.) Teva's press releases included GSK's revenue for the infringing use, underscoring that it intended to capture that revenue. (Appx6347; Appx6353.) That is no surprise—heart failure was the main use of Coreg® at the time, (*e.g.*, Appx10643–10644), so Teva had a commercial incentive to promote infringement and make more money in the process. *See, e.g.*, *Grokster*, 545 U.S. at 939–40 (holding that the fact "the commercial sense of [defendants'] enterprise turns on high volume use, which the record shows is infringing" supported an inference of intent).

Teva was also careful not to discourage doctors from using its product for the infringing use, electing not to put any disclaimers in its marketing materials, mention that it had removed language from the product label, or retract any of its statements that it received approval for all uses. That further demonstrates its unlawful intent. *See, e.g.*, *Grokster*, 545 U.S. at 939 & n.12 (holding that other evidence of unlawful intent was "given added significance" because neither defendant "attempted to

develop filtering tools or other mechanisms to diminish the infringing activity using their software"). And the jury could properly infer that Teva not only intended to promote the infringing use, but that it actually succeeded, given all the other direct and circumstantial evidence on that point. The district court's JMOL of no inducement during the partial label period should thus be reversed.

3. The Jury Could Properly Find that Teva Caused Infringement During the Full Label Period.

The jury's inducement finding for the full label period was also supported by substantial evidence. Throughout the full label period, Teva continued all the promotional activities that made it liable during the partial label period. Teva also expanded its promotion of the infringing use even further during the full label period, explicitly adding to its label that the product was approved for "mild-to-severe chronic heart failure" to "increase survival." (Appx5532.) GSK's expert explained, without contradiction, that Teva's full label instructed doctors to use the drug in a manner covered by all the remaining claim limitations too, including instructions on the therapeutically effective amount, (Appx5531), co-administration with diuretics, ACE inhibitors, and digitalis, (Appx5532), and treatment for a maintenance period for over 6 months to reduce the risk of mortality. (Appx5532, Appx5547; *see also* Appx10623–10631.)

Likewise, Teva's Prescribing References, which are specifically addressed to doctors, instructed that its product should be used for "Mild to severe heart failure

(HF) to increase survival," as well as "[t]o reduce cardiovascular mortality" in post-MI LVD patients suffering from heart failure. (Appx6194, Appx6200; *see also* Appx6203, Appx6208; Appx10608–10612.) Those same marketing materials specifically instructed doctors to read Teva's label, telling them to "be familiar with the full product labeling provided by the manufacturer or distributor of the drug," which of course included its generic carvedilol. (Appx6196, Appx6205.) Moreover, GSK's expert testified that he read Teva's label. (Appx11663.) The jury could thus reasonably infer that these additional marketing materials intentionally instructing the infringing use were communicated to doctors and caused them to infringe. *See, e.g., Power Integrations*, 843 F.3d at 1332–35; *Ericsson*, 773 F.3d at 1220, 1222; *Toshiba*, 681 F.3d at 1365; *Lucent*, 580 F.3d at 1323; *Arthrocare*, 406 F.3d at 1377; *Mentor H/S*, 244 F. 3d at 1379; *Moleculon*, 793 F.2d at 1272. Indeed, this issue is an open-and-shut case under the Court's Hatch-Waxman law, which holds that instructing the infringing use on the label is sufficient to trigger liability for inducement before a generic product launches. *See, e.g.*, *Vanda*, 887 F.3d at 1130; *Sanofi*, 875 F.3d at 646; *Eli Lilly*, 845 F.3d at 1369; *AstraZeneca*, 633 F.3d at 1056.

The jury's inducement verdict is also well-supported by all the same considerations and evidence discussed above for the partial label period. Teva had been promoting the product for the infringing use since it first announced its tentative approval in 2004, and it had misled doctors into thinking it was approved for treating heart failure throughout the relevant period. GSK's expert testified that Teva's

actions had caused him to think Teva's product was approved for the treatment of all kinds of heart failure and that he would not have prescribed it otherwise. (Appx11659–11663.) The jury properly combined this evidence with Teva's description of the infringing use on its label to conclude that it had caused doctors to infringe. The district court's contrary JMOL should be reversed.

B. The District Court's Rationale in Granting JMOL Was Erroneous.

1. The District Court Ignored or Improperly Reweighed Key Evidence Supporting the Jury Verdict.

The district court's grant of JMOL was initially flawed because it ignored or erroneously reweighed evidence that the jury heard and credited. *See, e.g.*, *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 255 (1986) ("Credibility determinations, the weighing of the evidence, and the drawing of legitimate inferences from the facts are jury functions, not those of a judge, whether he is ruling on a motion for summary judgment or for a directed verdict"); *Marra*, 497 F.3d at 300 (holding that, on JMOL, the court "must refrain from weighing the evidence, determining the credibility of witnesses, or substituting our own version of the facts for that of the jury).

For example, the district court's analysis did not address Teva's 2004 press release, in which it explicitly advertised that its drug was approved for the infringing use or its 2007 press release in which it communicated the same thing through its use of the term "cardiovascular agent." (Appx6347, Appx6353.) In particular, the court made no mention of GSK's expert testimony that the 2007 press release's reference to

the generic as a "cardiovascular agent" would give doctors the impression that it was generally approved for all types of heart failure. (Appx11659–11660.) That was a critical omission, as those press releases set the stage for Teva's subsequent marketing of its product by comparing it to the "Brand Equivalent" Coreg®, which continued after GSK's patent reissued in January 2008, and colored how doctors interpreted that marketing. Having been twice told by Teva that its product was generally approved for the infringing use, it is no surprise that doctors used it in that manner after seeing Teva continue to compare it to Coreg®. Moreover, Teva put the press releases on its website throughout the infringing period (2008-2015), which made them independent acts of inducement during the relevant period regardless of the fact that they were first released before the '000 patent issued.

Likewise, the district court gave short shrift to Teva's product catalogs from 2008–2015 directly comparing its product to Coreg® and did not mention any of the expert testimony regarding them. The district court found the materials inadequate because they did not expressly mention heart failure, and it erroneously focused on the AB-rating alone, substituting its view that this implied the products were equivalent for only the uses on the label, not all uses. (Appx16–18.) But the jury properly found that Teva's label ***did*** always teach the infringing use—during the "partial label" period it did so for heart failure patients with post-MI LVD, and during the "full label" period it did so for all congestive heart failure patients. So the AB-

rating would convey the product should be used to infringe throughout the relevant period even if Teva's conduct were only tied to the label.

In addition, Teva did more than just obtain an AB-rating: it directly compared its product to Coreg® and said they were "equivalent." GSK's regulatory expert testified that the FDA views such a direct comparison between the generic and the brand as conveying that they have the same uses, (Appx10544–10545, Appx10582–10583), and GSK's cardiologist expert testified that doctors would interpret this comparison to teach that the products are "therapeutically interchangeable." (Appx10634–10636.) The jury reasonably inferred from that testimony that Teva's product catalogs encouraged the infringing use for treating heart failure. *See, e.g., Power Integrations*, 843 F.3d at 1332–35; *Ericsson*, 773 F.3d at 1222.

Having failed to mention these key aspects of GSK's case, the district court compounded its error by incorrectly reweighing evidence *de novo*. There was no basis for the district court to set aside the jury's well-supported finding that Teva's partial label instructed doctors to use the product for treating heart failure in patients with post-MI LVD. (Appx15–16 & n.9; *see also* Appx6 (table incorrectly stating the '000 patent does not cover treating post-MI LVD patients with heart failure).) The court acknowledged there "may be some overlap between populations of patients suffering from CHF," but thought this insufficient because there was not 100% overlap between post-MI LVD and heart failure. (Appx16 n.9.) The court also questioned whether administering carvedilol to post-MI LVD patients actually reduces their risk

of death from heart failure. (*Id.*) But this all misses the point. GSK's expert established (and Teva's expert conceded) that some post-MI LVD patients have symptomatic heart failure. (Appx10602–10605; Appx11226.) GSK's expert also explained, without contradiction, that Teva's partial label instructs use of the product to treat those post-MI LVD patients with heart failure in a manner that meets every limitation of claim 1, including in a way that reduces the risk of mortality from heart failure. (Appx10622–10631; Appx5506–5530.) The jury could have reasonably credited that testimony over Teva's arguments. *See, e.g.*, *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1362 (Fed. Cir. 2012) (holding that, when there is "conflicting expert testimony," the jury is "free to make credibility determinations and believe the witness it considers more trustworthy").

It does not matter, for liability purposes, that the partial label instructed the infringing use for only a subset of heart failure patients (*i.e.*, post-MI LVD patients with symptomatic heart failure). The label itself still establishes induced infringement for at least that population, which is sufficient to sustain the jury's liability finding. *See, e.g.*, *Lucent*, 580 F.3d 1317 ("[A] finding of infringement can rest on as little as one instance of the claimed method being performed during the pertinent time period."). And, of course, GSK's other evidence showed that Teva promoted its product for use with all heart failure patients during the partial label period. *See, e.g.*, *Power Integrations*, 843 F.3d at 1332–35; *Ericsson*, 773 F.3d at 1220, 1222; *Toshiba*, 681 F.3d at 1365;

Lucent, 580 F.3d at 1323; *Arthrocare*, 406 F.3d at 1377; *Mentor H/S*, 244 F. 3d at 1379; *Moleculon*, 793 F.2d at 1272.

The district court's treatment of GSK's expert cardiologist testimony with respect to causation was also erroneous. (Appx13–14.) The court focused on the statement that he did not read Teva's partial label before beginning to prescribe the drug, (Appx11662–11663), but it ignored the rest of his testimony, where he said that Teva's other promotional materials had caused him to believe that the drug was approved for the infringing use and thus led him to infringe. (Appx11660–11663.) Moreover, the expert also testified that other doctors read the label, that he eventually read the label, and that Teva's marketing materials tell doctors to read the label. (*See* pp. 15–16.) These points were more than sufficient for the jury to infer that at least some doctors did read the label and that it caused them to prescribe the drug for the infringing use (*i.e.*, post-MI LVD patients with symptomatic heart failure in the partial label period, and all heart failure patients in the full label period). *See, e.g.*, *Vanda*, 887 F.3d at 1130; *Sanofi*, 875 F.3d at 646; *Eli Lilly*, 845 F.3d at 1369; *AstraZeneca*, 633 F.3d at 1056. Thus, the jury's factual finding on causation has to stand.

Finally, the district court's analysis of the full label period is unsupportable given the jury's factual findings. (Appx23–24.) The court's error here was, again, based largely on assuming Teva's acts to link its generic carvedilol to Coreg® could be ignored and then attributing the resulting direct infringement to GSK, which is wrong as discussed in the next section. In addition, the court also observed the doctors'

behavior did not appear to change after Teva switched to the full label in 2011. (Appx24.) But the jury could properly infer that Teva had ***already*** caused doctors to use its product in an infringing manner during the prior partial label period through its press releases and comparisons of its drug to Coreg®. So Teva's acts continued to cause doctors' infringement during the full label period—the changed label was simply additional evidence of Teva's marketing of the infringing use. And even if there was a difference between the promoted use of Teva's generic carvedilol and Coreg®, Teva eliminated any difference with the full label. Allowing Teva's even more elaborate copying to provide grounds for a noninfringement defense is contrary to law and common sense.

2. The District Court's Treatment of the Other Factors that Influenced Doctors' Behavior Was Erroneous.

The district court's other overarching error was its treatment of the evidence that doctors' direct infringement was influenced both by Teva's acts and other sources. (Appx14, Appx19–20, Appx23–24 *citing* Appx10666–10669, Appx10676–10678.) In particular, the court observed that "when generic companies (including Teva) began selling carvedilol, doctors relied on guidelines and research, as well as their own experience, in addition to GSK marketing." (Appx19.) The court erroneously added that no expert "viewed generic labeling, including Teva's label, as impacting prescribing behavior," (*id.*), although GSK's expert had in fact testified that the label would influence doctors who followed Teva's instructions to read it and

further testified that Teva's promotional materials other than the label certainly influenced him. (*See* pp. 15–18.) The court thus wrongly concluded that "[i]n this context, there was no reasonable basis for the jury to have found that anything Teva did including selling generic carvedilol, giving it a 'skinny label,' and all aspects of how Teva marketed its carvedilol - caused even a single doctor to prescribe carvedilol for the treatment of" heart failure. (Appx19–20.)

The court's view of GSK's marketing and the heart failure guidelines was erroneous and represents yet another improper reweighing of the facts. As an initial matter, the court seemed to think that Teva's conduct was totally unrelated to GSK's marketing or the heart failure guidelines. But the jury rightly concluded that Teva purposely connected itself to GSK's marketing and the heart failure guidelines through its advertisements comparing its generic to Coreg® and encouraging doctors to use them in the exact same way. *See, e.g.*, *Power Integrations*, 843 F.3d at 1334 (encouraging infringement by reference to industry standard); *Ericsson*, 773 F.3d at 1222 (same). Viewed in that light, Teva's acts were absolutely responsible for doctors' use of its product in an infringing manner. Teva gave doctors the impression that they should use its product just like they had been using GSK's Coreg®, knowing that this would cause doctors to use the generic to treat heart failure (the infringing use). GSK's cardiologist expert testified that he would not have used Teva's product in that manner had Teva's marketing materials not led him to believe that he could. (Appx11659–11663.) And, indeed, even Teva's cardiologist expert admitted that the

reason he prescribed generic carvedilol the same as Coreg® and thought the heart failure guidelines were applicable to both was because he viewed the products as therapeutically interchangeable. (Appx11176, Appz11168.) The jury reasonably found that it was Teva's marketing that led doctors to think the products were interchangeable. So the fact that Teva's marketing piggybacked on GSK's prior marketing and the heart failure guidelines was no basis to set aside the jury's factual finding on causation.

The district court appeared to believe that this evidence was insufficient because it was GSK, not Teva, that originally educated doctors that carvedilol could be used to treat heart failure. But there is nothing in the statute that lets a defendant off the hook when it induces infringement by capitalizing on the innovator's own efforts to build the market for the patented treatment. The statute refers to "induc[ing]" infringement, *see* 35 U.S.C. § 271(b), which the Supreme Court has noted means "[t]o lean on; to influence; to prevail upon; to move by persuasion." *Global-Tech*, 553 U.S. at 760. None of those definitions precludes liability where the defendant encourages infringement by telling customers to use its product just like the patentee's product. Nor should those actions be immune from liability—they are one of the most egregious forms of copying.

The legislative history of § 271(b) is consistent with this interpretation. The statute imposes common law principles of aiding and abetting liability: "Paragraph (b) recites in broad terms that one who aids and abets an infringement is likewise an

infringer." S. Rep. No. 1979, 82nd Cong., 2d Sess., at 9 (1952). Both this Court and its predecessors have interpreted the statute consistent with that understanding. *See, e.g.*, *Water Techs. Corp. v. Calco, Ltd.*, 850 F.2d 660, 668, (Fed. Cir. 1988) ("[W]e have recognized that 35 U.S.C. § 271(b) provides a remedy against actively and knowingly aiding and abetting another's direct infringement."); *Sims v. Western Steel Co.*, 551 F.2d 811, 817 (10th Cir. 1977) ("This subsection contemplates that the inducer shall have been an active participant in the line of conduct of which the actual infringer was guilty. Thus he should be in the nature of an accessory before the fact.").

A person is liable as an aider and abettor so long as they provide any successful assistance to the wrongful act, regardless of how exactly they provide that assistance. The quintessential examples come from criminal law. *See, e.g.*, *United States v. Jaramillo*, 42 F.3d 920, 923 (5th Cir. 1997) (requiring proof only "that the defendant acted in some affirmative manner designed to aid the venture"); *United States v. Powell*, 113 F.3d 464, 467 (3d Cir. 1997) ("To convict for aiding and abetting, the government must prove that the defendant associated himself with the venture, that he participated in it as something that he wished to bring about, and that he sought by his action to make it succeed."). Teva's acts certainly met this standard—by affirmatively telling doctors that its product was the "equivalent" of Coreg®, it ensured that the doctors would use it in the same way (including for heart failure), while also knowing that doctors would infringe GSK's patent when they followed that instruction. And if Teva's actions meet the criminal standard for aiding and abetting, then surely they meet the

civil standard as well. Criminal punishment requires stricter standards than civil damages.

In fact, the common law imposes civil liability where one "knows that the other's conduct constitutes a breach of duty and gives substantial assistance or encouragement to the other so to conduct himself." RESTATEMENT (SECOND) OF TORTS § 876(b). "If the encouragement or assistance is a substantial factor in causing the resulting tort, the one giving it is himself a tortfeasor and is responsible for the consequences of the other's act." *Id.* at cmt. d. Again, this common law does not impose any restrictions on the form that the assistance or encouragement takes. It simply asks whether the defendant encouraged the third-party to act in a tortious manner. Teva certainly did that. It doesn't matter that Teva could short-cut the process by relying on what doctors already knew and simply telling them to use its product just like Coreg®.

Consistent with those principles, this Court has not allowed a defendant to escape liability simply because its actions encouraging infringement built upon what the innovator had previously done. As discussed above, this Court has affirmed jury findings of inducement (and thus causation) where, as here, the defendant intentionally and successfully advertises the infringing use, even if it does so by invoking something else, like an infringing standard. *See, e.g.*, *Power Integrations*, 843 F.3d at 1332–35; *Ericsson*, 773 F.3d at 1220, 1222; *Lucent*, 580 F.3d at 1323; *Arthrocare*, 406 F.3d at 1377; *Mentor H/S*, 244 F. 3d at 1379; *Moleculon*, 793 F.2d at 1272; *see also*

Toshiba, 681 F.3d at 1365. The jury found that Teva met this threshold by invoking doctors' prior knowledge about carvedilol and ensuring them that they could apply it to Teva's product and thereby infringe. That should be the end of the inquiry.

The approach reflected in the statute, common law, and this Court's precedent is a wise one. A defendant who is liable for inducement knows of the patent, takes affirmative acts to encourage others to infringe, and intends that they do so. *See, e.g.*, *Power Integrations*, 843 F.3d at 1332. That defendant has already engaged in guilty acts with a heightened *mens rea*. There is no need to insulate it from liability simply because the form of its encouragement was to tell third-parties to use its product just like the innovator's product, knowing full well that this would cause infringement. Indeed, eliminating liability would encourage parties to copy innovative products, piggyback on the innovator's prior marketing, and reap the profits of that activity while destroying the innovator's market. The result would diminish innovators' ability to use the patent system to recoup the costs necessary to bring their products to market, ultimately harming the public.

The facts here illustrate the problem. GSK invested hundreds of millions in a new heart failure treatment that has extended the lives of many. (*See* pp. 3–5, 7.) GSK introduced doctors to the product and showed them how to use it to extend lives, and that ultimately resulted in the relevant medical associations changing their guidelines for heart failure treatment to reflect GSK's better standard of care. Teva then entered the market, after telling doctors its product was approved for the

treatment of heart failure and equivalent to Coreg®, and leading them to believe they could use it in the same way. So Teva caused doctors' resulting infringement: as GSK's expert testified, he and other doctors pay careful attention to Teva's marketing and would not have infringed without Teva's actions. (Appx11659–11663.)

Teva should not be allowed to escape liability by pointing to GSK's prior work in informing doctors how to use the product. After all, Teva's marketing relied and built upon what GSK had already taught the profession, and then convincing doctors that its product was equivalent to GSK's for all uses. To allow Teva to escape liability in those circumstances would allow any copyist—in the pharmaceutical field or in other areas—to induce infringement with impunity. The perplexing result would be that only non-practicing patentees, who had done no prior marketing of their own, could pursue inducement claims, as none of their activity could be identified as an alternative cause of infringement. That cannot be right.

C. The Jury's Findings on the Other Elements of Inducement Were Also Supported by Substantial Evidence.

The discussion above demonstrates that the district court's JMOL must be reversed on the ground on which it was entered. For completeness, we show that JMOL of no inducement cannot be sustained on any other ground either, because the jury's finding on each of the other elements was supported by substantial evidence.

First, there was ample evidence from which the jury could infer that doctors actually used Teva's product to infringe. As discussed above, Teva's marketing

materials, and, in particular, both its partial and full labels, encourage the infringing use and describe use of its product to treat heart failure in a manner that meets each claim limitation. (Appx10622–10631; Appx5506–5530; Appx5531–5553.) That was sufficient under this Court's precedent for the jury to infer that doctors follow those instructions and use the product in an infringing manner. *See, e.g., Toshiba*, 681 F.3d at 1365; *Lucent*, 580 F.3d at 1323; *Moleculon*, 793 F.2d at 1272. In addition, GSK presented survey evidence showing that a significant percentage of doctors used Teva's product in an infringing manner throughout the relevant period. (Appx10727, Appx10736.)

Teva argued below that all this evidence was insufficient because it supposedly did not show that doctors administered its product with the intent to reduce the risk of mortality from heart failure. (Appx11 n.7.) But the jury could properly reject this argument. Teva's partial label instructed doctors to use its product "to reduce cardiovascular mortality" in post-MI LVD patients with symptomatic heart failure, and its full label included the further instruction to use the product for "the treatment of mild-to-severe chronic heart failure . . . to increase survival." (Appx5508; Appx5532; Appx10629, Appx10623–10624.) GSK's cardiologist expert explained that this language (and the accompanying clinical data) taught doctors that using the product to treat heart failure would result in a statistically significant reduction in the risk of mortality. (Appx10651–10652, Appx10656.) The whole purpose of using Coreg® to treat heart failure was to reduce the risk of mortality, (Appx10361–10362,

Appx10373, Appx10385, Appx10651, Appx11357), and, by equating its product to Coreg® in its marketing materials, Teva communicated to doctors they should also use generic carvedilol to reduce the risk of mortality. The jury thus reasonably inferred that the doctors who use carvedilol to treat heart failure use it to reduce mortality, just as Teva instructs and encourages. *See, e.g., Toshiba*, 681 F.3d at 1365; *Lucent*, 580 F.3d at 1323; *Moleculon*, 793 F.2d at 1272.

Second, there was no question that Teva knew that the acts it induced constituted patent infringement. Teva knew of the '000 patent throughout the relevant period. (Apx5383; Appx10465.) Teva admitted that it knew that doctors would use its product to treat heart failure, (Appx10488, Appx10491, Appx10453), it repeatedly instructed doctors to use it for heart failure in an infringing manner, (*see* pp. 9–16), and it stood to make more money from them doing so. What's more, Teva tried to hide its move back to the "full" label from GSK in failing to provide a paragraph IV certification on the '000 patent at that time, even though both regulatory experts agreed that FDA regulations required it to do so. (Appx10569–1052, Appx10976, Appx11049–11050; Appx5554–5559.) That shows Teva's consciousness of guilt—it knew that its label instructed use of its product to treat heart failure, otherwise it would have had no reason to conceal that fact from GSK. The jury could thus properly infer that Teva acted with the required mental state. *See, e.g., Power Integrations*, 843 F.3d at 1332–35; *Ericsson*, 773 F.3d at 1220, 1222; *Toshiba*,

681 F.3d at 1365; *Lucent*, 580 F.3d at 1323; *Arthrocare*, 406 F.3d at 1377; *Mentor H/S*, 244 F. 3d at 1379; *Moleculon*, 793 F.2d at 1272.

CONCLUSION

For the reasons above, the Court should reverse the JMOL of no inducement and reinstate the jury's verdict.

Dated: July 16, 2018

Respectfully submitted,

/s/ Craig E. Countryman

Craig E. Countryman
Fish & Richardson P.C.
12390 El Camino Real
San Diego, CA 92130
(858) 678-5070
countryman@fr.com

Attorneys for Appellants GlaxoSmithKline LLC and SmithKline Beecham (Cork) Limited

ADDENDUM

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GLAXOSMITHKLINE LLC and SMITHKLINE BEECHAM (CORK) LIMITED,	:	
Plaintiffs,	:	
v.	:	C.A. No. 14-878-LPS-CJB
TEVA PHARMACEUTICALS USA, INC.,	:	
Defendant.	:	

Douglas E. McCann, Elizabeth M. Flanagan, FISH & RICHARDSON P.C., Wilmington, DE

Michael J. Kane, William R. Woodford, Phillip W. Goter, FISH & RICHARDSON P.C., Minneapolis, MN

Juanita R. Brooks, Jonathan E. Singer, Michael A. Amon, Craig E. Countryman, Robert M. Yeh, FISH & RICHARDSON P.C., San Diego, CA

Attorneys for Plaintiffs GlaxoSmithKline and SmithKline Beecham (Cork) Limited.

John W. Shaw, Karen E. Keller, David M. Fry, SHAW KELLER LLP, Wilmington, DE

Ira J. Levy, Andrew E. Riley, GOODWIN PROCTER LLP, New York, NY

Daryl L. Wiesen, J. Anthony Downs, Christopher T. Holding, Elaine Herrmann Blais, Lana S. Shiferman, Robert Frederickson, III, Alexandra Lu, GOODWIN PROCTER LLP, Boston, MA

Attorneys for Defendant Teva Pharmaceuticals USA, Inc.

MEMORANDUM OPINION

March 28, 2018
Wilmington, DE

STARK, U.S. District Judge:

Beginning on June 12, 2017, the Court held a seven-day jury trial in this patent infringement action (D.I. 457, 458, 459, 460, 461, 462, 463 (hereinafter, "Tr.")), resulting in a verdict of: (1) willful induced infringement of claims 1, 2, and 3 of U.S. Patent No. RE40,000 ("the '000 patent") by Defendant Teva Pharmaceuticals USA, Inc. ("Teva") during the "skinny label" (also referred to as "partial label" or "carve-out") period; (2) no induced infringement of claims 6, 7, 8, and 9 of the '000 patent by Teva during the skinny/partial label period; (3) willful induced infringement of all asserted claims (claims 1-3 and claims 6-9) of the '000 patent by Teva during the "full label" (also referred to as "amended label") period; (4) no invalidity of the '000 patent; and (5) an award to Plaintiffs GlaxoSmithKline and SmithKline Beecham (Cork) Ltd. ("GSK") of $234,110,000 in lost profits and $1,400,000 in reasonable royalty damages. (D.I. 448)

Pending before the Court are the parties' post-trial motions. Teva filed a renewed motion for judgment as a matter of law ("JMOL"), or in the alternative for a new trial, on five grounds: (1) no inducement of infringement of any claims at any time – that is, during either the skinny label or full label periods – and no lost profits; (2) no inducement of any claims during the skinny label period; (3) no inducement of claims 6 and 7 during the full label period; (4) no willful infringement; and (5) invalidity. (D.I. 464)[1] GSK filed a motion for enhanced damages, attorney fees, and pre- and post-judgment interest. (D.I. 466) Finally, Teva has moved to strike multiple

[1]During oral argument on the pending motions, Teva also argued that if the Court found liability, the proper remedy was a remittitur of damages to a figure not to exceed $1.4 million for a reasonable royalty, rather than a new trial on damages which would, in Teva's view, be futile. (D.I. 484 (hereinafter, "Hr'g Tr.") at 27-28)

exhibits GSK submitted in support of its post-trial motion that Teva contends were not part of the trial record. (D.I. 474)

The Court heard oral argument on October 26, 2017. Having considered the parties' briefing (D.I. 465, 467, 471, 472, 475, 476, 477, 478, 479) and letters regarding supplemental authority (D.I. 483, 485, 486, 487), and for the reasons discussed below, the Court will grant in part and deny in part Teva's JMOL motion (D.I. 464), and deny as moot both GSK's motion (D.I. 466) and Teva's motion to strike (D.I. 474).[2]

I. BACKGROUND

Congestive heart failure ("CHF") is a chronic condition that occurs when a diseased heart is unable to deliver sufficient oxygenated blood to the rest of the body. (*See generally* '000 patent; Lukas Tr. at 359-60[3]) CHF affects over five million people in the United States, and half of those who develop CHF will die within five years of diagnosis. Prior to 1997, CHF treatment included limitation of physical activity, restriction of salt intake, and the use of a diuretic – a drug that decreases excess fluid – and digoxin – a drug that stabilizes heart rhythm. (*See* '000 patent; Lukas Tr. at 361) Angiotensin converting enzyme ("ACE") inhibitors were also prescribed in

---

[2]On July 27, 2017, the Court advised the parties of its inclinations (D.I. 456) concerning the issues the parties indicated they intended to raise (D.I. 455) in their post-trial motions. The Court's ruling today in favor of Teva on the key issue of GSK's liability for induced infringement is different than the previously-announced inclinations. (*See* D.I. 456 at 2 ("I am inclined to disagree with Teva that no reasonable juror could have concluded that Teva's actions induced even a single physician to administer Teva's carvedilol to a patient for use in an infringing manner."); *but see also generally id.* at 3 ("I conclude by emphasizing that the views expressed in this letter do not constitute an order but are merely my present inclinations, based principally on my recollection of the trial and the parties' limited post-trial submissions. I will only be able to make final decisions after receiving the forthcoming briefing and conducting oral argument."))

[3]Citations to the trial transcript are in the format: "[Witness name] Tr. at [page number]."

conjunction with a diuretic, digoxin, or both. (*See* '000 patent) While ACE inhibitors caused an improvement in CHF mortality rates, doctors were still looking for other solutions. (Lukas Tr. at 362)

In the late 1980s, GSK and its research partner, Boehringer Mannheim GmbH, began researching the possibility of using carvedilol to treat CHF. (Ruffalo Tr. at 1271-72) Carvedilol belongs to a class of chemical compounds known as beta-blockers, which are drugs used to treat high blood pressure or hypertension. In the early 1990s, beta-blockers, which slow the heart rate and depress the heart's contractility – that is, its ability to pump – were clinically contraindicated for CHF, as CHF patients are critically dependent on how well their heart pumps. (*See* Lukas Tr. at 357-58) Treating high blood pressure with beta-blockers worsened a patient's heart failure due to the beta-blocker's depressive effect on the heart's pumping function. (*See id.*)

GSK's research led to unexpected results showing that "the patients who were receiving carvedilol were staying alive whereas the patients on placebo were the ones who were dying." (*Id.* at 364-67, 370-72; PTX-879) These results prompted GSK to file New Drug Application ("NDA") No. 20-297 with the U.S. Food and Drug Administration ("FDA"), seeking approval of carvedilol in combination with ACE inhibitors, diuretics, or digoxin to reduce the risk of mortality caused by heart failure, as well as an application for a patent on a method of using carvedilol to decrease the risk of mortality caused by CHF. (Lukas Tr. at 373, 379-81; PTX-229) In May 1997, the FDA approved carvedilol as the first beta-blocker for the treatment of CHF, leading to GSK's launch of Coreg®, the brand name of its carvedilol tablets. (Lukas Tr. at 377) The patent issued in June 1998 as U.S. Patent No. 5,760,069 (the "'069 patent"), entitled "Method of Treatment for Decreasing Mortality Resulting from Congestive Heart Failure."

GSK ultimately received approval from the FDA to market Coreg® for three indications: (1) hypertension; (2) mild-to-severe CHF; and (3) left ventricular dysfunction ("LVD") following myocardial infarction (heart attack) in clinically stable patients ("Post-MI LVD"). (*See* Lukas Tr. at 382-83) Despite receiving FDA approval for three indications, GSK only marketed Coreg® in the United States for the CHF indication. The FDA published the '069 patent in the Orange Book[4] with use code U-233, "decreasing mortality caused by congestive heart failure." (*See* Pastore Tr. at 889)

GSK undertook further patent prosecution efforts, including to correct certain errors in the '069 patent. Consequently, on January 8, 2008, the '069 patent reissued as the '000 patent. (*See* Lukas Tr. at 373-74, 405, 409-10) Claim 1 of the '000 patent, the only independent claim, recites:

> A method of decreasing mortality caused by congestive heart failure in a patient in need thereof which comprises administering a therapeutically acceptable amount of carvedilol in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of an angiotensin converting enzyme inhibitor (ACE), a diuretic, and digoxin,
>
> *wherein the administering comprises administering to said patient daily maintenance dosages for a maintenance period to decrease a risk of mortality caused by congestive heart failure, and said maintenance period is greater than six months.*

(emphasis in original) After issuance of the '000 patent, the '069 patent was de-listed from the Orange Book, and the '000 patent was listed with the same use code, i.e., U-233, "decreasing

[4]The Orange Book is the name commonly used to refer to the FDA's publication, *Approved Drug Products with Therapeutic Equivalence Evaluations*. It includes a listing of approved drug products and, among other things, information about the patents that cover each drug product. *See Intendis GmbH v. Glenmark Pharm. Inc., USA*, 822 F.3d 1355, 1359 (Fed. Cir. 2016); *see also* 21 U.S.C. § 355(b)(1); 21 C.F.R. §§ 314. 3, 314.53.

mortality caused by congestive heart failure." (Karst Tr. at 1042)

Meanwhile, back in March 2002, Teva had filed with the FDA Abbreviated New Drug Application ("ANDA") No. 76-373, seeking permission to market generic carvedilol tablets. (*See* Pastore Tr. at 442-43) Teva initially submitted a paragraph IV certification asserting that the '069 patent was invalid and requesting that its ANDA not be given final approval until a second Orange Book listed patent (one which covered the carvedilol compound) expired in March 2007.[5] Then, however, in August 2007, Teva sought FDA approval of its ANDA pursuant to 21 U.S.C. § 355(j)(2)(A)(viii) – a "section viii carve out" – so that it could label its generic carvedilol tablets as indicated only for uses not covered by GSK's '000 patent: that is, for treatment of hypertension and post-MI LVD. (*See* Pastore Tr. at 456-57; Lietzan Tr. at 534-37) At this point, since the '000 patent only claimed a method of using carvedilol for treatment of mild to severe CHF, Teva's position was that its "skinny label" generic product would not run afoul of the '000 patent because Teva's product would not be approved – or labeled as being approved – for the infringing use of treatment of CHF.

In 2007, with the expiration of the '067 patent, GSK's period of exclusivity with respect to carvedilol ended and generic carvedilol entered the market. Fourteen companies marketed generic carvedilol, including Teva. (*See* Zusman Tr. at 1164; *see also* Pastore Tr. at 897-98; Hofmann Tr. at 1533) Specifically, on September 5, 2007, Teva received FDA approval of its generic tablets and launched its drug product with the carved out/skinny label – that is, excluding the CHF indication. (*See* Pastore Tr. at 461)

---

[5]U.S. Patent No. 4,503,067 (the "'067 patent"), not at issue here, covers the carvedilol compound.

In April 2011, the FDA sent Teva a letter in response to the de-listing of certain GSK patents from the Orange Book, instructing Teva to "revise [its] labeling to include the information associated with [the de-listed] patent." (*Id.* at 461-63; PTX-15) One of the patents that had been de-listed was GSK's '069 patent, which had been reissued in 2008 as the '000 patent. (*See* PTX-15; Lukas Tr. at 352-53) Teva, therefore, amended its label in 2011 to be essentially a copy of GSK's full label, thereby covering all three indications: hypertension, CHF, and post-MI LVD. (Pastore Tr. at 461-65) The '000 patent expired on June 7, 2015, the date the '069 patent was originally set to expire.

The following table is helpful for understanding the principal issues that were in dispute at trial and are again presented by the pending motions.

Indications Implicated at Various Points

Indication	**GSK's '000 patent**	**GSK's FDA Approval**	**GSK's Marketing of Coreg®**	**GSK's Orange Book Listing**	**Teva's Skinny a.k.a. Partial a.k.a. Carve-Out Label (Jan. 2008 - April 2011)**	**Teva's Full a.k.a. Amended Label (May 2011-June 2015)**
hypertension	No	Yes	No	No	Yes	Yes
mild/severe CHF	Yes	Yes	Yes	Yes (U-233)	No	Yes
post-MI LVD	No	Yes	No	No	Yes	Yes

As shown, GSK's patent-in-suit only claims a method of using carvedilol for the treatment of mild to severe CHF. (PTX-1; *see* Lukas Tr. at 352-54) Although GSK obtained FDA approval to market carvedilol as safe and effective also for the treatment of hypertension and post-MI LVD, it did not have patent protection on such uses, and it has never marketed its

branded drug, Coreg®, to be used to treat anything other than CHF. (*See* Lukas Tr. at 350-52) The Orange Book listing for the '000 patent refers only to CHF, and not also to hypertension or post-MI LVD. (*See* Karst Tr. at 1040-44; Pastore Tr. at 888-90; Lietzan Tr. at 527-29, 566-67) When Teva initially launched and sold its generic carvedilol, during the skinny label period of January 2008 through April 2011, its label identified as approved indications only hypertension and post-MI LVD. (*See* Karst Tr. at 1027-28) It was not until the full label period, May 2011 through the expiration of the '000 patent in June 2015, that Teva's label also included the previously-patented method of use – treatment of CHF – as an approved indication for Teva's generic product. (*See* Pastore Tr. at 461-62; Zusman Tr. at 1229)

II. LEGAL STANDARDS

A. Judgment as a Matter of Law

Judgment as a matter of law is appropriate if "the court finds that a reasonable jury would not have a legally sufficient evidentiary basis to find for [a] party" on an issue. Fed. R. Civ. P. 50(a)(1). "Entry of judgment as a matter of law is a sparingly invoked remedy," one "granted only if, viewing the evidence in the light most favorable to the nonmovant and giving it the advantage of every fair and reasonable inference, there is insufficient evidence from which a jury reasonably could find liability." *Marra v. Phila. Hous. Auth.*, 497 F.3d 286, 300 (3d Cir. 2007) (internal quotation marks omitted).

To prevail on a renewed motion for judgment as a matter of law following a jury trial, the moving party "must show that the jury's findings, presumed or express, are not supported by substantial evidence or, if they were, that the legal conclusions implied [by] the jury's verdict cannot in law be supported by those findings." *Pannu v. Iolab Corp.*, 155 F.3d 1344, 1348 (Fed.

Cir. 1998) (internal quotation marks omitted). "'Substantial' evidence is such relevant evidence from the record taken as a whole as might be accepted by a reasonable mind as adequate to support the finding under review." *Perkin-Elmer Corp. v. Computervision Corp.*, 732 F.2d 888, 893 (Fed. Cir. 1984).

In assessing the sufficiency of the evidence, the Court must give the non-moving party, "as [the] verdict winner, the benefit of all logical inferences that could be drawn from the evidence presented, resolve all conflicts in the evidence in his favor, and in general, view the record in the light most favorable to him." *Williamson v. Consol. Rail Corp.*, 926 F.2d 1344, 1348 (3d Cir. 1991); *see also Perkin-Elmer Corp.*, 732 F.2d at 893. The Court may not assess the credibility of witnesses nor "substitute its choice for that of the jury between conflicting elements of the evidence." *Perkin-Elmer Corp.*, 732 F.2d at 893. Rather, the Court must determine whether the evidence reasonably supports the jury's verdict. *See Dawn Equip. Co. v. Ky. Farms Inc.*, 140 F.3d 1009, 1014 (Fed. Cir. 1998); *Gomez v. Allegheny Health Servs. Inc.*, 71 F.3d 1079, 1083 (3d Cir. 1995) (describing standard as "whether there is evidence upon which a reasonable jury could properly have found its verdict"); 9B Charles Alan Wright, Arthur R. Miller & Edward H. Cooper, Federal Practice & Procedure § 2524 (3d ed. 2008) ("The question is not whether there is literally no evidence supporting the party against whom the motion is directed but whether there is evidence upon which the jury properly could find a verdict for that party.").

B. New Trial

Federal Rule of Civil Procedure 59(a) provides in pertinent part, "[t]he court may, on motion, grant a new trial on all or some of the issues – and to any party – as follows: . . . after a

jury trial, for any reason for which a new trial has heretofore been granted in an action at law in federal court." New trials are commonly granted where "the jury's verdict is against the clear weight of the evidence, and a new trial must be granted to prevent a miscarriage of justice," where "newly-discovered evidence exists that would likely alter the outcome of the trial," where "improper conduct by an attorney or the court unfairly influenced the verdict," or where the jury's verdict was "facially inconsistent." *Zarow-Smith v. N.J. Transit Rail Operations*, 953 F. Supp. 581, 584-85 (D. N.J. 1997) (internal citations omitted).

The decision to grant or deny a new trial is committed to the sound discretion of the district court. *See Allied Chem. Corp. v. Daiflon, Inc.*, 449 U.S. 33, 36 (1980); *Olefins Trading, Inc. v. Han Yang Chem Corp.*, 9 F.3d 282, 289 (3d Cir. 1993) (reviewing "district court's grant or denial of a new trial motion" under "abuse of discretion" standard). Although the standard for granting a new trial is less rigorous than the standard for granting judgment as a matter of law, in that the Court need not view the evidence in the light most favorable to the verdict winner, ordinarily a new trial should only be granted "where a miscarriage of justice would result if the verdict were to stand," the verdict "cries out to be overturned," or the verdict "shocks [the] conscience." *Williamson*, 926 F.2d at 1352-53.

III. DISCUSSION

A. The Jury Could Not Reasonably Find that Teva Caused Doctors to Infringe

The jury found that Teva induced infringement of claims 1, 2, and 3 of the '000 patent during the skinny label period and of claims 1-3 and 6-9 during the full label period. (D.I. 448 at 2-3) Teva moves for JMOL of no inducement or no lost profits damages on the basis that the jury could not reasonably have found that Teva caused doctors to infringe these claims of GSK's

patent during the respective periods.[6] (D.I. 465 at 4) Having reviewed the record under the appropriate standard, including by drawing all reasonable inferences in favor of GSK as the verdict winner, the Court concludes that substantial evidence does not support the jury's findings on inducement in either the skinny or full label period. Therefore, the Court will grant this portion of Teva's JMOL motion.

To prove inducement, GSK was required to prove by a preponderance of the evidence that, among other things, "Teva's alleged inducement, ***as opposed to other factors***, actually ***caused*** the physicians to directly infringe." (D.I. 440 at 26) (emphasis added) The jury was instructed that "Teva cannot be liable for induced infringement where GSK does not show that Teva successfully communicated with and induced a third-party direct infringer ***and that the communication was the cause of the direct infringement by the third-party infringer***." (*Id.* at 31) (emphasis added) Thus, the Court must now evaluate whether substantial evidence supports the jury's finding that Teva did cause the alleged infringement.[7]

Teva contends that the substantial uncontroverted evidence presented at trial showed that alternative factors caused doctors to infringe GSK's patent. Teva thus asserts that a reasonable

---

[6]Teva requested a new trial as an alternative to JMOL, but explained that if the Court agreed there is a lack of evidence of inducement, a new trial would be futile. (*See* D.I. 465 at 10 n.3 ("[W]hile Teva requests a new trial under Rule 59 as an alternative remedy, that trial would inevitably result in a similar failure of proof."); *see also* Hr'g Tr. at 28) The Court agrees with Teva that, given the conclusions announced here, a new trial would be futile.

[7]As an alternative basis for JMOL of no inducement, Teva contends that GSK failed to "offer any evidence that any doctor – let alone ***all*** doctors – administer carvedilol with the specific intent to decrease mortality instead of to treat symptoms or for other purposes." (D.I. 465 at 9) Without proving such intent, Teva argues, there can be no direct infringement, and accordingly, no inducement. (*Id.* at 8-9) Because the Court finds GSK failed to prove the causation element, it need not address this argument.

jury could not conclude that even a single doctor – let alone the entire class of infringing doctors – was induced to infringe based on ***Teva's*** actions. Moreover, because GSK only asserted a "class" theory of liability – that is, that Teva induced doctors as a class to infringe – and failed to prove that theory, Teva's view is that GSK cannot now have the verdict upheld on an alternative theory of liability (i.e., the theory that "at least one" doctor was induced to infringe by Teva's actions). (*See* D.I. 465 at 1-2)

GSK responds that the jury's verdict should be sustained because GSK presented "ample evidence," including Teva's label and marketing materials, "from which [the jury] could infer Teva actually caused physicians to directly infringe." (D.I. 472 at 6) (internal quotation marks omitted) GSK argues that "JMOL of no inducement is only appropriate where the plaintiff fails to present sufficient evidence of even one act of direct infringement." (*Id.* at 9; *see also* Hr'g Tr. at 52 ("[T]he law doesn't require us to prove [inducement of the entire class]. What the law requires us to prove is just one of the class."); *id.* at 57 ("All we needed was circumstantial evidence of one doctor . . . ."); *see generally* D.I. 440 at 4.2.1 (instructing jury: "Proof of direct infringement may be based on circumstantial evidence.")) GSK contends that it provided substantial evidence through the testimony of its expert, Dr. Peter McCullough, permitting a reasonable factfinder to find that at least one doctor was induced to prescribe generic carvedilol by Teva's actions. (*Id.* at 71-72)

The Court agrees with Teva that neither sufficient nor substantial evidence supports the jury's finding of inducement. GSK failed to prove by a preponderance of the evidence that "***Teva's*** alleged inducement, as opposed to other factors, actually ***caused*** the physicians [i.e., as a class or even at least one of them] to directly infringe," by prescribing generic carvedilol and to

do so for the treatment of mild to severe CHF. (D.I. 440 at 26, 31) (jury instruction; emphasis added) Without proof of causation, which is an essential element of GSK's action, a finding of inducement cannot stand.[8]

GSK insists that Dr. McCullough identified himself as at least one doctor who was induced to prescribe generic carvedilol to a patient for the treatment of mild to severe CHF due to Teva's actions (or inactions), including Teva's label. (*See* Hr'g. Tr. at 52-53 (discussing GSK slide 4); *id.* at 69-72 (discussing GSK slides 32-33)) But the portion of Dr. McCullough's testimony to which GSK points (*see* McCullough Tr. at 631, 1659-63) does not show Dr. McCullough stating what GSK seems to think he said. Dr. McCullough merely said, in a conclusory manner, that Teva's labels (partial and full) "meet each and every limitation of claim 1" and a doctor performing the method of the claim would be the direct infringer. (*See id.* at 631) But even if the label were enough in a post-launch world, Dr. McCullough specifically stated that he did not read Teva's label prior to administering generic carvedilol, but "just

---

[8]The parties dispute whether the "class" theory and the "at least one" theory are really two separate theories and, if so, which theory GSK was required to prove. (Hr'g Tr. at 14-15, 24-26, 52) While Teva argues that the Federal Circuit clearly outlined two separate theories for proving induced infringement, *see Dynacore Holdings Corp. v. U.S. Philips Corp.*, 363 F.3d 1263, 1274 (Fed. Cir. 2004); *see also* Hr'g Tr. at 14-15, GSK maintains that the two theories "are actually one and the same" (Hr'g Tr. at 78, 52). The Court agrees with Teva that the two theories are distinct from one another. *See Dynacore*, 363 F.3d at 1274-75 ("Plaintiffs who identify ***individual*** acts of direct infringement must restrict their theories of vicarious liability – and tie their claims for damages or injunctive relief – to the ***identified*** act. Plaintiffs who identify an entire category of infringers (e.g., the defendant's customers) may cast their theories of vicarious liability more broadly, and may consequently seek damages or injunctions across the entire category.") (internal citations omitted); *see also Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, 2004 WL 2898061, at *3 (D. Del. Dec. 14, 2004) (requiring plaintiffs to "adduce evidence that 100% of the defendants' . . . units [infringed]" after plaintiffs' position at trial was that "all" of defendants' units infringed). The Court need not decide which theory GSK was required to prove as, under either theory, GSK failed to prove causation.

assume[d] they were the same" based on the information the generic company provided. (*See id.* at 1659-63) As Dr. McCullough concedes that he did not read Teva's label, he cannot state, for instance, that he noticed or otherwise knew what (if anything) that label said about using carvedilol to treat CHF. Moreover, Dr. McCullough testified that he relied on various other sources, none of which are attributable to Teva, in deciding to prescribe carvedilol, both before and after generics entered the market. (*See* McCullough Tr. at 666-69, 676-78) GSK, therefore, has not met its burden to show inducement.

Below, the Court describes with more particularity its conclusion with respect to first the skinny label period and then the full label period.

1. The Skinny Label Period

The skinny label period, January 8, 2008 through April 30, 2011, is the period during which Teva's label carved out the CHF indication pursuant to 21 U.S.C. § 355(j)(2)(A)(viii) ("section viii"). The Court agrees with Teva that the record lacks substantial evidence that Teva's skinny label, in combination with other acts Teva took (or refrained from taking) during this period, caused of any physician's direct infringement. (*See* D.I. 465 at 13-25) Instead, as Teva argues, the record conclusively demonstrated – and a reasonable jury could only have found – that any infringing use by any physician during the skinny label period was caused by factors unrelated to Teva.

The unrebutted evidence presented at trial showed that Teva's skinny label omitted from its label the language contained on GSK's Coreg® label concerning the use of carvedilol to treat CHF. (*See* Lietzan Tr. at 539, 541; Zusman Tr. at 1190-91) It is further undisputed that Teva's generic carvedilol, during the skinny label period, was not approved for treatment of CHF,

making such use an "off-label" use. Moreover, GSK's expert, Dr. McCullough, conceded that he would not prescribe generic carvedilol for CHF if it was not an approved use on the label. (*See* McCullough Tr. at 1660-61) The Court may, indeed must, consider unrebutted evidence presented at trial that supports the moving party on JMOL, in evaluating whether the jury had substantial evidence to support a reasonable finding against the moving party. *See Integra Lifesciences I, Ltd. v. Merck KGaA*, 496 F.3d 1334, 1345 (Fed. Cir. 2007) ("The rule that a jury verdict is reviewed for support by 'substantial evidence' does not mean that the reviewing court must ignore the evidence that does not support the verdict. . . . [T]he court should give credence to the evidence favoring the nonmovant as well as that evidence supporting the moving party that is uncontradicted and unimpeached.") (internal quotation marks omitted).

Teva's skinny label did not instruct doctors to prescribe generic carvedilol for an off-label use, i.e., treatment of CHF. *See Warner-Lambert v. Apotex Corp.*, 316 F.3d 1348, 1364-65 (Fed. Cir. 2003) ("[T]he request to make and sell a drug labeled with a permissible (non-infringing) use cannot reasonably be interpreted as an act of infringement (induced or otherwise) with respect to a patent on an unapproved use, as the ANDA does not induce anyone to perform the unapproved acts required to infringe."). Similarly, Teva's skinny label identified the approved indications as being hypertension and post-MI LVD, which were not covered by GSK's patent, and which cannot be considered infringing uses. *See id.*[9]

---

[9]GSK contends that certain post-MI LVD language in Teva's skinny label provides instructions for "treating heart failure patients" and that "patients with post-MI LVD . . . suffer from an early stage of heart failure." (D.I. 472 at 14; *see also* PTX-1080.0003 (Teva skinny label: "Carvedilol is 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) . . . .")) To GSK, this language on Teva's label "encourages doctors to use carvedilol to reduce the risk of death from symptomatic

While GSK's evidence of inducement during the skinny label period consisted principally of Teva's label (and testimony about it), GSK did present other evidence. In seeking to prove inducement, GSK relied on Teva's "AB rating" as well as Teva's 2008 and 2009 product catalogs and Teva's October 2009 Generic Product Reference Guide. (PTX-1208; PTX-1212; PTX-1226) These marketing materials trumpeted Teva's AB rating, without expressly stating that Teva's generic carvedilol was not approved for treatment of CHF. In the Court's view, even the totality of this evidence, taken in the light most favorable to GSK, and drawing all reasonable inferences in favor of GSK, cannot support a reasonable finding that Teva caused any infringement of GSK's '000 patent.

The jury was instructed that "[t]he fact that Teva obtained an AB rating for its generic product is not by itself a sufficient basis to find that Teva had an intent to infringe." (D.I. 440 at 29) GSK argues that Teva did something more than "obtain[] an AB rating;" Teva also listed and marketed Teva's generic carvedilol as AB rated ***to Coreg®***, without specifying that Teva's generic carvedilol – unlike GSK's Coreg® – was ***not*** approved for the CHF indication. (*See* D.I.

---

congestive heart failure, as required by the claims." (D.I. 472 at 14) The Court disagrees. While there may be some overlap between populations of patients suffering from CHF – the treatment of which is within the scope of the '000 patent's claims – and those suffering from post-MI LVD – whose treatment is outside the scope of the claims – the two indications are distinct and require different clinical testing and different FDA approvals to treat. (*See* Zusman Tr. at 1183-84 (explaining difference between post-MI LVD patients and CHF patients); *see also* Shusterman Tr. at 1522-23 (explaining that studies for each indication involved "[f]undamentally different patient group[s]" and "[f]undamentally different physiology going on in those two periods of time"); McCullough Tr. at 605-06 (differentiating post-MI LVD patients from CHF patients); *id.* at 682 (admitting that post-MI LVD is broader than CHF, as not all post-MI LVD patients suffer from CHF)) To infringe the '000 patent, carvedilol must have been prescribed to treat the risk of mortality ***caused by CHF***. Accordingly, a reasonable juror could not have found that Teva's inclusion of post-MI LVD language in its skinny label caused or even encouraged direct infringement of the '000 patent's claimed method of use of treating CHF.

472 at 5, 15) But this fact does not support a reasonable finding that Teva caused infringement. As both parties showed at trial, being AB rated signifies that a generic drug is therapeutically equivalent to a branded drug. (*See* Lietzan Tr. at 542; Karst Tr. at 1031-32) The undisputed evidence demonstrates that a generic drug cannot be listed as "AB rated" generally, as "AB rated" is a relative term; it necessarily requires a comparison between the generic drug and some branded reference drug. (*See* Lietzan Tr. at 534; *see also* Karst Tr. at 1031-32)

In addition, as GSK conceded, there is no FDA requirement that a generic drug company specify for which uses it is (or is not) AB rated. (*See* Lietzan at 577-78) Nor had either party's experts ever seen such a clarifying statement in any press release or product catalog. (*See* Lietzan Tr. at 548-49, 577-78; Karst Tr. at 1030)[10] The Orange Book states that therapeutic equivalent determinations are not made for unapproved off-label indications. (*See* DTX-2171; Karst Tr. at 1035) GSK's expert, Professor Erika Lietzan, acknowledged that "the meaning of therapeutically equivalent of AB rating is if the generic drug is used ***in accordance with its label***, you would expect it to have the same clinical effect in a person as if that person had taken the brand drug." (Lietzan Tr. at 534 (emphasis added); *see also id.* at 542 ("AB rating means . . . if a

[10]Teva contends that "GSK seeks to impose on Teva (and the entire industry) an affirmative duty to correct the incorrect ***assumption*** that doctors purportedly make by misunderstanding the FDA's AB-rating designation, or risk being held liable for ***all*** conduct of the doctors." (D.I. 465 at 2-3) This is not the only unprecedented "duty" GSK seeks to impose. GSK also asks that this case make clear that when a generic adds an indication to its label by eliminating a previous carve-out it must send the branded company a new paragraph IV notice (*see* Hr'g Tr. at 120; Tr. at 1840-41 (GSK closing argument)), and provide "disclaimers clarifying its product was not approved for heart failure" (*see, e.g.*, D.I. 472 at 15). GSK points to no authority to support the obligations it would have the Court create, duties which appear to be inconsistent with governing law. *See generally Warner-Lambert*, 316 F.3d at 1365 ("[I]ntent to induce infringement cannot be inferred even when the defendant has actual knowledge that some users of its product may be infringing the patent.").

patient took the generic carvedilol for one of the uses in its label, you would expect it to have the same clinical effect as if the patient is taking Coreg.")) Teva's skinny label, as addressed above, omitted substantial information regarding the CHF indication and, instead, stated that the product was approved for hypertension and post-MI LVD indications. Accordingly, there is not legally sufficient evidence to support a finding that Teva, by listing its carvedilol as AB rated to Coreg® in product catalogs and reference guides, encouraged infringement.

Additionally, a reasonable juror would had to have found, based on the record presented at trial, that in July 2007, prior to the launch of generic carvedilol (including by Teva), doctors deciding to write a prescription for carvedilol relied on various sources ***other than Teva's label and marketing materials***. In addition to the knowledge and experience that ordinarily skilled cardiologists had acquired by July 2007 about the benefits of treatment with carvedilol, such doctors had access to American Heart Association and American College of Cardiology guidelines, carvedilol research studies published in the *New England Journal of Medicine*, *The Lancet*, and the *British Heart Journal*, GSK's own Coreg® label and product insert, and GSK's extensive promotional activity – totaling nearly $1 billion (*See* Vojir Tr. at 508-09) – which included sending doctors to hospitals, giving seminars, and detailing, marketing, and advertising Coreg®. (*See* D.I. 465 at 7-8; Vojir Tr. at 497-511; McCullough Tr. at 666-69, 676-77; Zusman Tr. at 1151, 1164-65; PTX-78; DTX-2655.4; PTX-534)

Further, Teva showed that once generic carvedilol entered the market in September 2007, and continuing beyond 2007, doctors continued prescribing carvedilol (be it Coreg® or a generic) in the same manner as they had prior to the generics' entrance, as they based their prescription decisions on the various factors addressed above without relying on Teva's – or any

other generic manufacturers' – label. (*See* McCullough Tr. at 677-78) GSK's expert, Dr. McCullough, testified that he had not read Teva's generic label before he started writing prescriptions for carvedilol. (*See id.* at 1662-63)[11] As GSK concedes, prior to the generics' entrance into the market in 2007, physicians already knew how to use carvedilol for treating CHF. (Hr'g Tr. at 85-86) Three cardiologists testified at trial – GSK's expert, Dr. McCullough, and Teva's experts, Drs. Zusman and Rosendorff – and all three agreed that even in September 2007, when generic companies (including Teva) began selling carvedilol, doctors relied on guidelines and research, as well as their own experience, in addition to GSK marketing. (*See* McCullough Tr. at 676-79; Zusman Tr. at 1164-72, 1176-77; Rosendorff Tr. at 1296-97) None viewed generic labeling, including Teva's label, as impacting prescribing behavior. (*See id.*)[12] In

---

[11]The specific testimony was as follows:

> Q. Now, before you started administering generic carvedilol to your patients, whether you wrote it as Coreg or not, did you read Teva's generic label?
>
> A. No, I didn't.
>
> Q. Why not?
>
> A. I just assume they were the same.

The Court also agrees with Teva that Dr. McCullough failed to acknowledge the causation requirement of an inducement claim. (*See, e.g.*, D.I. 477 at 3) (citing, e.g., McCullough Tr. at 614-17)

[12]The only "exception" to this is Dr. Randall Zusman's testimony regarding the hypothetical scenario of what might be called an "unfrozen caveman cardiologist" (*see also Saturday Night Live: Unfrozen Caveman Lawyer* (NBC television broadcast 1991-96)) – that is, "someone who is inexperienced, somehow has missed all of this education during the course of the their training, now they are going to treat a patient with heart failure, and they somehow came upon Teva's skinny label." (Zusman Tr. at 1153-54) Even such a doctor (who would not have been a person of ordinary skill in the art at any pertinent date) "would immediately see that the [CHF] indication is not included" on Teva's skinny label and would then have turned to various

this context, there was no reasonable basis for the jury to have found that anything Teva did – including selling generic carvedilol, giving it a "skinny label," and all aspects of how Teva marketed its carvedilol – caused even a single doctor to prescribe carvedilol for the treatment of CHF.

Teva's uncontroverted evidence of alternative factors that caused physicians to prescribe carvedilol in an infringing manner cannot be ignored. *See Integra*, 496 F.3d at 1345 ("The rule that a jury verdict is reviewed for support by 'substantial evidence' does not mean that the reviewing court must ignore the evidence that does not support the verdict. . . . [T]he court should give credence to the evidence favoring the nonmovant as well as that evidence supporting the moving party that is uncontradicted and unimpeached.") (internal quotation marks omitted).

As Teva correctly notes, no direct evidence was presented at trial that any doctor was ever induced to infringe the '000 patent by Teva's label (either skinny or full). There was no direct evidence that Teva's label caused even a single doctor to prescribe generic carvedilol to a patient to treat mild to severe CHF. Hence, in order to uphold the verdict, the Court must find in the record substantial evidence to render it reasonable for the jury to have inferred that at least one doctor was so induced. GSK, as the verdict winner, is entitled to the benefit of all reasonable inferences that may be drawn from the evidence presented to the jury. The Court's determination, however, is that – given the dearth of evidence that doctors read and understand and are affected by labels, and given the vast amount of evidence that doctors' decisions to prescribe carvedilol during the relevant periods were influenced by multiple non-Teva factors –

---

non-Teva guidelines, textbooks, and research to gather information necessary to making a prescribing decision. (*See id.*)

such an inference was an unreasonable one for the jury to have drawn. *See McAnally v. Gildersleeve*, 16 F.3d 1394, 1500 (8th Cir. 1994) ("[Courts] cannot accord the jury with the benefit of unreasonable inferences, or those at war with the undisputed facts.") (internal quotation marks omitted).[13]

GSK suggests that the Court cannot (or at least should not) grant Teva's JMOL because it

---

[13]In reaching this conclusion, the Court is applying the same legal standards on which it instructed the jury, including its instructions on "Induced Infringement" and "Inducement Must Cause Direct Infringement." (D.I. 440 at 4.2 (listing each element GSK must prove to show inducement, including "that Teva's alleged inducement, as opposed to other factors, actually caused the physicians to directly infringe"); *id.* at 4.2.4 ("Teva cannot be liable for induced infringement where GSK does not show that Teva successfully communicated with and induced a third-party direct infringer and that the communication was the cause of the direct infringement by the third-party infringer. . . . GSK is not required to present hard proof of any direct infringer physician stating, for example, that she read Teva's labels or other Teva materials and that these labels or other Teva materials caused her to prescribe Teva's generic carvedilol in an infringing manner. GSK must prove that Teva's actions led physicians to directly infringe a claim of the '000 patent, but GSK may do so with circumstantial – as opposed to direct – evidence."))

The Court recognizes that these are not the instructions GSK proposed. (*See generally* D.I. 431 at 27-29) GSK, while not waiving any objections, has not renewed its objections nor raised any argument that the Court should, in evaluating Teva's JMOL motion, apply a standard different than the one on which it instructed the jury. (*See generally* Tr. at 1414-15, 1430-32) Teva contends that the jury instructions were correct and emphasizes that GSK has not contended the Court should not apply them to the motion. (*See* Hr'g Tr. at 6 ("The jury instructions correctly set out the law. . . . And we, we think, to be clear, that the instructions are correct. But we think that GSK hadn't argued specifically that you should apply a different standard."))

Therefore, the Court perceives no basis to conclude that its instructions were incorrect and, for purposes of Teva's JMOL motion, the Court has applied the standards it provided in its jury instructions. (*See also* D.I. 411 at 3-5 (holding that in post-launch context, patentee must prove actual inducement); Tr. at 1414 (GSK counsel conceding, in context of post-launch inducement, "the law is and . . . the [C]ourt's rulings have shown there [are] causation requirements"); *see generally Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 975 (Fed. Cir. 1995) ("While the jury's factual findings receive substantial deference on motion for JMOL, the legal standards that the jury applies, expressly or implicitly, in reaching its verdict are considered by the district court and by the appellate court de novo to determine whether those standards are correct as a matter of law."))

denied Teva's motion for summary judgment. (*See, e.g.*, D.I. 472 at 2) ("Teva's JMOL request should be denied because it repeats the same arguments the Court has rejected before trial, wrongly argues that GSK's evidence is insufficient even though the Court already concluded it could support a jury verdict, asks the Court to substitute its judgment for the jury's on disputed facts, and ignores the jury charge.") The Court disagrees. In connection with adopting Magistrate Judge Burke's recommendation to deny Teva's motion for summary judgment of non-infringement, the Court wrote:

> Defendants may prevail at trial based on their view that GSK's "long chain of inferences" does not establish causation. But that is a matter for the jury to decide after hearing the conflicting evidence (e.g., what the label instructs versus whether anyone read it, how Teva marketed its generic product versus whether cardiologists already knew to use carvedilol before GSK even obtained its patent, etc.) to be presented by both sides. The Court does not find, on the record before it, that "GSK's proposed inferences [are] unreasonable."

(D.I. 411 at 5) (internal citations omitted) After reviewing the entirety of the record GSK actually created at trial, as well as the unrebutted trial evidence presented by Teva, the Court now concludes (as it is free to do, notwithstanding the assessment it made prior to trial), that the inference of causation that GSK asks be drawn is not reasonable, as it is not supported by substantial evidence in the trial record.

Considering the record as a whole, substantial evidence does not support a finding by a reasonable factfinder that even at least one doctor was induced to prescribe generic carvedilol to be used in an infringing manner due to ***Teva's*** actions, as opposed to the various other factors

supported in the record, during the skinny label period.[14] Therefore, the Court cannot uphold the verdict of infringement with respect to the skinny label period.

2. The Full Label Period

The full label period, May 1, 2011 through June 7, 2015, runs from when Teva amended its label to include the CHF indication until the '000 patent expired. In attempting to prove inducement during the full label period, GSK presented evidence of Teva's full label along with various other materials, including Teva's 2004 and 2007 press releases, Teva's 2011 product catalog, the 2012 and 2013 editions of Teva's Monthly Prescribing Reference ("MPR"), and Teva's AB rating (including as it was listed on Teva's website). (*See* PTX-1297; PTX-1301;

---

[14]Following oral argument, the parties notified the Court on several occasions of subsequent authority they believe is pertinent to the issues pending before the Court. (*See* D.I. 483, 485, 486, 487) The Court has considered these new cases, and they do not alter the outcome announced in this opinion.

For instance, GSK directs the Court to *Sanofi v. Watson Laboratories Inc.*, 875 F.3d 636, 646 (Fed. Cir. 2017), for the proposition that the marketing of a generic drug with labeling that encourages infringement can be viewed as causing infringement despite the fact that the innovator company published the results of clinical studies and promoted the patented use. (*See* D.I. 485 at 2) That case does not persuade the Court to reach a different conclusion than described above. *Sanofi* involved the ordinary Hatch-Waxman framework, "where a claim of induced infringement is filed ***before*** the generic has launched its product, and necessarily, before the generic has even attempted to communicate with any direct infringer." (D.I. 411 at 3) (emphasis added) In those cases, as this Court held during earlier portions of this case, "the focus must be on intent, rather than actual inducement." (*Id.*) Here, by contrast, "GSK filed its case almost seven years after Defendants launched their generic carvedilol products into the market. Hence, GSK's inducement claims are not premised on a hypothetical, but instead must be supported by sufficient evidence as to what actually happened during the relevant time period." (*Id.* at 3-4) (internal citations and quotation marks omitted) This Court has decided that reliance on a label and speculation about what may occur in the future cannot substitute for actual evidence about what has actually occurred in the past when, as in this case, there has been a period of actual, past conduct that is pertinent to infringement. Additionally, unlike the label involved in *Sanofi*, Teva's skinny label expressly carved out the patented use from its label. Therefore, the skinny label here does not support the same sort of inducement inferences the court found present in *Sanofi*.

PTX-1165; PTX-1203; PTX-1205; PTX-0860; McCullough Tr. at 635-36)

As addressed above, however, Teva presented substantial, unrebutted evidence of multiple factors unrelated to Teva that actually caused doctors to infringe the '000 patent. A reasonable factfinder could only have found that these alternative, non-Teva factors were what caused the doctors to prescribe generic carvedilol for an infringing use. Regardless of Teva's actions after it amended its label in May of 2011, including its elimination of the carve-out from its label, physicians were already prescribing generic carvedilol to treat CHF at that time. No substantial evidence was presented at trial to support a finding that anything about doctors' behavior – either as a class, or even a single doctor – was induced to change by Teva's label, or by anything else Teva did (or failed to do).[15] GSK conceded that physicians' reasons for and methods of prescribing carvedilol did not change when generics entered the market. (*See* McCullough Tr. at 677-78) For all these reasons, a reasonable jury could not find that Teva caused any direct infringement and, therefore, Teva cannot be held liable for inducement of infringement.

In sum, substantial evidence does not support the jury's finding on causation, and therefore does not support its verdict that Teva is liable for induced infringement, during both the skinny and full label periods. The Court will grant Teva's JMOL. Without a finding of infringement, there is no liability, so Teva cannot be found to be a willful infringer and cannot be ordered to pay GSK any damages. Accordingly, the Court will grant Teva's JMOL motion on

---

[15]In coming to this conclusion, the Court is not holding that a full label will never be sufficient to prove causation, only that, in the context of this specific case, confronting Teva's specific motion, Teva's full label (along with the other evidence presented at trial) is insufficient. (*See* Hr'g Tr. at 87) (GSK's counsel acknowledging that "this is such a fact specific case")

each of these grounds.[16]

---

[16]Both sides of this case identify important policy questions they see as being implicated by their disputes. GSK contends that a finding in favor of Teva, absolving the generic from liability for a method of treatment claim, will cause "the entire Hatch-Waxman framework [to] come[] crashing down" because it will result in "every generic dragging their feet so as not to go to trial during the 30-month stay in the Hatch-Waxman cases and then launch at risk and they're home free," because the innovator branded company will necessarily already have educated the market to use the drug. (Hr'g Tr. at 86-87) This reality, it is argued, combined with the Court's determination that the branded company cannot rely exclusively on the generic's label when the generic has already begun marketing its product, create a formula for generics to insulate themselves from any possible liability for induced infringement. (*See id.*; *see also* D.I. 472 at 11 (warning that acceptance of Teva's view "creates an incentive for generic manufacturers to launch at risk, destroy the innovator's market, and then argue it was not liable because its label was not the 'sole cause' of the direct infringement"))

For its part, Teva asserts that "GSK is fundamentally trying to use this case to put the [Hatch-Waxman] system on trial." (Hr'g Tr. at 30) In particular, in Teva's view, upholding the jury's verdict and allowing GSK to collect enormous damages (well beyond Teva's carvedilol revenues, and orders of magnitude above its profits on the product (*see id.* at 47-48, 117)) would eviscerate the section viii carve-out, as there would be no way a generic could avoid inducing infringement even if all the infringement is based on an off-label use. (*See id.* at 31 (arguing carve-outs are "part of the statute," which was "designed to enable the sale of drugs for non-patented uses [that are addressed on the skinny label] even though this would result in some off-label infringing uses"); *see also* D.I. 477 at 10-11 ("The implications of GSK's position cannot be understated: GSK seeks to place an affirmative obligation on generic pharmaceutical companies to police and affirmatively correct doctors' misunderstanding of AB-ratings. This is not the law."); D.I. 465 at 23 n.11 ("By endorsing [GSK's] legal theory, the Court would create a new rule that would dramatically upset the delicate balance struck by the Hatch-Waxman Act."). Since section viii is in the statute, it would be wrong and problematic, in Teva's view, to effectively read it out of the Hatch-Waxman Act. *See Caraco Pharma. Labs., Ltd. v. Novo Nordisk A/S*, 566 U.S. 399, 415 (2012) ("[S]ection viii provides the mechanism for a generic company to identify those [unpatented] uses, so that a product with a label matching them can quickly come to market."); *Takeda Pharms. U.S.A., Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 630 (Fed. Cir. 2015) ("[A] generic manufacturer may avoid infringement by proposing a label that does not claim a patented method of use, ensuring that one patented use will not foreclose marketing a generic drug for other unpatented ones.") (internal quotation marks omitted); *id.* at 631 ("[Hatch-Waxman] was designed to enable the sale of drugs for non-patented uses even though this would result in some off-label infringing uses.").

The Court notes the parties' concerns and hopes neither side is correct in its predictions as to the dire consequences of the Court's ruling. Beyond prompting these observations, however, the parties' policy arguments have not impacted the Court's ruling on the pending

B. Substantial Evidence Supports the Jury's Finding of No Invalidity

Teva additionally seeks JMOL of invalidity, or a new trial, on two grounds: (1) the Kelly reference anticipates the asserted claims; and (2) the asserted claims are obvious in light of Kelly and Garg. (*See* D.I. 465 at 27-29) The Court is not persuaded by Teva and will deny this aspect of Teva's JMOL motion.

Regarding anticipation, before trial, the Court identified three genuine disputes of material fact: (1) whether Kelly disclosed a maintenance period greater than six months; (2) whether Kelly's patient population was the same as that covered by the claims; and (3) whether Kelly was "too theoretical" to be considered enabling. (*See* D.I. 380 at 2-3, 5-6; D.I. 417 at 1-2 & n.1) On each of these factual questions, Teva contends that the jury's findings for GSK were unreasonable. (*See* D.I. 465 at 27-29) The Court disagrees.

GSK presented sufficient evidence to support a reasonable inference that the Kelly reference only taught treatment follow-up ***after*** six months, rather than ***continuing*** treatment for six months (*see, e.g.*, McCullough Tr. at 1673, 1677-78, 1731-32) and that the study may have dealt with a different patient population, as more than one type of heart failure exists and Kelly did not specify which type of heart failure patients it was treating (*see, e.g.*, *id.* at 1672-73, 1681-82). GSK also presented sufficient evidence to support the inference that Kelly was too theoretical, as the study had not yet begun and could require undue experimentation. (*See, e.g.*, *id.* at 1678-79) Each of these factual disputes was for the jury to resolve, and its finding that Teva did not prove the contrary by clear and convincing evidence was reasonable based on the record.

---

motions.

Regarding obviousness, Teva contends that the questions left open by Kelly (as addressed above) were all answered by Garg. (*See* D.I. 465 at 29) Thus, Teva asserts that the claims are obvious and the jury's conclusion, even in light of GSK's evidence of secondary considerations of non-obviousness, was unreasonable. (*See id.* at 29-30) However, as GSK notes (and as the Court finds above), the jury's finding that Kelly did not disclose the three disputed claim elements was reasonable based on the record. Moreover, contrary to Teva's contention, GSK provided evidence through Dr. McCullough that Garg does not supply the duration element lacking in Kelly. (*See* McCullough Tr. at 1682) This evidence, in addition to GSK's evidence that the prior art taught away from and discouraged beta-blockers in heart failure, was sufficient to render the jury's finding that the patent was non-obvious reasonable. Therefore, the Court will deny Teva's motion for JMOL or a new trial on invalidity.

IV. CONCLUSION

For the reasons stated above, the Court will grant in part and deny in part Teva's motion for judgment as a matter of law. (D.I. 464) Because substantial evidence does not support a finding of induced infringement, there is no basis for enhanced damages, attorney fees, and interest. Accordingly, GSK's motion (D.I. 466) and Teva's motion to strike multiple exhibits GSK submitted in support of its motion (D.I. 474) will be denied as moot. An appropriate Order follows.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GLAXOSMITHKLINE LLC and SMITHKLINE BEECHAM (CORK) LIMITED,	:	
Plaintiffs,	:	
v.	:	C.A. No. 14-878-LPS-CJB
TEVA PHARMACEUTICALS USA, INC.,	:	
Defendant.	:	

ORDER

At Wilmington, this **28th** day of **March, 2018**:

For the reasons set forth in the Memorandum Opinion issued this date,

IT IS HEREBY ORDERED that:

1. Teva's motion for judgment as a matter of law, or in the alternative for a new trial (D.I. 464), is GRANTED IN PART and DENIED IN PART.

2. GSK's motion for enhanced damages, attorney fees, and interest (D.I. 466) is DENIED AS MOOT.

3. Teva's motion to strike (D.I. 474) is DENIED AS MOOT.

IT IS FURTHER ORDERED that the parties shall meet and confer and shall submit a joint status report, no later than April 2, 2018, advising the Court of any remaining order(s) it should enter in this case and how the case should now proceed.

UNITED STATES DISTRICT COURT

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GLAXOSMITHKLINE LLC and SMITHKLINE BEECHAM (CORK) LIMITED,	:	
Plaintiffs,	:	
v.	:	C.A. No. 14-878-LPS-CJB
TEVA PHARMACEUTICALS USA, INC.,	:	
Defendant.	:	

FINAL JUDGMENT

This action between Plaintiffs GlaxoSmithKline, LLC and SmithKline Beecham (Cork) Limited (collectively, "GSK") and Defendant Teva Pharmaceuticals USA, Inc. ("Teva") came before the Court for trial beginning on June 12, 2017, before a duly empaneled and sworn jury. The jury rendered a verdict on June 20, 2017. (*See* D.I. 448) Teva's defenses of equitable estoppel, unpatentable subject matter under 35 U.S.C. § 101, indefiniteness of claim 8, and improper dependency of claim 8 were reserved to be tried to the Court at a later date. (*See* D.I. 452 at 16-17; D.I. 451)

On August 25, 2017, the parties filed post-trial motions. (D.I. 464; D.I. 466) On March 28, 2018, the Court granted in part Teva's motion for judgment as a matter of law and denied as moot GSK's motion for enhanced damages, attorney fees, and interest. (D.I. 489; D.I. 490)

Therefore, pursuant to Federal Rules of Civil Procedure 50, 54, and 58, FINAL JUDGMENT is hereby entered in this matter as follows:

It is ORDERED AND ADJUDGED that final judgment be and hereby is entered in favor

of Teva and against GSK on GSK's claims that Teva induced infringement of the asserted claims of the '000 patent.

It is ORDERED AND ADJUDGED that final judgment be and hereby is entered in favor of GSK and against Teva on Teva's affirmative defenses that the asserted claims of the '000 patent are invalid as anticipated or obvious under 35 U.S.C. §§ 102 or 103, or for lack of written description under 35 U.S.C. § 112.

It is ORDERED AND ADJUDGED that all remaining claims and affirmative defenses are DISMISSED WITHOUT PREJUDICE, and any further proceedings with respect to these claims and affirmative defenses will be dependent on all applicable legal principles, including any remand order from the Court of Appeals.

SO ORDERED this 25th day of April, 2018.

CHIEF JUDGE LEONARD P. STARK

RE 7586383

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

June 01, 2016

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

U.S. PATENT: *RE40,000*
ISSUE DATE: *January 08, 2008*

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

W. MONTGOMERY
Certifying Officer

GSK00988381

Plaintiffs' Trial Exhibit
PTX 1
C.A. No. 14-878-LPS-CJB

PTX 1.0001

US00RE40000E

(19) **United States**
(12) **Reissued Patent**
Lukas-Laskey et al.

(10) **Patent Number: US RE40,000 E**
(45) **Date of Reissued Patent: *Jan. 8, 2008**

(54) **METHOD OF TREATMENT FOR DECREASING MORTALITY RESULTING FROM CONGESTIVE HEART FAILURE**

(75) Inventors: **Mary Ann Lukas-Laskey**, Rosemont, PA (US); **Robert Ruffolo, Jr.**, Spring City, PA (US); **Neil Howard Shusterman**, Wynnewood, PA (US); **Gisbert Sponer**, Laudenbach (DE); **Klaus Strein**, Hemsbach (DE)

(73) Assignee: **SB Pharmco Puerto Rico Inc.**, Hato Rey, PR (US)

(*) Notice: This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/721,020**

(22) Filed: **Nov. 25, 2003**

Related U.S. Patent Documents

Reissue of:
(64) Patent No.: **5,760,069**
Issued: **Jun. 2, 1998**
Appl. No.: **08/483,635**
Filed: **Jun. 7, 1995**

(30) **Foreign Application Priority Data**

Feb. 8, 1995 (DE) 19503.995

(51) **Int. Cl.**

A61K 31/40	(2006.01)
A61K 31/585	(2006.01)
A61K 31/54	(2006.01)
A61K 31/41	(2006.01)
A61K 31/34	(2006.01)

(52) **U.S. Cl.** **514/411**; 514/175; 514/223.2; 514/223.5; 514/381; 514/423; 514/471

(58) **Field of Classification Search** 514/411, 514/175, 223.2, 223.5, 423, 471
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,503,067	A		3/1985	Wiedemann et al.
4,888,179	A	*	12/1989	Appelgren et al. 424/480
5,308,862	A	*	5/1994	Ohlstein 514/411
5,312,828	A	*	5/1994	Finkelstein et al. 514/381
5,760,069	A	*	6/1998	Lukas-Laskey et al. 514/411
5,902,821	A	*	5/1999	Lukas-Laskey et al. 514/411

FOREIGN PATENT DOCUMENTS

CA	1259071	9/1989
DE	696 02 424 T2	11/1997
EP	0 808 162 B1	11/1997

OTHER PUBLICATIONS

Bristol Meyers Squib v. *Ben Venue Labs.*,246 F .3d 1368 (Fed. Cir. 2001).
Rapoport v. *Dement*, 254 F.3d 1053 (Fed. Cir.2001).
Jansen v. *Rexall Sundown, Inc.*,342 F.3d 1329, 1333–34 (Fed. Cir. 2003).
Glaxo Group Ltd. v. *Teva Pharma, Inc.*, 2004 U.S. Dist. LEXIS 16750, at *56–57 (D. Del. 2004).
Swedberg, Karl et al., "Prolongation of Survival in Congestive Cardiomyopathy by Beta–Receptor Blockade," Lancet 1374–1376 (Jun. 30, 1979).
Prichard, B.N.C. and Tomlinson, B., "Choice of Antihypertensive Drug Therapy," Am Heart J; 114 (4): 1030–40 (Oct. 1987).
Das Gupta et al., "Improvement in congestive heart failure following chronic therapy with a new vasodilating betablocker Carvedilol," Circulation, vol. 80, No. 4, Suppl. 2, II –117 (1989).

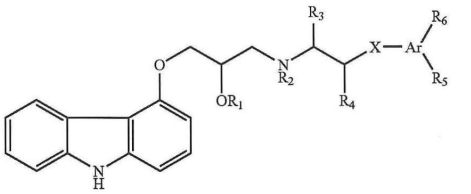
(Continued)

Primary Examiner—Kevin E. Weddington
(74) *Attorney, Agent, or Firm*—Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.

(57) **ABSTRACT**

A method of treatment using a compound of Formula I:

(I)



wherein:

R_1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of up to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R_4 together with R_5 can represent $—CH_2—O—$;

X is a valency bond, $—CH_2$, oxygen or sulfur;

Ar is selected from phenyl, naphthyl, indanyl and tetrahydronapthyl;

R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a $—CONH_2—$ group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkysulphinyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

R_5 and R_6 together represent methylenedioxy;

or a pharmaceutically acceptable salt thereof, alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of ACE inhibitors, diuretics, and digoxin for decreasing mortality resulting from congestive heart failure (CHF) in mammals, particularly humans.

9 Claims, No Drawings

Copy provided by USPTO from the PIRS Image Database on 05/23/2016

OTHER PUBLICATIONS

DiBanco, Robert et al., "A Comparison of Oral Milrinone, Digoxin, and Their Combination in the Treatment of Patients with Chronic Heart Failure," New England J. Med., vol. 320, No. 11, 677–683 (Mar. 16, 1989).

Das Gupta, P. et al., "Value of carvedilol in congestive heart failure secondary to coronary artery disease," American Journal of Cardiology, vol. 66, No. 15, pp. 1118–1123, (Nov. 1, 1990).

Krukemyer, J., "Use of Beta–Adrenergic Blocking Agents in Congestive Heart Failure," Clin Pharm 9(11): 853–63 (Nov. 1990).

Strein, K. and Sponer, G, "Experimental and clinical pharmacology of carvedilol and other drugs combining vasodilation and beta–adrenoceptor antagonism in a single molecule," Z Kardiol 79 Suppl. 3, pp. 89–98 (1990).

Das Gupta, P. et al., "The effects of intravenous carvedilol, a new multiple action vasodilatory beta–blocker, in congestive heart failure.," J Cardiovasc Pharmacol, vol. 18, Suppl. 7, pp. S 12–16 (1991).

Di Lenarda, Andrea, "Acute Hemodynamic Effects of Carvedilol Versus Metoprolol in Idiopathic Dilated Cardiomyopathy.," Abstract —JACC vol. 17(2), 142A (Feb. 1991).

Hamburger, S.A. et al., "Carvedilol (Kredex®) reduces infarct size in a canine model of acute myocardial infarction," Pharmacology, vol. 43, pp. 113–120 (1991).

Ruffolo, R. et al., "Carvedilol (Kredex®): A Novel Multiple Action Cardiovascular Agent," Drugs of Today 27(7): 465–492 (1991).

Bristow, M.R. et al., "Effects of carvedilol on adrenergic receptor pharmacology in human ventricular myocardium and lymphocytes," Clinical Investig 70 Suppl 1: S105–13 (1992).

Das Gupta, P. et al., "Can intravenous beta–blockade predict long–term hemodynamic benefit in chronic congestive heart failure secondary to ischemic heart disease?" J. Cardiovasc Pharmacol, vol. 19, Suppl. I, pp. S62–7 (1992).

De Cree, J. et al., "Comparative cardiac haemodynamics of bisoprolol, celiprolol, carvedilol and nebivolol in normal volunteers," Int J Clin Pharmacol Res., vol. 12, No. 4, pp. 159–163 (1992).

Feuerstein, G.Z. et al., "Myocardial protection with Carvedilol," J Cardiovasc Pharmacol, vol. 19, Suppl. 1, pp. S138–41 (1992).

Senior, R.; Müller–Beckmann, B., Das Gupta, P., van der Does, R. and Lahiri, A. "Effects of carvedilol on ventricular arrhythmias," J Cardiovasc Pharmacol 19 Suppl. 1:S117–21 (1992).

Sponer, G. et al., "Vasodilatory action of Carvedilol," J Cardiovasc Pharmacol 19 Suppl 1:S5–11 (1992).

Bristow, M.R., "Pathophysiologic and Pharmacologic Rationales for Clinical Management of Chronic Heart Failure with Beta–Blocking Agents," Am J Cardiol 71(9):12C–22C (1993).

Cheng, H.–Y., et al., "Physical chemical investigation of antioxidant properties of carvedilol a cadioprotective drug," International Congress Series No. 1058, Frontiers of reactive oxygen species in biology and medicine, 349–350 (1994).

Feuerstein, G.Z. et al., "Myocardiol protection by the novel vasodilating beta–blocker, carvedilol: potential relevance of anti–oxidant activity," J Hypertens, vol. 11, No. Suppl. 4, pp. S41–8 (Jun. 1993).

Fowler, M.B., "Controlled trials with beta blockers in heart failure: metoprolol as the prototype," Am J Cardiol vol. 71, No. 9, pp. 45C–53C (Mar. 25, 1993).

Kelly, David T., "Carvedilol in Heart Failure," Cardiology 82(suppl 3):45–49 (1993).

Krum, Henry et al., "Controlled Clinical Trials in Heart Failure I: Beta–Blockers," JACC vol. 21, No. 2: 114A, Abstract 725–1 (Feb. 1993).

Lessem, J. N. and Lukas, M.A., "Development of a multiaction beta blocker. Scientific challenges and regulatory needs," Cardiology vol. 82, Suppl 3, pp. 50–58 (1993).

McTavish, Donna, et al., "Carvedilol: A Review of its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Efficacy," Drugs, vol. 45, No. 2, pp. 232–258 (Feb. 1993).

Ohlstein, E.H. et al., "Carvedilol, a cardiovascular drug, prevents vascular smooth muscle cell proliferation, migration, and neointimal formation following vascular injury," Proc Natl. Acad. Sci U.S.A., vol. 90, No. 13, pp. 6189–6193 (Jul. 1993).

Olsen, Stephanie et al., "Controlled Clinical Trials in Heart Failure I: Beta Blockers," JACC vol. 21, No. 2:141A, Abstract 725–2 (Feb. 1993).

Metra, M. et al., "Effects of acute and chronic Carvedilol on resting and exercise hemodynamics of patients with idiopathic cardiomyopathy," JACC vol. 21, No. 2:141A, Abstract 725–3 (Feb. 1993).

Rosendorff, C., "Beta–blocking agents with vasodilator activity," J Hypertens Suppl vol. 11, No. 4, pp. S37–40 (Jun. 1993).

Ruffolo, R.R. et al., "Preclinical and clinical pharmacology of Carvedilol," J Hum Hypertens vol. 7 Suppl. 1, pp. S2–15 (Feb. 1993).

Waagstein, Finn, "Beneficial Effects of metoprolol in idiopathic dilated cardiomyopathy," Lancet, vol. 342. 1441–46 (Dec. 11, 1993).

Unknown, "SB to file seven NDAs, launch Havrix hepatitis A vaccine in 1995; No major drugs come off patent through 2000: Genomics work as synergy with diagnostics—BBS," F–C–D Reports—"The Pink Sheet" , vol. 56, No. 51, pp. 17–18 (Dec. 19, 1994).

CIBIS Investigators and Committees, "A Randomized Trial of Beta–Blockade in Heart Failure—The Cardiac Insufficiency Bisoprolol Study (CIBIS)," Circulation, vol. 90(4), 1765–1773 (1994).

Doughty, R.N. et al., "Beta–Blockers in Heart Failure: Promising or Proved?" J Am Coll Cardiol 23(3):814–21 (1994).

Hampton, J.R., "Choosing the right beta–blocker. A guide to selction," Drugs 48(4):549–68 (Oct. 1994).

Hjalmarson, Ake et al., "The Role of Beta–Blockers in the Treatment of Cardiomyopathy and Ischaemic Heart Failure," Drugs 47 (Suppl. 4): 31–40 (1994).

Louis, W.J. et al., "A risk–benefit assessment of carvedilol in the treatment of cardiovascular disorders," Drugs Safety 11(2):86–93 (Aug. 1994).

Metra, Marco et al., "Effects of Short– and Long–Term Carvedilol Administration on Rest and Exercise Hemodynamic Variables, Exercise Capacity and Clinical Conditions in Patients with Idiopathic Dilated Cardiomyopathy," J Am Coll Cardiol vol. 24, No. 7 1678–87 (Dec. 1994).

Unknown, "Smithkline Expands Testing of Carvedilol Due to Effectiveness," Wall St. J. (Midwest Ed) 76(82):B7 (1995).

Copy provided by USPTO from the PIRS Image Database on 05/23/2016

Unknown, "Survival Chance Improved—BBS," Manufacturing Chemist 66(12):13 (Dec. 1995).
Unknown, "Low dose carvedilol trial success," Pharmaceutical Journal 255(6868):719 (Nov. 1995).
Unknown, "SmithKline Beecham COREG (carvedilol) decreases mortality by 67%—BBS," F–D–C Reports — "The Pink Sheet" vol. 57, No. 47: (T & G 14–T & G 15) (Nov. 20, 1995).
Unknown, "Success halts US trials of carvedilol—BBS," Pharmaceutical Journal, vol. 254, No. 6828, p. 216 (Feb. 18, 1995).
Unknown, "SmithKline expands testing on carvedilol due to effectiveness—BBS," Wall Street Journal, vol. 225, No. 28, p. B6 (Feb. 9, 1995).
Unknown, "Smithkline Beecham/Boehringer Mannheim, UK/Germany: Carvedilol marketed," Bulletin International d'Informations (Droit et Pharmacie) No. 10, pp. 82–83 (Oct. 23, 1995).
Unknown, "SmithKline Beecham to stop its placebo controlled trials for carvedilol in the US," European Chemical News vol. 63, No. 1654, p. 23 (Feb. 1995).
Unknown, "Boerhringer Mannheim and SmithKline Beecham strengthen collaboration to market Carvedilol worldwide," Press Release, p. 1 (Oct. 5, 1995).
Unknown, "SmithKline Beecham: unexpected success halts drug trial," Chemistry and Industry (London): No. 4, p. 123 (Feb. 20, 1995).
Green, Daniel, "UK Company News: SB heart drug proves effective," Financial Times, p. 26 (Feb. 9, 1995).
Australia–New Zealand Heart Failure Research Collaborative Group, "Effects of carvedilol, a vasodilator–beta blocker, in patients with congestive heart failure due to ischemic heart disease," Circulation vol. 92, No. 2, pp. 212–218 (Jul. 15, 1995).
Colucci, W.S. et al., "Carvedilol inhibits clinical progression in patients with mild heart failure—BIO," Circulation, vol. 92, No. 9, Suppl., p. I–395, Abstract 1884 (1995).
Ghali, J.K., "Carvedilol Therapy in Heart Failure—I," J Am Coll Cardiol 26(5):1399 (1995).
Carbajal, E.V., "Carvedilol Therapy in Heart Failure—II," J Am Coll Cardiol 26(5):1399–1400 (1995).
Lee, Y.C., "Carvedilol Therapy in Heart Failure—III," J Am Coll Cardiol 26(5): 1400 (1995).
Olsen, S.L. et al., "Carvedilol Therapy in Heart Failure (Reply)," J Am Coll Cardiol 26(5):1400–1 (1995).
Feuerstein et al., "Carvedilol update III: Rationale for use in congestive heart failure," Drugs of Today, vol. 31 (Suppl. F), pp. 1–23 (Feb. 1995).
Krum, Henry et al., "Double–Blind, Placebo–Controlled Study of the Long–Term Efficacy of Carvedilol in Patients With Severe Chronic Heart Failure," Circulation 92(6): 1499–1506 (Sep. 15, 1995).
Lahiri, A. et al., "Reduction of adverse cardiac events by carvedilol after acute myocardial infarction," European Heart Journal 16(Abstr.Suppl.), p. 36, Abstract P306 (1995).
Olsen, S.L. et al., "Carvedilol Improves Left Ventricular Function and Symptoms in Chronic Heart Failure: A Double–Blind Randomized Study," J Am Coll Cardiol 25(6):1225–31 (May 1995).
Raftery, E.B., "Vasodilating beta–blockers in heart failure," Eur Heart J 16 Suppl F:32–7; erratum in Eur Heart J 16(10): 1451 (1995).
Sackner–Bernstein, J. and Mancini, D.M., "Rationale for Treatment of Patients with Chronic Heart Failure with Adrenergic Blockade," JAMA vol. 274, No. 18, pp. 1462–1467 (1995).
Tham, T.C.K. et al., "The Dose Dependency of the Alpha– and Beta–Adrenoceptor Antagonist Activity of Carvedilol in Man," Br J Clin Pharmacol 40(1):19–23 (1995).
Welter, E.A. and Semchuk, W.M., "The Role of Beta–Blockers in Congestive Heart Failure," J Can Pharm Hosp 48(6):328–35 (1995).
White, M. et al., "What patient with congestive heart failure respond to beta–blocking agents: A Meta–Analysis," Journal of Heart and Lung Transplantation vol. 14, No. 1, p. S85, Abstract 196 (1995).
Winslow, R., "Experimental SmithKline drug shown to combat congestive heart failure—BBS," Wall Street Journal vol. 226, No. 95, p. B 14 (Nov. 14, 1995).
Bonarjee, V.V. and Dickstein, K., "Novel drugs and current therapeutic approaches in the treatment of heart failure," Drugs 51(3):347–58 (Mar. 1996).
Dracup, K., "Heart failure secondary to left ventricular systolic dysfunction. Therapeutic advances and treatment recommendations," Nurse Pract 21(9):57,58,61,65–68 (Sep. 1996).
Feuerstein, G.Z. and Ruffolo, R.R., "Carvedilol, a novel vasodilating beta–blocker with the potential for cardiovascular organ protection," Eur Heart J 17 Suppl B:24–9 (Apr. 1996).
Krum, H. et al, "Changes in plasma endothelin–I levels reflect clinical response to beta–blockade in chronic heart failure," Am Heart J 131(2):337–41 (Feb. 1996).
Packer, M. et al., "The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group," N Engl J Med Med 334(21): 1349–55 (May 23, 1996).
Raftery, E.B. "The preventative effects of vasodilating beta–blockers in cardiovacular disease," Eur Heart J 17 Suppl B:30–8 (Apr. 1996).
Sharpe, N., Beta–blockers in heart failure. Future directions, Eur Heart J 17 Suppl B:39–42 (Apr. 1996).
Beta–Blocker Evaluation of Survival Trial Investigators, "A Trial of the Beta–Blocker Bucindolol in Patients with Advanced Chronic Heart Failure," New England J. Med. 344(22), 1659–1667 (May 31, 2001).
Ruffolo, R.R., et al., "Cardioprotective Potential of Carvedilol," Cardiology, 82(suppl 3), 24–28 (1993).
Cohn, J.N., et al., "Effect of Vasodilator Therapy on Mortality in Chronic Congestive Heart Failure," New England J. Med, 314(24), 1547–52 (Jun. 12, 1986).
Whitfield, H.N., et al., "The effect of adrenergic blocking drugs on outflow resistance," Brit. J. Urology, 47, 823–827 (1976).
Caine, M., et al., "The Use of Alpha–adrenergic blockers in Benign Prostatic Obstruction," Brit. J. Urology, 48, 255–263 (1976).
Buchwald, A., et al., Z. Kardiol, 79, 424–28 (1990).
Tepper, D., "Multicenter Oral Carvedilol Heart Failure Assessment (MOCHA)," Frontiers in CHF, 2(1), 39–40 (1996).
Waagstein, F., et al., "Effect of chronic beta–adrenergic receptor blockade in congestive cardiomyopathy," Brit. Heart J., 37, 1022–36 (1975).
Waagstein F. et al., "Beta–blockers in dilated cardiomyopathies: they work," Eur. Heart J., 4(Supp A), 173–78 (1983).

Copy provided by USPTO from the PIRS Image Database on 05/23/2016

Novopharm, Notice of Allegation and Detailed Statement—Carvedilol 3.125 mg, 6.25 mg, 12.5 mg, and 25 mg Tablets (Nov. 28, 2001).

Notice of Application, *Hoffmann–La Roche Ltd and Smithkline Beecham Corp.* v. *Minister of Health and Novopharm Ltd.*, Court No. T–84–02, Federal Court, Trial Division (Canada) (Jan. 16, 2002).

Pharmascience, Notice of Allegation regarding carvedilol, 3.125 mg, 6.25 mg, 12.5 mg, and 25 mg (Aug. 30, 2001).

Notice of Application, *GlaxoSmithKline Inc. and SmithKline Beecham Corp.* v. *Minister of Health and Pharmascience Inc.*, Court No. T–1871–01, Federal Court, Trial Division (Canada) (Oct. 18, 2001).

Reasons for Order and Order, *GlaxoSmithKline Inc. and SmithKline Beecham Corp.* v. *Minister of Health and Pharmascience Inc.*, Court No. T–1871–01, Federal Court, Trial Division (Canada) (Jul. 18, 2003).

Apotex Inc., Notice of Allegation in respect to Canadian Letters Patent No. 2,212,548 (Jun. 19, 2003).

Swedberg, K., et al., "Beneficial effects of long–term beta–blockade in congestive cardiomyopathy," Brit Heart J., 44, 117–33 (1980).

Swedberg, K., et al., "Adverse effects of beta–blockade withdrawal in patients with congestive cardiomyopathy," Brit. Heart J., 44, 134–42 (1980).

Drexler, H. et al., Characterization of skeletal muscle β–adrenergic receptors in patients with chronic heart failure, Circulation 80(4), II–116 (1989).

Diehm, C., Antihypertensive therapy in arterial occlusive disease, Vasa Suppl, 33, 71–4 (1991) (English language abstract only).

Sponer, G., et al., "Pharmacological profile of β–adrenoceptor blockers with vasodilating properties, especially Carvedilol—rationale for clinical use," Clin. Investig., 70, S20–S26 (1992).

Lessem, J.N., Weber, M.A., "Antihypertensive treatment with a dual–acting beta–blocker in the elderly," J. Hypertens Suppl., 11(4), S29–36 (1993) (Abstract only).

Olsen, S.L., et al., "β–Blocker related improvement in submaximal exercise tolerance in heart failure from idiopathic dilated cardiomyopathy (IDC)", JACC, 19, 146A, Abstract 747–5 (Mar. 1, 1992).

Harder S., et al., "Lack of pharmacokinetic interaction between carvedilol and digitoxin or phenprocoumon," Eur. J. Clin. Pharmacol, 44(6), 583–6 (1993) (Abstract only).

Bristow, M.R., et al., "The β–blocking agents metopolol and Carvedilol affect cardiac adrenergic drive differently in subjects with heart failure from idiopathic dilated cardiomyopathy," JACC, 21(2), 314A (Feb. 1993) (Abstract only).

Australia/New Zealand Heart Failure Research Collaborative Group, "Randomised, placebo–controlled trial of Carvedilol in patients with congestive heart failure due to ischaemic heart disease," Lancet, 349, 375–80 (Feb. 8, 1997).

Teva, Patent Certification Notice Letter re U.S. Patent Nos. 5, 760,069 and 5,902,821 (May 24, 2002).

Packer, M., "Effect of Carvedilol on Survival in Severe Chronic Heart Failure," New England J. Med., 344(22), 1651–1658 (May 31, 2001).

Judgment, German Federal Republic Judgment nullity action 3 Ni 44/00 relating to DE 696 02 424 (EP 0 808 162), *Egis Gyogyszergyar RT* v. *F. Hoffmann–La Rocha AG* (Sep. 18, 2001) (English language translation).

Defendant's Answer to Summons of Jul. 6, 2001, German Federal Republic nullity action 3 Ni 44/00 relating to DE 696 02 424 (EP 0 808 162), *Egis Gyogyszergyar RT* v. *Hoffmann–La Roche AG* (Aug. 23, 2001) (English language translation).

Plaintiff's Brief, German Federal Republic nullity action 3 Ni 44/00 relating to DE 696 02 424 (EP 0 808 162), *Egis Gyogyszergyar RT* v. *Boeringer Hoofmann–La Roche AG* (Aug. 7, 2001) (English language translation).

Substantiation of Opposition of Sep. 21, 2000, German Federal Republic nullity action 3 Ni 44/00 relating to DE 696 02 424 (EP 0 808 162), *Egis Gyogyszergyar RT* v. *Boehringer Hoffmann–La Roche AG* (Dec. 8, 2000) (English language translation).

Nullification Petition, German Federal Republic nullity action relating to DE 696 02 424 (EP 0 808 162), *Egis Gyogyszergyar RT* v. *Boehringer Hoffmann–La Roche AG* (Aug. 4, 2000) (English language translation).

Judgment, German Federal Republic Judgment nullity action 3 Ni 57/91 relating to DE 36 12 537 (Oct. 27, 1992) (English language translation).

Ruling, German Federal Republic, Federal Patent Court, concerning Patent 22 23 237 (Jan. 13, 1989) (English Language Translation).

Official Action, German Patent Office, Application No. P. 195 03 995.5–41 (Aug. 17, 1995).

Official Action, German Patent Office, Application No. P. 195 03 995.5–41 (Nov. 7, 1995).

Affidavit of Dr. William T. Abraham (Mar. 8, 2002), filed in *Hoffmann–La Roche Ltd and Smithkline Beecham Corp.* v. *Minister of Health and Novopharm Ltd.*, Court No. T–84–02, Federal Court, Trial Division (Canada), further including: Exhibit A: Curriculum Vitae of Dr. William T. Abraham, Exhibit B: Novopharm, Notice of Allegation and Detailed Statement—Carvedilol 3.125 mg, 6.25 mg, 12.5 mg, and 25 mg Tablets (Nov. 28, 2001), Exhibit C: Canadian Patent No. 2,212,548, Exhibit D: Glossary of Terms, and Exhibit E: Commentary of Remaining Prior Art in Appendices A & B of the Novopharm Notice of Allegation.

Affidavit of Dr. Mark Lautens (Mar. 8, 2002), filed in *Hoffmann–La Roche Ltd and Smithkline Beecham Corp.* v. *Minister of Health and Novopharm Ltd.*, Court No. T–84–02, Federal Court, Trial Division (Canada), further including: Exhibit A: Curriculum Vitae of Dr. Mark Lautens, Exhibit B: Novopharm, Notice of Allegation and Detailed Statement—Carvedilol 3.125 mg, 6.25 mg, 12.5 mg, and 25 mg Tablets (Nov. 28, 2001), and Exhibit C: Canadian Patent No. 1,259,071.

Affidavit of Edwin J. Gale (Mar. 8, 2002), filed in *Hoffmann–La Roche Ltd and Smithkline Beecham Corp.* v. *Minister of Health and Novopharm Ltd.*, Court No. T–84–02, Federal Court, Trial Division (Canada), further including: Exhibit A: Canadian Patent No. 2,21,548, Exhibit B: Novopharm, Notice of Allegation and Detailed Statement—Carvedilol 3.125 mg, 6.25 mg, 12.5 mg, and 25 mg Tablets (Nov. 28, 2001), Exhibit C: Chart of Claim Types and Allowability in Canada, Exhibit D: Notice concerning acceptable claim types, Canadian Patent Office Record (May 9, 1989), Exhibit E: Canadian Patent Office Manual of Patent Office Practice, §§ 11.10–11.10.02 (Mar. 1998), and Exhibit F: Chart of Claims of Canadian Patent No. 2,212, 548, with claims grouped by type.

Copy provided by USPTO from the PIRS Image Database on 05/23/2016

Affidavit of Dr. Nadia S. Giannetti (Mar. 8, 2002), filed in *Hoffmann–La Roche Ltd and Smithkline Beecham Corp.* v. *Minister of Health and Novopharm Ltd.*, Court No. T–84–02, Federal Court, Trial Division (Canada), further including: Exhibit 1: Curriculum Vitae of Dr. Nadia S. Giannetti, Exhibit 2: Novopharm, Notice of Allegation and Detailed Statement—Carvedilol 3.125 mg, 6.25 mg, 12.5 mg, and 25 mg Tablets (Nov. 28, 2001), Exhibit 3: Canadian Patent No. 2,212,548, Exhibit 4: Chart of Articles and Patents, Exhibit 5: Letter of Feb. 18, 2002, from Nika V. Ketis, Ph.D., LL.B. (Heenan Blaikie LLP) to Judith Robinson (Ogilvy Renault) regarding Case T–84–02.

Affidavit of Dr. John Parker (Mar. 11, 2002), filed in *Hoffman–La Roche Ltd. and Smithkline Beecham Corp.* v. *Minister of Health and Novopharm Ltd.*, Court No. T–84–02, Federal Court, Trial Division (Canada), further inlcuding: Exhibit A: Curriculum Vitae of Dr. John Parker, Exhibit B: Novopharm, Notice of Allegation and Detailed Statement—Carvedilol 3.125 mg, 6.25 mg, 12.5 mg, and 25 mg Tablets (Nov. 28, 2001), Exhibit C: Canadian Patent No. 2,212,548, Exhibit D: Glossary of Terms, Exhibit E: Packer, M., et al., "The Effect of Carvedilol on Morbidity and Morality in Patients with Chronic Heart Failure," New England J. Med. 334(21), 1349–1355 (May 23, 1996), Exhibit F: Waagstein, F., "Beneficial Effects of Metoprolol in Idiopathic Dilated Cardiomyopathy," Lancet, 342, 1441–1446 (Dec. 11, 1993), Exhibit G: CIBIS Investigators and Committees, "A Randomized Trial of β–Blockade in Heart Failure," Circulation, 90(4), 1765–1773 (Oct. 1994),

Exhibit H: Pfeffer, M.A., et al., "β–Adrenergic Blockers and Survival in Heart Failure," New England J. Med. 334(21), 1396–97 (May 23, 1996), Exhibit I: Packer, M., "Effect of Carvedilol on Survival in Severe Chronic Heart Failure," New England J. Med., 344(22), 1651–1658 (May 31, 2001), Exhibit J: Beta–Blocker Evaluation of Survival Trial Investigators, "A Trial of the Beta–Blocker Bucindolol in Patients with Advanced Chronic Heart Failure," New England J. Med. 344(22), 1659–1667 (May 31, 2001) and Exhibit K: Commentary on Remaining Prior Art in Appendices A & B of the Novopharm Notice of Allegation.

Affidavit of Dr. Ian Winterborn (Mar. 11, 2002), filed in *Hoffmann–La Roche Ltd and Smithkline Beecham Corp.* v. *Minister of Health and Novopharm Ltd.*, Court No. T–84–02, Federal Court, Trial Division (Canada), further including Exhibit A: Curriculum Vitae for Dr. Ian Winterborn, Exhibit B: Novopharm, Notice of Allegation and Detailed Statement—Carvedilol 3.125 mg, 6.25 mg, 12.5 mg, and 25 mg Tablets (Nov. 28, 2001), Exhibit C: Notice of Application, *Hoffmann–La Roche Ltd and Smithkline Beecham Corp.* v. *Minister of Health and Novopharm Ltd.*, Court No. T–84–02, Federal Court, Trial Division (Canada) (Jan. 16, 2002), Exhibit D: Canadian Patent No. 2,212,548, Exhibit E: Canadian Patent No. 1,259,071, Exhibit F: Canadian Patent No. 1,129,416, and Exhibit G: United States Patent No. 4,503,067.

Affidavit of Dr. Mary Ann Lukas (Mar. 7, 2002), filed in *Hoffmann–La Roche Ltd and Smithkline Beecham Corp.* v. *Minister of Health and Novopharm Ltd.*, Court No. T–84–02, Federal Court, Trial Division (Canada), further including: Exhibit A: Curriculum Vitae for Dr. Mary Ann Lukas, Exhibit B: Canadian Patent No. 2,212,548, Exhibit C: German Patent Application No. 195 03 995.5 (PCT/EP 96/00498), Exhibit D: English Translation of German Patent Application No. 195 03 995.5 (PCT/EP 96/00498), Exhibit E: U.S. Appl. No. 08/483,635, Exhibit F: Novopharm, Notice of Allegation and Detailed Statement—Carvedilol 3.125 mg, 6.25 mg, 12.5 mg, and 25 mg Tablets (Nov. 28, 2001), Exhibit G: Loeg, H.S., et al., "Effect of Enalapril, Hyralazine Plus Isosorbide Dinitrate, and Prazonsin on Hospitalization in Patients with Chronic Congestive Heart Failure," Circulation 87(6), VI78–VI87 (Jun. 1993),

Exhibit H: DiBianco, R., et al., "A Comparison of Oral Milrinone, Digoxin, and Their Combination in the Treatment of Patients with Chronic Heart Failure," New England J. Med., 320(11), 677–683 (Mar. 1989) Exhibit I: Packer, M., et al., "Effect of Oral Milrinone on Mortality in Severe Chronic Heart Failure," New England J. Med. 325(21), 1468–75 (Nov. 21, 1991), Exhibit J: Feldman, A.M., et al., "Effects of Vesnarinone on Morbidity and Mortality in Patients with Heart Failure," New England J. Med., 329(3), 149–155 (Jul. 15, 1993) Exhibit K: Kamoterol in severe heart failure study group, "Xamoterol in Severe Heart Failure," Lancet, 336, 1–6 (Jul. 7, 1990), Exhibit L: Waagstein, F., et al., "Beneficial Effects of Metoprolol in Idiopathic Dilated Cardiomyopathy," Lancet 342, 1441–1446 (Dec. 11, 1993),

Exhibit M: CIBIS Investigators and Committees, "A Randomized Trial of β–Blockade in Heart Failure," Circulation, 90(4), 1765–1773 (Oct. 1994), Exhibit N: Packer, M., et al., "The Effect of Carvedilol on Morbidity and Morality in Patients with Chronic Heart Failure," New England J. Med. 334(21), 1349–1355 (May 23, 1996), Exhibit O: Pfeffer, M.A.., et al., "β–Adrenergic Blockers and Survival in Heart Failure," New England J. Med. 334(21), 1396–97 (May 23, 1996), Exhibit P: Packer, M., "Effect of Carvedilol on Survival in Severe Chronic Heart Failure," New England J. Med., 344(22), 1651–1658 (May 31, 2002) and Exhibit Q: Commentary on Remaining Prior Art in Appendices A and B of the Novopharm Notice of Allegation.

Respondent's Record (Pharmascience Inc.) vol. I of III filed in *GlaxoSmithKline Inc., and Smithkline Beecham Corporation* v. *The Minister of Health, and Pharmascience Inc.*, Court File No. T–1871–01 (Canada), containing an index and: Exhibit A: Exhibits to cross–examination of Dr. William T. Abraham taken on Jun. 4, 2002. "77thCardiovascular and Renal Drugs Advisory Committee meeting dated May 2, 1996," pp. 1–356.

Copy provided by USPTO from the PIRS Image Database on 05/23/2016

Respondent's Record (Pharmascience Inc.) vol. II of III filed in *GlaxoSmithKline Inc., and Smithkline Beecham Corporation* v. *The Minister of Health and Pharmascience Inc.*, Court File No. T–1871–01 (Canada), containing an Index and: Continuation of Exhibit A to Dr. William T. Abraham's cross–examination (pp. 357–572) Exhibit B: Exhibits to cross–examination of Dr. Nadia S. Giannetti taken on Jun. 21, 2002. "Study regarding sauna induced myocardial ischemia in patients with coronary artery disease," pp. 573–578. Exhibit C: Exhibits to cross–examination of Dr. Mary Ann Lukas taken on Jul. 12, 2002. 1) Precise Trial Documentation, pp. 579–752 and 2) CPS Coreg Reference, pp. 753–756.

Respondent's Record (Pharmascience Inc.) vol. III of III filed in *GlaxoSmithKline Inc., and Smithkline Beecham Corporation* v. *The Minister of Health and Pharmascience Inc.*, Court File No. T–1871–01 (Canada), containing an index and: Exhibit D: Memorandum Fact and Law, pp. 755–802. Appendix A ("Anticipation by Kelly") to Respondent's Memorandum Fact and Law, pp. 788–801.

Applicant's Record vol. 1 of 6 filed in *GlaxoSmithKline Inc. and Smithkline Beecham Corporation* v. *The Minister of Health Pharmascience Inc.*, Court No. T–1871–00 (Canada), containing an Index and: Exhibit A: Pharmascience Inc. Notice of Allegation dated Aug. 30, 2001, pp. 1–11; Exhibit B: Notice of Application issued Oct. 18, 2001 (Canada, Federal Court–Trial Division, Court No. 1871–01), pp. 12–27; Exhibit C: Pharmascience Inc. Notice of Appearance dated Oct. 26, 2001 (Canada, Federal Court–Trial Division, Court No. 1871–01), pp. 28–31; Exhibit D: Order of Prothonotary Lafreniére dated Dec. 13, 2001 (Canada, Federal Court–Trial Division, Court No. 1871–01), pp. 32–35; Exhibit E: Order of Prothonotary Lafreniére dated Mar. 7, 2002 (Canada, Federal Court–Trial Division, Court No. 1871–01), pp. 36–39; Exhibit F: Order of Prothonotary Lafreniére dated Jun. 11, 2002 (Canada, Federal Court–Trial Division, Court No. 1871–01), pp. 40–44;

Exhibit G: Confidentiality Order of Prothonotary Lafreniére dated Aug. 2, 2002 (Canada, Federal Court–Trial Division, Court No. 1871–01), pp. 45–55; Exhibit H: Affidavit of Dr. William T. Abraham sworn Jan. 29, 2002 (Canada, Federal Court–Trial Division, Court No. 1871–01), pp. 56–96, further including: Exhibit A: *Curriculum vitae*, pp. 97–142; Exhibit B: Notice of Allegation, pp. 143–154; Exhibit C: Canadian Letters Patent No. 2,212,548, pp. 155–186; Exhibit D: Glossary of medical terms, pp. 187–193; Exhibit E: Further commentary on prior art, pp. 194–209; Exhibit I: Transcript of cross–examination of Dr. Abraham taken on Jun. 4, 2002 (Canada, Federal Court–Trial Division, Court No. 1871–01), pp. 210–350, further including Exhibit 1 (Vogel et al., 24 Am. J. Cardiology 198–207 (1969)), Exhibit 2 (Bristow et al., 94 Circulation 2807–2816 (1996)), Exhibit 3 (Gilbert et al., 94 Circulation 2817–2825 (1996)), and Exhibit 4 (Shakar et al., 31 JACC 1336–1340 (1998));

Exhibit J: Affidavit of Dr. Nadia S. Giannetti sworn Jan. 30, 2002 (Canada, Federal Court–Trial Division, Court No. 1871–01), pp. 351–371, further including: Exhibit 1: *Curriculum vitae*, pp. 372–384; Exhibit 2: Notice of Allegation, pp. 385–396; Exhibit 3: Canadian Letters Patent No. 2,212, 548, pp. 397–428; Exhibit 4: List of prior art referenced in Notice of Allegation, pp. 429–438; Exhibit K: Transcript of cross–examination of Dr. Giannetti taken on Jun. 21, 2002 (Canada, Federal Court–Trial Division, Court No. 1871–01), pp. 439–529.

Applicants' Record vol. 2 of 6 filed in *GlaxoSmithKline Inc., and Smithkline Beecham Corporation* v. *The Minister of Health and Pharmascience Inc.*, Court No. T–1871–00 (Canada), containing an Index and: Exhibit L: Affidavit of Patricia N. Jansons sworn Jan. 24, 2002 (Canada, Federal Court–Trial Division, Court No. 1871–01), pp. 530–540, further including: Exhibit A: Certified copy of Canadian Letters Patent No. 1,259,071, pp. 541–583; Exhibit B: Certified copy of the Abstract of Title for Canadian Letters Patent No. 1,259,071, pp. 584–585; Exhibit C: Certified copy of Canadian Letters Patent No. 2,212,548, pp. 586–617; Exhibit D: Certified copy of the Abstract of Title for Canadian Letters Patent No. 2,212,548, pp. 618–619; Exhibit E: Copy of CPS entry for COREG™, pp. 620–625; Exhibit F: Copies of the 76 prior art references listed as paragraphs 1 to 13 and Appendix A of the Notice of Allegation (Tabs 1–46), pp. 626–1022.

Applicants' Record vol. 3 of 6 filed in *GlaxoSmithKline Inc., and Smithkline Beecham Corporation* v. *The Minister of Health and Pharmascience Inc.*, Court No. T–1871–00 (Canada), containing an Index and: Exhibit L (cont.): Exhibit F: Copies of the 76 prior art references listed at paragraphs 1 to 13 and Appendix A of the Notice of Allegation (Tabs 47–76), pp. 1023–1186; Exhibit M: Affidavit of Dr. Mary Ann Lukas sworn Jan. 30, 2002 (Canada, Federal Court–Trial Division, Court No. 1871–01), pp. 1187–1212, further including: Exhibit A: *Curriculum vitae*, pp. 1214–1221, Exhibit B: Canadian Letters Patent No. 2,212,548, pp. 1222–1253; Exhibit C: German Patent Application No. 19503995.5 dated Feb. 8, 1995, pp. 1254–1260; Exhibit D: English translation of German Application, pp. 1261–1267; Exhibit E: U.S. Appl. No. 08/483,635 dated Jun. 7, 1995, pp. 1268–1290; Exhibit F: Notice of Allegation, pp. 1291–1302; Exhibit G: Loeb publication, 1993, pp. 1303–1313;

Exhibit H: DiBianco publication, 1989, pp. 1314–1321; Exhibit I: Packer publication, 1991, pp. 1322–1330; Exhibit J: Feldman publication, 1993, pp. 1331–1338; Exhibit K: Results of Xamoterol Trial, pp. 1339–1345; Exhibit L: Results of Metoprolol in Dilated Cardiomyopathy (MDC) Trial, pp. 1346–1352; Exhibit M: Results of the CIBIS I Trial, pp. 1353–1362; Exhibit N: Results of the U.S. Carvedilol Trials, pp. 1363–1370; Exhibit O: Pfeffer editorial on U.S. Carvedilol Trials, pp. 1371–1373; Exhibit P: Results of COPERNICUS Trial, pp. 1374–1382; Exhibit Q: Further commentary om prior art, pp. 1383–1393.

Applicants' Record vol. 4 of 6 filed in *GlaxoSmithkline Inc., and Smithkline Beecham Corporation* v. *The Minister of Health and Pharmascience Inc.*, Court No. T–871–00 (Canada), containing an Index and: Exhibit N: Transcript of cross–examination of Dr. Lukas taken on Jul. 12, 2002 (Canada, Federal Court–Trial Division, Court No. T–1871–01), pp. 1394–1795, further including Exhibit 1 (SmithKline Beecham Pharm., SK&F 105517/Carvedilol, protocol 220 (Oct. 20, 1993), Exhibit 2 (SmithKline Beecham Pharm., SK&F 105517/Carvedilol, protocol 221 (Oct. 20, 1993)), Exhibit 3 (SmithKline Beecham Pharm., SK&F 105517/Carvedilol, protocol 239 (Jun. 9, 1994)), Exhibit 4 (SmithKline Beecham Pharm., SK&F 105517/Carvedilol, protocol 240 (Jan. 25, 1994)); Exhibit O: Affidavit of Dr. John Parker sworn Jan. 31, 2002 (Canada, Federal Court–Trial Division, Court No. T–1871–01), pp. 1796–1828, further including: Exhibit A: *Curriculum vitae*, pp. 1829–1851;

Copy provided by USPTO from the PIRS Image Database on 05/23/2016

Exhibit B: Notice of Allegation, pp. 1852–1863; Exhibit C: Canadian Letters Patent No. 2,212,548, pp. 1864–1896; Exhibit D: Glossary of medical terms, pp. 1897–1903; Exhibit E: Results of U.S. Carvedilol Trials, pp. 1904–1910; Exhibit F: Results of Metoprolol in Dilated Cardiomyopathy (MDS) Trials, pp. 1911–1917; Exhibit G: Results of CIBIS I Trial, pp. 1918–1927; Exhibit H: Pfeffer editorial on U.S. Carvedilol Trials, pp. 1928–1930; Exhibit I: Results of COPERNICUS Trial, pp. 1931–1939; Exhibit J: Results of BEST Trial, pp. 1940–1949; Exhibit K: Further commentary in prior art, pp. 1950–1959; Exhibit P: Transcript of cross–examination of Dr. Parker taken on Jul. 3, 2002, pp. 1960–2082.

Applicants' Record vol. 5 of 6 filed in *GlaxoSmithKline Inc., and Smithkline Beecham Corporation* v. *The Minister of Health and Pharmascience Inc.*, Court No. T–1871–00, containing an Index and: Exhibit Q: Affidavit of Dr. Bertram Pitt sworn Apr. 1, 2002 (Canada, Federal Court–Trial Division, Court No. T–1871–01), pp. 2083–2121, further including Exhibit A: *Curriculum vitae*, pp. 2122–2193; Exhibit B: Comparison document prepared by Hitchman & Sprigings, pp. 2194–2209; Exhibit R: Transcript of cross–examination of Dr. Pitt taken on Jun. 24, 2002 (Canada, Federal Court–Trial Division, Court No. T–1871–01), pp. 2210–2284; Exhibit S: Affidavit of Dr. Robert Rangno sworn Apr. 1, 2002 (Canada, Federal Court–Trial Division, Court No. T–1871–01), pp. 2285–2324, further including Exhibit 1: *Curriculum vitae*, pp. 2325–2342; Exhibits 2–4 not included: Documents struck by Canadian Court order dated Jun. 11, 2002

Exhibit T: Transcript of cross–examination of Dr. Rangno taken on Jun. 26, 2002 (Canada, Federal Court–Trial Division, Court No. T–1871–01), pp. 2346–2411; Exhibit U: Affidavit of Patrick Taylor sworn Apr. 2, 2002 (Canada, Federal Court–Trial Division, Court No. T–1871–01), pp. 2412–2414, further including: Exhibit A: Product Monograph for COREG™ (carvedilol), pp. 2415–2419; Exhibit B: Further Detailed Information of the Prior Art References found in Appendix "A" to the Pharmascience notice of Allegation, pp. 2420–2463; Exhibits C–F not included: Documents struck by Canadian Court order dated Jun. 11, 2002; Exhibit V: Affidavit of Dr. Lawrence Zisman sworn Apr. 1, 2002 (Canada, Federal Court–Trial Division, Court No. T–1871–01), pp. 2469–2490, further including Exhibit A: *Curriculum vitae*, pp. 2491–2504; Exhibit B: Comparison document prepared by Hitchman & Sprigings, pp. 2505–2521;

Exhibit W: Transcript of cross–examination of Dr. Zisman taken on Jul. 10, 2002, pp. 2522–2592.

Applicants' Record vol. 6 of 6 filed in *GlaxoSmithKline Inc., and Smithkline Beecham Corporation* v. *The Minister of Health and Pharmascience Inc.*, Court No. T–1871–00, further including: Exhibit X: Written Representations, Applicants' Memorandum of Fact and Law, pp. 2593–2623.

Affidavit of Edwin J. Gale, Mar. 8, 2002, filed in *Hoffmann–La Roche Limited, and Smithkline Beecham Corporation* v. *The Minister of Health, and Novopharm Limited*, Court No. T–84–02, further including: Exhibit A: Copy of Canadian Letters Patent No. 2,212,548; Exhibit B: Notice of Allegation dated Nov. 28, 2001 from Novapharm Limited to Hoffmann–La Roche; Exhibit C: Chart of Edwin J. Gale illustrating various claim types used to cover pharmaceuticals including first and second medical uses and pharmaceuticals: Exhibit D: Practice Notice regarding Chemical Patent Practice from the Canadian Patent Office Record of May 9, 1989; Exhibit E: Copy of section on Method of Use and Use claims from the Canadian Manual of Patent Office Practice dated Mar. 1998; Exhibit F: Copy of Canadian Patent No. 2,212,548 claims grouped by type.

Applicants' Record filed in *GlaxoSmithKline Inc. and Smithkline Beecham Corporation* v. *Apotex Inc. and The Minister of Health*, Court File No. T–2105–02 (Canadian Federal Court–Trial Division), containing an Index and: Exhibit A: Apotex Inc. Notice of Allegation dated Nov. 1, 2003, pp. 1–2; Exhibit B: Notice of Application dated Dec. 16, 2002, pp. 3–13; Exhibit C: Apotex Inc. Notice of Appearance dated Dec. 20, 2002, pp. 14–16; Exhibit D: Minister of Health Notice of Appearance dated Dec. 31, 2002, pp. 17–18; Exhibit E: Affidavit of Lidia O. Derewlany sworn on Feb. 14, 2003, pp. 19–23, further including: Exhibit 1: Canadian Patent No. 2,212,548, pp. 24–54; Exhibit 2: Abstract of title for Canadian Patent No. 2,212,548, pp. 55–56; Exhibit 3: German Patent Application No. 19503995.5, pp. 57–63; Exhibit 4: English translation of German Patent Application No. 19503995.5, pp. 64–70; Exhibit 5: U.S. Appl. No. 08/483,635, pp. 71–92;

Exhibit 6: Notice of Compliance dated Feb. 17, 1995 and approved product monograph for Kredex tablets, pp. 93–115; Exhibit 7: Cover page of the S/NDS dated Dec. 13, 1995 for Coreg™ tablets (redacted), pp. 116–118; Exhibit 8: Correspondence from Viera Pastorek, Health Canada, dated Jan. 10, 1996, pp. 119–121; Exhibit 9: Notice of Compliance dated Sep. 30, 1996, pp. 122–160; Exhibit 10: Health Canada Patent Lists filed by Hoffman–La Roche for Coreg™ tablets, pp. 161–165; Exhibit 11: Cover page for the Sep. 13, 2001 S/NDS filed by GlaxoSmithKline Inc., pp. 166–167; Exhibit 12: Correspondence from A. Minkiewicz–Janda dated Oct. 29, 2001, pp. 168–171; Exhibit 13: Health Canada Patent Lists filed by GlaxoSmithKline Inc., pp. 172–176; Exhibit 14: Notice of Compliance dated Apr. 10, 2002 and approved product monograph for Coreg™ tablets, pp. 177–227; Exhibit F: Transcript of cross–examination of Lidia O. Derewlany taken Apr. 24, 2003, pp. 229–269;

Exhibit G: Correspondence dated May 23, 2003 for Ogilvy Renault to Goodmans LLP, pp. 270–271; Exhibit H: Affidavit of Dianne Kathleen Grisé sworn on Feb. 14, 2003, pp. 272–275; Exhibit I: Transcript of cross–examination of Dianne Kathleen Grisé taken May 6, 2003, pp. 276–312; Exhibit J: Affidavit of Bernard Sherman sworn on Mar. 7, 2003, pp. 313–315; Exhibit K: Written Representations, memorandum of Fact and Law, of GlaxoSmithKline and SmithKline Beecham Corporation dated Jun. 5, 2003, pp. 316–346.

Copy provided by USPTO from the PIRS Image Database on 05/23/2016

Applicants' Record, vol. 1 of 7, filed in *Hoffmann–La Roche Limited and Smithkline Beecham Corporation* v. *The Minister of Health and Novopharm Limited*, Court No. T–84–02 (Canadian Federal Court–Trial Division), containing an Index and: Exhibit A: Novopharm Limited Notice of Allegation dated Nov. 28, 2001, pp. 1–20; Exhibit B: Notice of Application issued Jan. 16, 2002, pp. 21–36; Exhibit C: Novopharm Limited Notice of Appearance dated Jan. 18, 2002, pp. 37–39; Exhibit D: Minister of Health Notice of Appearance dated Jan. 24, 2002, pp. 40–41; Exhibit E: Order of Prothonotary Lafreniére dated Feb. 11, 2002, pp. 42–44; Exhibit F: Confidentiality Order of Prothonotary Lafreniére dated Feb. 11, 2002, pp. 45–52; Exhibit G: Correspondence dated Feb. 18, 2002 from Heenan Blaikie, counsel for the Respondent, Novopharm Limited to Ogilvy Renault, counsel for the Applicants, pp. 53–55;

Exhibit H: Order of Prothonotary Lafreniére dated Nov. 4, 2002, pp. 56–57; Exhibit I: Correspondence dated Jan. 27, 2003 from Heenan Blaikie, counsel for the Respondent, Novopharm Limited to Ogilvy Renault, counsel for the Applicants, pp. 53–57a; Exhibit J: Affidavit of Patricia N. Jansons sworn Mar. 4, 2002, pp. 58–72, further including: Exhibit A: Certified copy of Canadian Letters Patent No. 1,259,071, pp. 73–115; Exhibit B: Certified copy of the Abstract of Title for Canadian Letters Patent No. 1,259,071, pp. 116–117; Exhibit C: Certified copy of Canadian Letters Patent No. 2,212,548, pp. 118–146; Exhibit D: Certified copy of the Abstract of Title for Canadian Letters Patent No. 2,212,548, pp. 147–148; Exhibit E: Copy of CPS entry for COREG™, pp. 149–154; Exhibit F: Copies of the 104 prior art references listed at page 5 & 6 and Appendix A & B of the Novopharm Notice of Allegation, pp. 155–534.

Applicants' Record, vol. 3 of 7, filed in *Hoffmann–La Roche Limited, and Smithkline Beecham Corporation* v. *The Minister of Health and Novopharm Limited*, Court No. T–84–02, further including: Exhibit K: Affidavit of Dr. Mary Ann Lukas sworn Mar. 7, 2002, pp. 1026–1059, further including: Exhibit A: *Curriculum vitae*, pp. 1060–1067; Exhibit B: Canadian Letters Patent No. 2,212,548, pp. 1068–1105; Exhibit C: German Patent Application No. 19503995.5 dated Feb. 8, 1995, pp. 1106–1112; Exhibit D: English translation of German Application, pp. 1113–1119; Exhibit E: U.S. Appl. No. 08/483,635 dated Jun. 7, 1995, pp. 1120–1141; Exhibit F: Novopharm Notice of Allegation (Nov. 28, 2001), pp. 1142–1162; Exhibit G: Loeb et al., 87 Circulation VI–78 to VI–87 (1993), pp. 1163–1173; Exhibit H: DiBianco et al., 320 N.E.J. Med. 677–683 (1989), pp. 1174–1181; Exhibit I: Packer et al., 325 N.E.J. Med. 1468–1475 (1991), pp. 1182–1190;

Exhibit J: Feldman et al., 329 N.E.J. Med. 149–155 (1993), 1191–1198; Exhibit K: Results of Xamoterol Trial, 336 Lancet 1–6 (1990), pp. 1199–1205; Exhibit L: Results of the Metoprolol in Dilated Cardiomayopathy (MDS) Trial, 342 Lancet 1441–46 (1993), pp. 1206–1212; Exhibit M: Results of the CIBIS I Trial, 90 Circulation 1765–1773 (1994), pp. 1213–1222; Exhibit N: Results of the U.S. Carvedilol Trials, 334 N.E.J. Med. 1349–1355, pp. 1223–1230; Exhibit O: Pfeffer editorial on U.S. Carvedilol Trials 334 N.E.J. Med. 1396–1397, pp. 1231–1233; Exhibit P: Results of COPERNICUS Trial, 344 N.E.J. Med. 1651–1658, pp. 1234–1242; Exhibit Q: Further commentary on prior art, pp. 1243–1256; Exhibit L: Transcript of cross–examination of Dr. Lukas taken on Jan. 28, 2003, pp. 1257–1333; Exhibit M: Affidavit of Dr. William T. Abraham sworn Mar. 8, 2002, pp. 1334–1382, further including: Exhibt A: *Curriculum vitae*, pp. 1383–1428; Exhibit B: Notice of Allegation (pp. 3–19), pp. 1429–1449;

Exhibit C: Canadian Letters Patent No. 2,212,548, pp. 1450–1481; Exhibit D: Glossary of medical terms, pp. 1482–1488, Exhibit E: Further commentary on prior art, pp. 1489–1506; Exhibit N: Transcript of cross–examination of Dr. Abraham taken on Nov. 26, 2002, pp. 1507–1628, further including: Exhibit 1: Abraham et al., 39 Advances in Internal Medicine, 22–47 (1994); Exhibit 2: Results of CONSENSUS Trial, 316 N.E.J. Med. 1429–1435 (1987); Exhibit 3: Bristow et al., 94 Circulation, 2807–16 (1996); Exhibit 4: Shakar et al., 31 JACC 1336–1340 (1998), Exhibit 5: Gilbert et al., 94 Circulation 2817–25 (1996); Exhibit 6: Abraham et al., 22 Hepatology, 737–743 (1995).

Applicants' Record, vol. 4 of 7, filed in *Hoffmann–La Roche Limited, and Smithkline Beecham Corporation* v. *The Minister of Health, and Novopharm Limited*, Court No. T–84–02, containing an Index and: Exhibit O: Affidavit of Dr. Nadia S. Giannetti sworn Mar. 8, 2002, pp. 1629–1656 further includingg Exhibit 1: *Curriculum vitae*, pp. 1657–1669; Exhibit 2: Novopharm Notice of Allegation (Nov. 28, 2001), pp. 1670–1690; Exhibit 3: Canadian Letters Patent No. 2,212,548, pp. 1691–1723; Exhibit 4: List of prior art referenced in Notice of Allegation, pp. 1724–1737; Exhibit 5: Correspondence from Heenan Blaikie to Ogilvy Renault dated Feb. 18, 2002, pp. 1739–1742; Exhibit P: Transcript of cross–examination of Dr. Giannetti taken on Dec. 20, 2002, pp. 1743–1842, further including Exhibit 1: Johnstone et al., 10 Can. J. Cardiol 613–631 (1994); Exhibit 2: Giannetti et al., 107 Am. J. Med., 228–233 (1999);

Exhibit 3: Cecere et al., Can J Cardiol, vol. 17, Supp C, Abstract 272 (Sep. 2001); Exhibit 4: Cecere et al., Can J Cardiol, vol. 17, Supp C, Abstract 376 (Sep. 2001); Exhibit 5: Cantarovich et al., J. Heart Lung Trans, vol. 20(2), Abstract 246 (2001); Exhibit 6: Cantarovich et al., J. Heart Lung Trans, vol. 20(2), Abstract 166 (2001); Exhibit Q: Affidavit of Dr. Mark Lautens sworn Mar. 8, 2002, pp. 1843–1847, further including Exhibit A: *Curriculum vitae*, pp. 1848–1877; Exhibit B: Novopharm Notice of Allegation (Nov. 28, 2001), pp. 1878–1898; Exhibit C: Canadian Letters Patent No. 1,259,071, pp. 1899–1941; Exhibit R: Affidavit of Edwin Gale sworn Mar. 8, 2002, pp. 1942–1951, further including: Exhibit A: Copy of Canadian Letters Patent No. 2,212,548, pp. 1952–1983; Exhibit B: Novopharm Notice of Allegation (Nov. 28, 2001), pp. 1984–2004; Exhibit C: Chart illustrating various claim types used to cover pharmaceuticals, pp. 2005–2006;

Copy provided by USPTO from the PIRS Image Database on 05/23/2016

Exhibit D: Practice Notice regarding Chemical Patent Practice taken from the Canadian Patent Office Record of May 9, 1989, pp. 2007–2008; Exhibit E: Section 11.10.02 entitled "Method of Use and Use Claims" from the Canadian Manual of Patent Office Practice, pp. 2009–2013; Exhibit F: Canadian Letters Patent No. 2,212,548 claims grouped by type, pp. 2014–2015.

Applicants' Record, vol. 5 of 7 , filed in *Hoffmann–La Roche Limited, and Smithkline Beecham Corporation* v. *The Minister of Health, and Novopharm Limited*, Court No. T–84–02, containing an Index and: Exhibit S: Affidavit of Dr. John Parker sworn Mar. 11, 2002, pp. 2016–2054, further including: Exhibit A: *Curriculum vitae*, pp. 2055–2077; Exhibit B: Notice of Allegation, pp. 2078–2098; Exhibit C: Canadian Letters Patent No. 2,212, 548, pp. 2099–2130; Exhibit D: Glossary of medical terms, pp. 2131–2137; Exhibit E: Parker et al., 334 N.E.J. Med. 1349–1355 (1996), pp. 2138–2145; Exhibit F: Results of the Metoprolol in Dilated Cardiomyopathy (MDC) Trial 342 Lancet 1441–1446 (1993), pp. 2146–2152; Exhibit G: Results of CIBIS I Trial 90 Circulation, 1765–1773 (1994), pp. 2153–2162; Exhibit H: Pfeffer editorial on U.S. Carvedilol Trials, 334 N.E.J. Med. 1396–1397 (1996), pp. 2163–2165;

Exhibit I: Results of COPERNICUS Trial, 344 N.E.J. Med. 1651–1658 (2001), pp. 2166–2174; Exhibit J: Results of BEST Trial, 334 N.E.J. Med. 1659–1667 (2001), pp. 2175–2184; Exhibit K: Further commentary on prior art, pp. 2185–2196; Exhibit T: Transcript of cross–examination of Dr. Parker taken on December 18, 2002, pp. 2197–2364, further including Exhibit 1: Johnstone et al., 10 Can J. Cardiol 613–631 (1994); Exhibit 2: Parker, 19 Eur. Heart J. Suppl. I 115–119 (1998); Exhibit 3: Rapaport et al., 101 Am. J. Med. 4A–61S–4A70S (1996); Exhibit 4: Al–Hesayen et al., 39 JACC 1269–1274 (2002); Exhibit 5: Azevedo et al., Circulation 2053–2056 (2000); Exhibit 6: Parker et al., 84 Circulation 1040–1048 (1991); Exhibit 7: Azevedo et al., 33 JACC 186–191 (1999); Exhibit 8: Azevedo et al., Circulation 274–279 (1999); Exhibit U: Affidavit of Dr. Ian Winterborn sworn Mar. 11, 2002, pp. 2365–2380, further including: Exhibit A: *Curriculum vitae*, pp. 2381–2385;

Exhibit B: Notice of Allegation (Nov. 28, 2001), pp. 2386–2406; Exhbit C: Notice of Application, pp. 2407–2423; Exhibit D: Canadian Letters Patent No. 2,212, 548, pp. 2424–2455; Exhibit E: Canadian Letters Patent No. 1,259,071, pp. 2456–2498; Exhibit F: Canadian Letters Patent No. 1,129,416, pp. 2499–2548; Exhibit G: United States Letters Patent No. 4,503,067, pp. 2549–2559.

Applicants' Record, vol. 6 of 7, filed in *Hoffmann–La Roche Limited, and Smithkline Beecham Corporation* v. *The Minister of Health, and Novopharm Limited*, Court No. T–84–02, containing an Index and: Exhibit V: Affidavit of Dr. Mitchell Arnold Henry Levine sworn Aug. 15, 2002, pp. 2560–2583, further including: Exhibit A: *Curriculum vitae*, pp. 2584–2614; Exhibit W: Transcript of cross–examination of Dr. Mitchell Arnold Henry Levine taken on Nov. 29, 2002, pp. 2615–2673, further including Exhibit A: Book entitled "Drugs of Choice: A Formulary for General Practice" (Canadian Medical Association: Toronto, 1995), pp. 2674–2849; Exhibit X: Affidavit of Dr. Michael Bohm sworn Aug. 16, 2002, pp. 2850–2875, further including Exhibit A: *Curriculum vitae*, pp. 2876–2980; Exhibit Y: Transcript of cross–examination of Dr. Michael Bohm taken on Dec. 9, 2002, pp. 2981–3028, further including:

Exhibit 1: Article entitled "Different Intrinsic Activities of Bucidolol, Carvedilol and Metoprolol in Human Failing Myocardium," British Journal of Pharmacology (2000), 130, 1131–1139, pp. 3029–3037; Exhibit 2: Article entitled "Prospective Crossover Comparison of Carvedilol and Metoprolol in Patients with Chronic Heart Failure," American College of Cardiology, 38(4), 934–46 (2001), pp. 3038–3045; Exhibit 3: "β–Blocker Treatment of Chronic Heart Failure with Special Regard to Carvedilol" from book entitled "Heart Rate is a Determinant of Cardiac Function—Basic Mechanism and Clinical Significance," G. Hasenfuss et al. ed. (Steinkopff Verlung Darmstadt 2000) pp. 3046–3067. Exhibit Z: Affidavit of Dr. Robert Rangno sworn Aug. 20, 2002, pp. 3068–3094, further including Exhibit A: *Curriculum vitae*, pp. 3095–3102. Exhibit AA: Transcript of cross–examination of Dr. Rangno taken on Nov. 15, 2002, pp. 3103–3152.

Affidavit of Dr. Mark Lautens filed in *GlaxoSmithKline Inc., and Smithkline Beecham Corporation* v. *The Minister of Health, and Apotex Inc.*, Court No. T–149–02, further including: Exhibit A: *Curriculum vitae*; Exhibit B: Dec. 12, 2001 Notice of Allegation from Apotex Inc. to Smithkline Beecham Pharma Inc.; Exhibit C: Canadian Letters Patent No. 1,259,071;

Notice of Application filed in *GlaxoSmithKline Inc., and Smithkline Beecham Corporation* v. *The Minister of Health, and Apotex Inc.*, Court No. T–149–02.

Record of the Respondent, Apotex Inc., filed in *GlaxoSmithKline Inc. and Smithkline Beecham Corporation* v. *The Minister of Health and Apotex Inc.*, Court File No. T–149–02, further including: Exhibit 1: Memorandum of Fact and Law of the Respondent, Apotex Inc.

Reasons for Order and Order, filed in *GlaxoSmithKline Inc. and Smithkline Beecham Corporation* v. *The Minister of Health and Pharmascience Inc.*, Court No. T–1871–01.

Amended Reasons for Order and Order, filed in *GlaxoSmithkline Inc. and Smithkline Beecham Corporation* v. *The Minister of Health and Pharmascience Inc.*, Court No. T–1871–01.

J. of Cardiovascular Pharm: DasGupta. et al., "The Effects of Intravenous Caredilol. A New Multiple Action Vasodilatory β–Blocker, in Cogestive Heart Failure" 1991, vol. 18, (Suppl 1): pp. S12–S16.*

J. of Cardiovascular Pharm; DasGupta et al., 1990 vol. 19, (Suppl. 1): pp. 562–567.*

Circulation; H. Krum et al., "Effects of Carvedilol, a Vasodilator–βBlocker in Patients with Congestive Heart Failure Due to Ishchemic Heart Disease". 1995, vol. 92, No. 2. pp. 212–218.*

CBS–TV; CBS Evenings News Transcript Jan. 27, 1993, 6:30–7:00 pm.*

CNBC; Steals and Deals, Transcript Jan. 29, 1993, 8:30pm.*

Circulation, DasGupta. et al., 1989, vol. 80, No. 4, (Suppl. II): pp. 116–117.*

Jan. 23, 2007 Office Action issued in U.S. Appl. No. 10/721,122, 7 pages.

As–filed Apr. 2, 2007, Response to Jan. 23, 2007, Office Action in U.S. Appl. No. 10/721,022, 68 pages.

Cleland et al., "Clinical trials update from the American College of Cardiology: darbepoetin alfa, Asteroid, Universe, paediatric carvedilol, Unload and Iceland," European Journal of Heart Failure, 8, pp. 326–329, 2006.

Copy provided by USPTO from the PIRS Image Database on 05/23/2016

Shaddy et al., "The pediatric randomized carvedilol trial in children with chronic heart failure: Rationale and design," American Heart Journal, vol. 44, No. 3, pp. 383–389, Sep. 2002.

Summary Report, Study No.: SK&F–105517/321, "A Multicenter, placebo–controlled, 8–month study of the effect of twice daily carvedilol in children with congestive heart failure due to systemic ventricular systolic dysfunction," pp. 1–9, Jul. 2006.

Clinical Study Report, Study No.: SK&F–105517/321, "A Multicenter, placebo–controlled, 8–month study of the effect of twice daily carvedilol in children with congestive heart failure due to systolic dysfunction," abstract and cover pp. 1–4 and Clinical Study Report pp. 1–238, 266, 342–360, Jul. 17, 2006.

Summary Report, Study No.: SK&F–105517/396, "A Multicenter Open–label Extension Study to Evaluate the Safety of Twice Daily Oral Carvedilol in Pediatric Subjects with Chronic Heart Failure," abstract and cover pages pp. 1–4.

Clinical Study Report, Study No.: SK&F–105517/396, "A Multicenter Open–label Extension Study to Evaluate the Safety of Twice Daily Oral Carvedilol in Pediatric Sujects with Chronic Heart Failure," abstract and cover pages pp. 1–4 and Clinical Study Report pp. 1–135,, Aug. 2006.

J. of Cardiovascular Pharm; Senior, et al. "Effects of Carvedilol on Ventricular Arrhythmais", 1992, vol. 19, (Suppl). 1): pp: S117–S121.*

British J. of Urology; Caine, et al., "The Use of Alpha–adrenergic Blockers in Benign Prostatic Obstruction", 1976, vol. 48, pp. 255–263.*

British J. of Urology; H.N. Whitfield, et al., "The Effect of Adrenergic Blocking Drugs on Outflow Resistance", 1976, vol. 47, pp. 823–827.*

American J. of Cardiology; DasGupta, et al., "Value of Carvedilol in Congestive Heart Failure Secondary to Coronary Artery Disease", 1990, vol. 66, pp. 1118–1123.*

Z. Kardiol; A. Buchwald, et al., "Acute Hemodynamic Effects of the Beta–blocker Carvedilol in Heart Failure", 1990, vol. 79, No. 6, pp. 424–428.*

JACC; CiLenarda, et al., "Acute Hemodynamic Effects of Carvedilol Versus Metroprolol In Idiopathic Dilated Cardiomyopathy", 1991, vol. 17, No. 2, Abstract 142A.*

J. of Hypertension, C. Rosendorff, "Beta–blocking agents with vasodilator activity ", 1993, vol. 11, (Suppl. 4): pp. S37–S40.*

Cardiology; J. Lessem, et al., "Development of a Multication Beta–blocker", 1993, vol. 82, (Suppl. 3): pp. 50–58.*

Drug Safety; W.J. Louis, et al., "A Risk–Benefit Assessment of Carvedilol in the Treatment of Cardiovascular Disorders", 1994, vol. 11 No. 2, pp. 86–93.*

Drugs; McTavis, et al., "Carvedilol—A Review of its Pharmacodynamic and Pharmacokinetic Properties, and Therepeutic Efficacy", 1993, vol. 45, No. 2, pp. 232–258.*

Drugs of Today; Ruffolo, et al., "Carvedilol (Kredex): A Novel Multiple Action Cadiovascular Agent", 1991, vol. 27, No. 7, pp. 465–492.*

* cited by examiner

Copy provided by USPTO from the PIRS Image Database on 05/23/2016

METHOD OF TREATMENT FOR DECREASING MORTALITY RESULTING FROM CONGESTIVE HEART FAILURE

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

FIELD OF THE INVENTION

The present invention relates to a new method of treatment using compounds which are dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists, in particular the carbazolyl-(4)-oxypropanolamine compounds of Formula I, preferably carvedilol, for decreasing the mortality of patients suffering from congestive heart failure (CHF). The invention also relates to a method of treatment using compounds which are dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists, in particular the carbazolyl-(4)-oxypropanolamine compounds of Formula I, preferably carvedilol, in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of angiotensin converting enzyme (ACE) inhibitors, diuretics, and digoxin, for decreasing the mortality of patients suffering from CHF.

BACKGROUND OF THE INVENTION

Congestive heart failure occurs as a result of impaired pumping capability of the heart and is associated with abnormal retention of water and sodium. Traditionally, treatment of chronic mild failure has included limitation of physical activity, restriction of salt intake, and the use of a diuretic. If these measures are not sufficient, digoxin, which is an agent that increases the force of mycardial contraction, is typically added to the treatment regiment. Subsequently, angiotensin converting enzyme inhibitors, which are compounds that prevent the conversion of angiotensin I into the pressor-active angiotensin II, are prescribed for chronic treatment of congestive heart failure, in conjunction with a diuretic, digoxin, or both.

Congestive heart failure is a condition that is associated with activation of both the renin-angiotenin system (RAS) and the sympathetic nervous system (SNS). Modulation of the RAS by angiotensin converting enzyme inhibitors has been shown to improve the symptoms associated with CHF. Sharpe, D. N., Murphy, J., Coxon, R. & Hannan S. F. (1984) Circulation, 70, 271–278. However, ACE inhibitors appear to have little effect on the enhanced SNS in CHF. Cohn, J. N., Johnson, G. & Ziesche, S., (1991) N. Engl. J. Med., 325, 293–302 and Francis, G. S., Rector, T. S. & Cohn, J. N. (1988) Am. Heart J., 116, 1464–1468. Therefore, there is a need for an agent that would be effective in blocking the activation of the SNS in CHF patients.

Also, congestive heart failure is a well-known cardiac disorder which results in an annual mortality in excess of 50 percent. Applefeld, M. M., (1986) Am. J. Med., 80, Suppl. 2B, 73–77. Therefore, therapeutic agents that would decrease the mortality resulting from CHF in patients suffering therefrom are highly desirable.

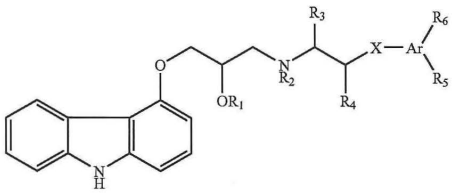
SUMMARY OF THE INVENTION

The present invention provides a new method of treatment using pharmaceutical compounds which are dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists and, in particular, the carbazolyl-(4)-oxypropanolamine compounds of Formula I, alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of ACE inhibitors, diuretics, and digoxin, as therapeutics for decreasing mortality resulting from congestive heart failure in mammals, particularly humans. In particular, the present invention preferably provides a method of treatment, alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of ACE inhibitors, diuretics, and digoxin, for the compound of Formula I wherein R_1 is —H, R_2 is —H, R_3 is —H, R_4 is —H, X is O, Ar is phenyl, R_5 is ortho —OCH_3, and R_6 is —H, said compound being better known as carvedilol, which is (1-(carbazol-4-yloxy-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol), or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

U.S. Pat. No. 4,503,067 discloses carbazolyl-(4)-oxypropanolamine compounds of Formula I:

(I)



wherein:

R_1 is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R_2 is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R_3 is hydrogen or lower alkyl of up to 6 carbon atoms;

R_4 is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R_4 together with R_5 can represent —CH_2—O—;

X is a valency bond, —CH_2, oxygen or sulfur;

Ar is selected from phenyl, naphthyl, indanyl and tetrahydronaphthyl;

R_5 and R_6 are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a —$CONH_2$— group, lower alkoxy of up to 6 carbon atoms, benzloxy, lower alkylthio of up to 6 carbon atoms, lower alkysulphinyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

R_5 and R_6 together represent methylenedioxy;

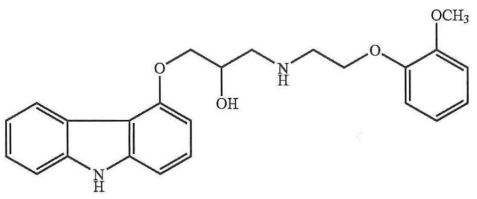
and pharmaceutically acceptable salts thereof.

This patent further discloses a compound of Formula I, better known as carvedilol, which is (1-(carbazol-4-yloxy-

Copy provided by USPTO from the PIRS Image Database on 05/23/2016

3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol), having the structure shown in Formula II:

(II)



Formula I compounds, of which carvedilol is exemplary, are novel multiple action drugs useful in the treatment of mild to moderate hypertension. Carvedilol is known to be both a competitive non-selective β-adrenoceptor antagonist and a vasodilator, and is also a calcium channel antagonist at higher concentrations. The vasodilatory actions of carvedilol result primarily from α_1-adrenoceptor blockade, whereas the β-adrenoceptor blocking activity of the drug prevents reflex tachycardia when used in the treatment of hypertension. These multiple actions of carvedilol are responsible for the antihypertensive efficacy of the drug in animals, particularly in humans. See Willette, R. N., Sauermelch, C. F. & Ruffolo, R. R., Jr. (1990) Eur. J. Pharmacol., 176,237–240; Nichols, A. J., Gellai, M. & Ruffolo, R. R., Jr. (1991) Fundam. Clin. Pharmacol., 5, 25–38; Ruffolo, R. R., Jr., Gellai, M., Hieble, J. P., Willette, R. N. & Nichols, A. J. (1990) Eur. J. Clin. Pharmacol., 38, S82-S88; Ruffolo, R. R., Jr., Boyle, D. A., Venuti, R. P. & Lukas, M. A. (1991) Drugs of Today, 27, 465–492; and Yue, T.-L. Cheng, H., Lysko, P. G., Mckenna, P. J., Feuerstein, R., Gu. J., Lysko, K. A., Davis, L. L. & Feuerstein, G. (1992) J. Pharmacol. Exp. Ther., 263,92–98.

The antihypertensive action of carvedilol is mediated primarily by decreasing total peripheral vascular resistance without causing the concomitant reflex changes in heart rate commonly associated with other antihypertensive agents. Willette, R. N., et al. supra; Nichols, A. J., et al. supra; Ruffolo, R. R., Jr., Gellai, M., Hieble, J. P., Willette, R. N. & Nichols, A. J. (1990) Eur. J. Clin. Pharmacol., 38, S82-S88., Carvedilol also markedly reduces infarct size in rat, canine and porcine models of acute myocardial infarction. Ruffolo, R. R., Jr., et al., Drugs of Today, supra, possibly as a consequence of its antioxidant action in attenuating oxygen free radical-initiated lipid peroxidation, Yue, T.-L., et al. supra.

Recently, it has been discovered in clinical studies that pharmaceutical compounds which are dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists, in particular the compounds of Formula I, preferably carvedilol, alone or in conjunction with conventional agents, said agents being ACE inhibitors, diuretics, and digoxin, are effective therapeutic agents for treating CHF. The use of agents, such as carvedilol in treating CHF is surprising, since, in general, β-blockers are contraindicated in patients suffering from heart failure, because β-blockers are known to have undesirable cardiodepressive effects. The most surprising observation from the studies in which the instant compounds were used to treat CHF is that said compounds, in particular carvedilol, are able to decrease the mortality resulting from CHF in humans by about 67 percent. Furthermore, this result is present across all classifications of CHF and both etiologies (eschemic and non-eschemic). This result is surprising since two recent mortality studies using the β-blockers

metoprolol (Waagstein, et al., (1993) Lancet, 342, 1441–1446) and bisoprolol (CIBIS investigators and committees, (1994) Circulation, 90, 1765–1773) in the treatment of CHF showed no difference in mortality between drug-treated patients and placebo-treated patients.

According to the method of treatment of the present invention, the desirable therapeutic effect of the compounds of Formula I, particularly carvedilol, may be augmented by using any one of said compounds, or any pharmaceutically acceptable salt of said compounds. In conjunction with ACE inhibitors, diuretics, and digoxin, which are effective therapeutic agents for the treatment of CHF. In particular, the preferred ACE inhibitors of the present invention are selected from the group consisting of captopril, lisinopril, and enalapril, or any pharmaceutically acceptable salts thereof and the preferred diuretics of the present invention are hydrochlorothiazide or furosemide, or any pharmaceutically acceptable salts thereof. The desirable therapeutic benefits of the compounds of Formula I, particularly carvedilol, are additive with those of such ACE inhibitors, or diuretics, or digoxin when administered in combination therewith. Captopril is commercially available from E. R. Squibb & Sons, Inc. Lisinopril, enalapril and hydrochlorothiaxide are commercially available from Merck & Co. Furosemide is commercially available from Hoechst-Roussel Pharmaceuticals, Inc. Digoxin is commercially available from Burroughs Wellcome Co.

Compounds of Formula I may be conveniently prepared as described in U.S. Pat. No. 4,503,067. Carvedilol is commercially available from SmithKline Beecham Corporation and Boehringer Mannheim GmbH (Germany).

Pharmaceutical compositions of the compounds of Formula I, including carvedilol, alone or in combination with ACE inhibitors, or diuretics, or digoxin may be administered to patients according to the present invention in any medically acceptable manner, preferably orally. For parenteral administration, the pharmaceutical composition will be in the form of a sterile injectable liquid stored in a suitable container such as an ampoule, or in the form of an aqueous or nonaqueous liquid suspension. The nature and composition of the pharmaceutical carrier, diluent or excipient will, of course, depend on the intended route of administration, for example whether by intravenous or intramuscular injection

Pharmaceutical compositions of the compounds of Formula I for use according to the present invention may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation is generally a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate solution. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as ethanol, polyvinyl-pyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

Alternatively, these compounds may be encapsulated, tableted or prepared in a emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Liquid carriers include syrup, peanut oil, olive oil, glycerin, saline, ethanol, and water. Solid carriers include starch, lactose, calcium

Copy provided by USPTO from the PIRS Image Database on 05/23/2016

sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

Dosing in humans for the treatment of disease according to the present invention should not exceed a dosage range of from about 3.125 to about 50 mg of the compounds of Formula I, particularly carvedilol, preferably given twice daily. As one of ordinary skill in the art will readily comprehend, the patient should be started on a low dosage regimen of the desired compound of Formula I, particularly carvedilol, and monitored for well-known symptoms of intolerance, e.g., fainting, to such compound. Once the patient is found to tolerate such compound, the patient should be brought slowly and incrementally up to the maintenance dose. The preferred course of treatment is to start the patient on a dosage regimen of either 3.125 or 6.25 mg, preferably given twice daily, for two weeks. The choice of initial dosage most appropriate for the particular patient is determined by the practitioner using well-known medical principles, including, but not limited to, body weight. In the event that the patient exhibits medically acceptable tolerance of the compound for two weeks, the dosage is doubled at the end of the two weeks and the patient is maintained at the new, higher dosage for two more weeks, and observed for signs of intolerance. This course is continued until the patient is brought to a maintenance dose. The preferred maintenance dose is 25 mg, preferably given twice daily, for patients having a body weight of up to 85 kg. For patients having a body weight of over 85 kg, the maintenance dose is between about 25 mg and about 50 mg, preferably given twice daily; preferably about 50 mg, preferably given twice daily.

Dosing in humans for the treatment of disease according to the present invention includes the combination of compounds of Formula I with conventional agents. For example, the usual adult dosage of hydrochlorothiazide is 25–100 mg daily as a single dose or divided dose. The recommended starting dose for enalapril is 2.5 mg administered once or twice daily. The usual therapeutic dosing range for enalapril is 5–20 mg daily, given as a single dose or two divided doses. For most patients the usual initial daily dosage of captopril is 25 mg tid, with most patients having a satisfactory clinical improvement at 50 or 100 mg tid.

It will be appreciated that the actual preferred dosages of the compounds being used in the compositions of this invention will vary according to the particular composition formulated, the mode of administration, the particular site of administration and the host being treated.

No unacceptable toxicological effects are expected when the compounds of Formula I, including the compound of Formula II, are used according to the present invention.

The example which follows is intended in no way to limit the scope of this invention, but is provided to illustrate how to use the compounds of this invention. Many other embodiments will be readily apparent to those skilled in the art.

EXPERIMENTAL

Mortality Studies in CHF Patients

Summary

To determine if β-adrenergic blockage might inhibit the deleterious effects of the sympathetic nervous system on survival in heart failure (CHF), 1052 patients with CHF were prospectively enrolled into a multicenter trial program, in which patients were randomly assigned (double-blind) to 6–12 months' treatment with placebo (PBO) or carvedilol (CRV).. After a common screening period, patients with class II–IV CHF (see next paragraph for the definitions of the classification of CHF) and an ejection fraction ≦0.35 were assigned to one of four protocols based on performance on a 6-minute walk test, PBO or CRV was added to existing therapy with digoxin, diuretics and an ACE inhibitor. All-cause mortality was monitored by a prospectively constituted Data and Safety Monitoring Board (DSMB). After 25 months of enrollment, the DSMB recommended termination of the program because of a favorable effect of CRV on survival. By intention-to-treat, mortality was 8.2% in the PBO group but only 2.9% in the CRV group (P=0.0001, Cochran-Mantel-Haensel analysis). This represented a reduction in risk of death by CRV of 67% (95% CI: 42% to 81%). The treatment effect was similar in patients with class II and class III–IV symptoms. Mortality was reduced in class II patients from 5.9% to 1.9%, a 68% reduction (95% CI: 20% to 97%) [P=0.015,], and in class III–IV patients from 11.0% to 4.2%, a 67% reduction (95% CI: 30% to 84%), [P=0.004, log-rank]. Importantly, the effect of CRV was similar in ischemic heart disease (risk reduced by 67%, P=0.003) and in non-ischemic dilated cardiomyopathy (risk reduced by 67%, P=0.014). In conclusion, the addition of CRV to conventional therapy is associated with a substantial (67%) reduction in the mortality of patients with chronic CHF. The treatment effect is seen across a broad range of severity and etiology of disease.

As used herein, by "Class II CHF" is meant patients with cardiac disease resulting in slight or moderate limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain. By "Class III CHF" is meant patients with cardiac disease resulting in marked limitations of physical activity. They are comfortable at rest. Less than ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain. By "Class IV CHF" is meant patients with cardiac disease resulting in inability to carry on any physical activity without discomfort, symptoms or cardiac insufficiency, or of the anginal syndrome. By "less than ordinary physical activity" is meant climbing one flight of stairs, or walking two hundred yards.

Design of Study

Patients on background therapy with diuretics, ACE inhibitors and/or digoxin were stratified on the basis of baseline submaximal exercise performance, into one of four trials:

study 220, a dose response study in moderate (NYHA II–IV) CHF with exercise testing as a primary endpoint

study 221, a dose titration study in moderate (NYHA II–IV) CHF with exercise testing as a primary endpoint

study 239, a dose titration study in severe (NYHA III–IV) CHF with quality of life as a primary endpoint

study 240, a dose titration study in mild (NYHA II–III) CHF with progression of CHF as a primary endpoint

Sixty-four centers in the US participated in the trial program. All sites conducted protocols 239 and 240, while 33 performed protocol 220 and 31 performed protocol 221.

Although each trial had its own individual objectives, the overall program objective defined prospectively was evalu-

Copy provided by USPTO from the PIRS Image Database on 05/23/2016

ation of all-cause mortality. Based upon a projected enrollment of 1100 patients, the program had 90% power to detect a 50% reduction in mortality (two-sided) between carvedilol and placebo, assuming a mortality rate in the placebo group of 12% over the duration of the trials (α=0.05).

Randomization was preceded by a screening and challenge period common to the four protocols The purpose of the screening period was to qualify patients for study entry, obtain reproducible baseline measurements, and stratify patients into the appropriate trial based on submaximal exercise testing. During the challenge period, patients received low-dose open-label carvedilol (6.25 mg b.i.d.) for two weeks. Patients unable to tolerate this dose did not proceed to randomization. Patients tolerating low-dose carvedilol were then randomized to blinded medication (carvedilol or placebo) with the dose titrated over several weeks in the range of 6.25 to 50 mg b.i.d. (or equivalent level of placebo). The maintenance phase of each study ranged from six to 12 months, after which patients had the option of receiving open-label carvedilol in an extension study.

Results

The analysis presented below corresponds to the data set on which the DSMB made the recommendation to terminate the trials. Included in this intent-to-treat analysis are all patients enrolled in the U.S. trials as of Jan. 20, 1995; 624 receiving carvedilol and 356 placebo. An analysis of baseline patient characteristics (Table 1) shows good balance between the randomized groups.

TABLE 1

US Carvedilol Heart Failure Trials - Reaction Characteristics

Characteristic	Placebo (n = 356)	Carvedilol (n = 624)
Age, mean ± SD (years)	59.9 ± 11.7	58.8 ± 11.8
Sex (% men)	62%	62%
Etiology (% ischemic)	43%	40%
Severity of CFP		
Class II	41%	41%
Class III–IV	40%	39%
Unknown	19%	20%
LV ejection function, mean ± SD	0.22 ± 0.07	0.25 ± 0.08
6 Minute walk (m ± SD)	373 ± 88	379 ± 81
Blood pressure (mmHg)	115/73	115/73
Heart rate (bpm ± SD)	85 ± 13	86 ± 13

The overall mortality results for the program are shown in Table 2. All deaths that occurred during the intent-to-treat period are included. Treatment with caredilol resulted in a 67% reduction in the risk of all-cause mortality. Analysis of mortality by certain baseline characteristics shows this to be a broad effect regardless of severity or etiology of CHF. The effect was uniform in patients with mild heart failure or moderate to severe heart failure. Similarly, the mortality reduction was equivalent in patients with ischemic or non-ischemic heart failure.

TABLE 2

Evaluation of Mortality in US Carvedilol CHF Studies

	Carvedilol	Placebo	Risk Reduction (95% CI)	p value[a]
All Cause Mortality	18/624 (2.9%)	29/356 (8.2%)	67% (42–81)	<0.0001

TABLE 2-continued

Evaluation of Mortality in US Carvedilol CHF Studies

	Carvedilol	Placebo	Risk Reduction (95% CI)	p value[a]
Class II CHF	7/361 (1.9%)	12/202 (5.9%)	68% (20–97)	0.015
Class III–IV CHF	11/263 (4.2%)	17/154 (11.0%)	66% (30–84)	0.004
Ischemic Etology	10/311 (3.2%)	16/178 (8.9%)	67% (32–85)	0.003
Non-Ischemic Etiology	8/313 (2.5%)	13/178 (7.3%)	67% (20–86)	0.014

[a]Cochran-Mantal-Haeneal Analysis

Conclusion

The U.S. Phase III trials were prospectively designed to evaluate the effects of carvedilol on the wellbeing and survival of patients with congestive heart failure. Twenty-five months after the program was initiated, the independent Data and Safety Monitoring Board recommended that the trials be terminated because of a 67% reduction in all-cause mortality. This effect was independent of the underlying severity or etiology of heart failure.

The foregoing is illustrative of the use of the compounds of this invention. This invention, however, is not limited to the precise embodiment described herein, but encompasses all modifications within the scope of the claims which follow.

What is claimed is:

1. A method of decreasing mortality caused by congestive heart failure in a patient in need thereof which comprises administering a therapeutically acceptable amount of carvedilol in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of an angiotensin converting enzyme inhibitor (ACE), a diuretic, and digoxin,

wherein the administering comprises administering to said patient daily maintenance dosages for a maintenance period to decrease a risk of mortality caused by congestive heart failure, and said maintenance period is greater than six months.

2. A method according to claim **1** which comprises administering carvedilol in a dosage range of from about 3.125 to about 50 mg given twice daily.

3. A method according to claim **1** which comprises administering carvedilol in a maintenance dose of about 25 mg given twice daily.

4. A method according to claim **1** which comprises administering carvedilol in a maintenance dose of between about 25 mg and about 50 mg given twice daily to patients whose weight exceeds about 85 kg.

5. A method according to claim **1** which comprises administering carvedilol in a maintenance dose of about 50 mg given twice daily in patients whose weight exceed about 85 kg.

6. A method according to claim **1** wherein said ACE inhibitor is captopril, lisinopril, or enalapril, or any pharmaceutically acceptable salt thereof.

7. A method according to claim **1** wherein said diuretic is hydrochlorothiazide or furosemide, or any pharmaceutically acceptable salt thereof.

8. A method according to claim 1, wherein the daily maintenance dosages and the maintenance period have been shown to statistically decrease the risk of mortality caused by congestive heart failure.

9. A method according to claim 1, wherein said patient has class II–IV congestive heart failure.

* * * * *

Copy provided by USPTO from the PIRS Image Database on 05/23/2016

CERTIFICATE OF SERVICE AND FILING

I certify that I electronically filed the foregoing document using the Court's CM/ECF filing system on July 16, 2018. All counsel of record were served via CM/ECF on July 16, 2018.

/s/ Craig E. Countryman
Craig E. Countryman

CERTIFICATE OF COMPLIANCE

The undersigned attorney certifies that GSK's Opening Brief complies with the type-volume limitation set forth in Fed. R. App. P. 32(a)(7)(B). The relevant portions of the brief, including all footnotes, contain 13,060 words, as determined by Microsoft Word.

Dated: July 16, 2018

/s/ Craig E. Countryman

Craig E. Countryman
Fish & Richardson P.C.
12390 El Camino Real
San Diego, CA 92130
(858) 678-5070
countryman@fr.com