2014-1282, -1291

United States Court of Appeals for the Federal Circuit

APOTEX INC.,

Plaintiff-Appellant,

v.

DAIICHI SANKYO, INC., AND DAIICHI SANKYO CO., LTD.,

Defendants-Appellees,

and

MYLAN PHARMACEUTICALS INC.,

Movant-Cross-Appellant.

Appeals from the United States District Court for the Northern District of Illinois in No. 1:12-cv-09295, Judge Sharon Johnson Coleman.

BRIEF FOR PLAINTIFF-APPELLANT APOTEX INC.

STEVEN E. FELDMAN
JAMES P. WHITE
SHERRY L. ROLLO
HUSCH BLACKWELL LLP
120 South Riverside Plaza, 22nd Floor
Chicago, Illinois 60661
Tal: (312) 655-1500
Fax: (312) 655-1501
steven.feldman@huschblackwell.com
james.white@huschblackwell.com
sherry.rollo@huschblackwell.com
Counsel for Appellants

May 30, 2014

CERTIFICATE OF INTEREST

Pursuant to FED. CIR. R. 47.4, counsel for Appellant Apotex, Inc. certifies the following:

1. The full name of every party represented by me is:

Apotex Inc.

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:

The party named in the caption is the real party in interest.

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

Apotex Pharmaceuticals, Inc. is the parent company of Apotex Inc.

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:

Steven E. Feldman, James P. White, and Sherry L. Rollo, all of Husch Blackwell LLP Chicago, Illinois;

/s/ Steven E. Feldman
Steven E. Feldman
Attorney for Plaintiff-Appellant
Apotex Inc.

May 30, 2014
Date

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STATEMENT OF RELATED CASES

No appeal in or from this same civil action in the lower court was previously before this or any other Court of Appeals.

JURISDICTIONAL STATEMENT

The district court had subject matter jurisdiction under 28 U.S.C. §§ 1331 and 1338 (a) because the case involves substantial claims arising under the United States Patent Act, 35 U.S.C. § 1 *et seq.*, under 28 U.S.C. §§ 2201 and 2202 because the case presents an actual controversy concerning the noninfringement, invalidity and/or unenforceability of the patents-in-suit, and under 21 U.S.C. § 355(j)(5)(C) as a civil action to obtain patent certainty brought in accordance with 35 U.S.C. §271(e)(5). Final Judgment in the district court dismissing Apotex's claims for lack of subject matter jurisdiction was entered on January 9, 2014. Apotex timely appealed on February 4, 2014. This Court has appellate jurisdiction under 28 U.S.C. § 1295.

STATEMENT OF THE ISSUE

Whether the district court legally erred in concluding that a patentee's disclaimer of a patent that continues to have an exclusionary effect by virtue of the patentee's listing of that patent in the FDA Orange Book deprives the court of subject matter jurisdiction to decide Apotex's civil action to obtain patent certainty under 21 U.S.C. § 355(j)(5)(C) and 35 U.S.C. § 271(e)(5), where the requisites of the statutes were satisfied and where, unless Apotex can obtain the declaratory judgment sought in this action, final FDA approval of its abbreviated new drug application will be delayed by at least 180 days.

STATEMENT OF FACTS AND OF THE CASE

A. Statutory And Regulatory Background.

The approval of prescription drugs is governed by the applicable provisions of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. § 301 *et seq.*, as amended by the Drug Price Competition and Patent Term Restoration Act of 1984 (known as the "Hatch–Waxman Act"), and the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 ("MMA" or "MMA Amendments"). The underlying legislative scheme is set forth in the district court's opinion (A2-A4.) *See also Dey Pharma. LP v. Sunovion Pharm. Inc.*, 677 F.3d 1158, 1164 (Fed. Cir. 2012); *Caraco Pharm. Labs. v. Forest Labs., Inc.*, 527 F.3d 1278, 1283-84 (Fed. Cir. 2008). To give context to this appeal, there are several points that are worth highlighting.

First, the Hatch-Waxman Act has always provided that any company seeking to obtain FDA approval for its drug submit a New Drug Application ("NDA") and identify all patents to which "a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug." 21 U.S.C. § 355(b)(1)(G); 21 C.F.R. § 314.53 (c). These patents are then published by the FDA, without scrutiny as to the scope of the patent claims, in the FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations," known as the Orange Book. *Caraco*, 527

F.3d at 1282. *See also* 68 Fed. Reg. 36676, 36683 (June 18, 2003) ("In addition to the absence of any statutory basis for a substantive agency review of patents, we have long observed that we lack expertise in patent matters. An administrative process for reviewing patents, assessing patent challenges, and de-listing patents would involve patent law issues that are outside both our expertise and our authority."); *Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S*, 132 S.Ct. 1670, 1677 (2012) (discussing 68 Fed. Reg. 36683 and FDA's lack of substantive review of patent listings in the Orange Book).

Second, the Hatch-Waxman framework also permits generic companies wishing to market a drug covered by a NDA to file an abbreviated new drug application ("ANDA"). (A3.) In cases where the generic manufacturer seeks approval to market the generic pharmaceuticals before the expiration of one or more Orange Book listed patents, the generic generally must submit a "Paragraph IV" certification to the FDA that the applicable patents listed in the Orange Book are invalid or will not be infringed by the manufacture, use, or sale of the drug covered by its ANDA. 21 U.S.C. § 355(j)(2)(A)(vii)(IV); 21 C.F.R. § 314.94(a)(12)(i)(A).

Third, a primary purpose of the Hatch-Waxman Act is to promote and expedite the public's access to lower priced generic drugs. *Teva Pharms. USA, Inc. v. Novartis Pharms. Corp.*, 482 F.3d 1330, 1344 (Fed. Cir. 2007) ("A central

purpose of the Hatch-Waxman Act and the subsequent ANDA declaratory judgment amendment to that Act is 'to enable competitors to bring cheaper, generic ... drugs to market as quickly as possible.'" [citing 149 Cong. Rec. S15885 (Nov. 25, 2003) (Statement of Sen. Kennedy)]). To achieve this purpose, the Hatch-Waxman Act facilitates early resolution of patent disputes between generic and brand drug companies by providing that the mere act of filing a Paragraph IV ANDA constitutes an "artificial" act of patent infringement. 35 U.S.C. § 271(e)(2); *Eli Lilly and Co. v. Medtronic, Inc.*, 496 U.S. 661, 678 (1990) ("Quite obviously, the purpose of subsection[] (e)(2) . . . is to enable the judicial adjudication upon which the ANDA . . . scheme[] depend[s].") Moreover, the Patent Statute states that "it shall be an act of infringement" to submit an ANDA "if the purpose of such submission is to obtain approval . . . to engage in the commercial manufacture, use, or sale of a drug . . . claimed in a patent or the use of which is claimed in a patent before the expiration of such patent." 35 U.S.C. § 271(e)(2). As this Court has explained, "§ 271(e)(2) is designed to create an *artificial* act of infringement for purposes of establishing jurisdiction in the federal courts." *Glaxo Group Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1351 (Fed. Cir. 2004) (emphasis in original).

Fourth, to incentivize challenges to weak or not infringed Orange Book listed patents, the Hatch-Waxman Act created a 180-day marketing exclusivity

period available to the first Paragraph IV ANDA filer. 21 U.S.C. § 355(j)(5)(B)(iv). During this 180 day period, the FDA cannot approve subsequent ANDA filer's applications. *Dey,* 677 F.3d at 1160. However, the first filer's eligibility for the 180-day exclusivity is not absolute, and there are several ways in which a first filer can forfeit this 180-day exclusivity if it cannot get its products to market quickly enough.

B. The 2003 MMA Amendments.

During the course of patent litigation arising out of the Hatch-Waxman prior to the 2003 MMA Amendments, it became clear that issues of gamesmanship were occurring between the brand and generic companies that undermined the underlying Hatch-Waxman goal of getting generic drugs to market quickly. *Novartis,* 482 F.3d at 1343-44 ("For example, the brand drug company might have several patents listed in the Food and Drug Administration's Orange Book with respect to a particular drug. It could be in the company's interest to bring suit within 45 days on one patent and to hold the others in reserve." (quoting 149 Cong. Rec. 15885 (Nov. 25, 2003)(remarks of Sen. Kennedy)).

The MMA Amendments involving the 180-day exclusivity forfeiture and declaratory judgment provisions were enacted to "close some loopholes that emerged and were exploited" in the original Hatch-Waxman legislation. 149

Cong. Rec. S16105-06 (Dec. 9, 2003) (remarks of Sen. Hatch); 149 Cong. Rec. S15882 (Nov. 25, 2003) (remarks of Sen. Kennedy, ranking member of the Senate HELP committee) ("[I]n recent years both brand-name and generic drug companies have exploited certain aspects of the Hatch-Waxman Act to delay generic competition. The changes to the [ ] Act…will stop these abuses.")

Before the MMA amendments to the Hatch–Waxman Act, the first generic filer's 180–day exclusivity period would begin to run if it began commercially marketing its drug or if there was a court judgment "holding the patent which is the subject of the certification to be invalid or not infringed." 21 U.S.C. § 355(j)(5)(B)(iv) (2000).

Under the pre-MMA regime, if a first Paragraph IV ANDA filer were found liable in a § 271(e)(2) infringement action or simply failed to market its generic drug, then it would not trigger its own exclusivity period through the court-judgment trigger or the commercial-marketing trigger. *Caraco*, 527 F.3d at 1284. In that case, a subsequent Paragraph IV ANDA filer needed to obtain a court-judgment that the NDA holder's Orange-Book-listed patents are invalid or not infringed by the drug described in its subsequent Paragraph IV ANDA to cause a triggering event. 21 U.S.C. § 355(j)(5)(B)(iv)(II) (2000). However, if the NDA holder could prevent the subsequent Paragraph IV ANDA filer's court challenge, it would be able to delay FDA approval of the subsequent Paragraph IV ANDA

and thus delay the subsequent Paragraph IV ANDA filer's entry into the market. As such, there was little incentive to the brand company to initiate a lawsuit against the subsequent filer because doing so might result in a triggering of the first filer's exclusivity. Yet the interests between the brand company and the subsequent generic still remained very much adverse because the brand company risks competition from two or more generic competitors as opposed to a single competitor. *See, e.g.*, *Caraco*, 527 F.3d at 1284, 1296-97.

The MMA Amendments addressed this issue by maintaining the first ANDA applicants' first commercial marketing of its drug product as a triggering event, but also by providing that the exclusivity period can be forfeited under certain conditions, including failure to launch after a final court judgment of noninfringement or invalidity. 21 U.S.C. § 355(j)(5)(D)(i)(I). The forfeiture provisions clarified that the 180-day marketing exclusivity was not to be treated as a vested property right but as a reward to generics who are successful in litigation and get their products to market. 149 Cong. Rec. S16105-06 (Dec. 9, 2003) (statements of Sen. Hatch) (discussing the forfeiture provisions added by the MMA Amendments.).

For example, if a subsequent generic filer challenges the Orange Book listed patents and wins, it can cause the first filer to forfeit the exclusivity if the first filer fails to market its product. 21 U.S.C. § 355(j)(5)(D)(i)(I). Importantly,

to cause this type of forfeiture event, the subsequent generic filer must have a final court decision from which no appeal (other than a petition to the Supreme Court for a writ of certiorari) has been or can be taken. 21 U.S.C. § 355(j)(5)(D)(i)(I)(bb)(AA). While the statute permits FDA to accept a consent decree as sufficient to cause a forfeiture event, a mere dismissal or a covenant not to sue is not sufficient. 21 U.S.C. § 355(j)(5)(D)(i)(I)(bb)(BB).

Through the MMA Amendments Congress also granted generic companies the right to initiate a "civil action to obtain patent certainty" 21 U.S.C. § 355(j)(5)(C). This provision provides in pertinent part that an ANDA filer who is not sued within 45 days after serving its Paragraph IV notice letter:

> . . . may, in accordance with section 2201 of title 28, bring a civil action under such section against the owner or holder referred to in such subclause (but not against any owner or holder that has brought such a civil action against the applicant, unless that civil action was dismissed without prejudice) for a declaratory judgment that the patent is invalid or will not be infringed by the drug for which the applicant seeks approval . . . .

21 U.S.C. § 355(j)(5)(C)(i)(II).

The Patent Statute also was amended to add a complimentary provision, 35 U.S.C. § 271(e)(5), which provides that where an NDA holder has not initiated a lawsuit within 45 days of receiving notice of a Paragraph IV certification "the courts of the United States *shall*, to the extent consistent with the Constitution, have subject matter jurisdiction in any action brought by such person under

section 2201 of title 28 for a declaratory judgment that such patent is invalid or not infringed." 35 U.S.C. § 271(e)(5).

C. Factual And Procedural Background.

Daiichi is the current holder of approved NDA Application No. 21-286 for Benicar® tablets containing olmesartan medoxomil 5 mg, 20 mg, and 40 mg tablets. (A4; A18.) Daiichi listed U.S. Patent Nos. 5,616,599 ("the '599 patent") and 6,878,703 ("the '703 patent") in the Orange Book as patents to which "a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug" products containing olmesartan. 21 U.S.C. § 355(b)(1)(G); 21 C.F.R. § 314.53(c). (A3-4; A47.)

Subsequently, on July 11, 2006, Daiichi disclaimed the term of every claim of the '703 patent. (A5; A7.) Daiichi also filed a request with FDA to have the '703 patent delisted. (A7.) However, as explained *infra* in Argument Section I(C)(2), the FDA is prohibited from delisting a patent under the circumstances of this case. As such, the '599 and '703 patents remain listed in the Orange Book with respect to NDA No. 21-286 and Daiichi continues to obtain unwarranted benefits from the preclusive effect of the '703 patent's listing in the Orange Book. (A47-48.) That is, as long as there is no final decision from a court entered as to the '703 patent, Daiichi is able to limit generic competition to a

single generic company for 180 days after the expiration of the ’599 patent. (A47-48; A50.); *Caraco,* 527 F.3d at 1284 (“NDA holders have a strong incentive to avoid litigation that would trigger the first Paragraph IV ANDA filer's exclusivity period and allow the FDA to approve subsequent Paragraph IV ANDAs 181 days after the triggering event.”)

Mylan, is believed to be the first Paragraph IV filer with respect to olmesartan medoxomil.[1] Mylan asserts that it filed its ANDA with a Paragraph IV certification to both the ’599 and ’703 patents on April 26, 2006, and as such is believed to be eligible for a 180-day exclusivity pursuant to 21 U.S.C. § 355 (j)(5)(B)(iv); (A4.)

On July 31, 2006, Daiichi filed suit against Mylan alleging infringement of the ’599 patent, but not the ’703 patent. (A5.) Mylan answered and filed a counterclaim asserting that the ’599 patent was invalid and not infringed, but did not bring any declaratory judgment counterclaims pertaining to the ’703 patent. (A5.) Mylan ultimately failed in its Paragraph IV challenge to the validity of the ’599 patent, and in 2010, the Federal Circuit affirmed the validity of the ’599 patent in *Daiichi Sankyo Co. v. Matrix Labs.,* 619 F.3d 1346 (Fed. Cir. 2010).

[1] Mylan filed a motion to intervene in the district court action here for purposes of filing a motion to dismiss Apotex’s complaint for lack of subject matter jurisdiction. (A4, n.3). That motion was denied as moot when the Court granted Daiichi’s own motion to dismiss. (A8.) Nevertheless, Mylan has filed a cross appeal seeking reversal of the district court’s denial of its intervention motion.

(A5; A49.) Because Mylan failed in its attempt to have the '599 patent held invalid, Mylan is required to wait until the expiration of the '599 patent and any applicable pediatric exclusivity before it can market its generic olmesartan products. 35 U.S.C. § 271(e)(2), (4); (A49-50.)

Despite Mylan's failure to invalidate the '599 patent, Mylan remains eligible for a 180-day exclusivity by virtue of Mylan's still existing Paragraph IV certification against the '703 patent. (A50.) Mylan could have challenged the '703 patent by filing its own declaratory judgment action pursuant to 35 U.S.C. § 271(e)(5) at the time it got sued under the '599 patent. (A49-50.) However, Mylan did not do so. (*Id.*) Under the forfeiture provisions of the MMA, if Mylan had brought such an action and won on the '703 patent while losing on the '599 patent, it would have caused its own forfeiture of its exclusivity period. 21 U.S.C. § 355(j)(5)(D)(i)(I)(bb)(AA).

Apotex also submitted an ANDA for a proposed drug product containing olmesartan medoxomil ("Apotex ANDA Product"). (A48.) Apotex's ANDA seeks FDA approval for the commercial manufacture, use, importation, offer for sale and sale of generic olmesartan medoxomil 5 mg, 20 mg, and 40 mg tablets. (A48.) Apotex filed a Paragraph IV certification stating *inter alia* that the '703 patent is invalid or will not be infringed by the manufacture, use, or sale of the Apotex ANDA Product. (A48.) At present, Apotex is not challenging the '599

patent that Mylan failed to invalidate, and has filed a Paragraph III certification with respect to that patent.

In accordance with 35 U.S.C. § 355(j)(2)(B) and 21 C.F.R. § 314.95, Apotex, on or about June 12, 2012, served Daiichi with a Notice Letter informing Daiichi of Apotex's ANDA seeking approval to engage in the commercial manufacture, use, importation, offer for sale, or sale of the Apotex ANDA Product before the expiration of the '703 patent. (A48-49.) Apotex's Notice Letter included a detailed factual and legal basis for its Paragraph IV certification, that the '703 patent would not be infringed by the manufacture, use, or sale of the Apotex ANDA Product because, *inter alia*, the term of every claim had been disclaimed. (A48-49.) Daiichi did not file suit against Apotex with respect to the '703 patent.

As such, on November 20, 2012, Apotex brought an action pursuant to the Hatch-Waxman civil action to obtain patent certainty provisions and 35 U.S.C. § 271(e)(5), seeking a declaratory judgment that its ANDA product does not infringe the '703 patent.[2] (A18-42.) In an effort to resolve this matter in a manner that would remove the '703 patent as a barrier to Apotex's regulatory approval, Apotex, through counsel, served Daiichi with a proposed consent decree

[2] Apotex filed an Amended Complaint on February 12, 2013, which included more detailed allegations establishing personal jurisdiction over Daiichi in Illinois. (A43-76.)

acknowledging that Apotex's generic olmesartan product does not infringe Daiichi's '703 patent. (A222-25.) Daiichi refused to enter into the consent decree. Therefore, unless a Court enters a decision as to the '703 patent, Apotex will be prohibited from selling its competing generic olmesartan product until 180 days after Mylan chooses to market its product, thereby injuring Apotex by depriving it of sales revenue for that period of time and injuring the public by depriving the public of the benefit of the generic competition that would otherwise be provided by Apotex's generic olmesartan product. (A50.) However, if a Court first declares the '703 patent unenforceable or not infringed by the Apotex ANDA Product, this obstacle to Apotex's FDA approval will be removed. (A50-51.)

Daiichi filed a motion to dismiss Apotex's complaint for lack of subject matter jurisdiction. (A5.) The district court granted Daiichi's motion to dismiss for lack of subject matter jurisdiction because Daiichi had disclaimed the '703 patent, even though it continues to preclude the FDA from approving Apotex's olmesartan ANDA, explaining: "Because Daiichi disclaimed all claims associated with the '703 Patent pursuant to 35 U.S.C. § 253, both Daiichi and Apotex no longer hold any meaningful interest in the now disclaimed patent." (A7.)

This appeal followed.

SUMMARY OF ARGUMENT

The district court legally erred in ruling that this case failed to meet the Article III case or controversy requirement because the '703 patent has been statutorily disclaimed pursuant to 35 USC § 253. The court reasoned that the effect of this disclaimer was as if the patent never existed and therefore it was no longer a barrier to Apotex obtaining approval to market its generic olmesartan product. (A7-8.) The court's rationale ignores that because the Hatch-Waxman framework creates a different set of circumstances than an ordinary patent infringement suit, the patent, despite being disclaimed, still is having an exclusionary effect because it remains listed in the FDA Orange Book. Unless Apotex can obtain a final court decision that the '703 patent is invalid or not infringed it will delay generic competition by preventing Apotex from obtaining final FDA approval to market its generic product until 180 days after Mylan begins marketing its own generic product. 21 U.S.C. § 355 (j)(5)(D)(i)(I)(bb)(AA); 21 U.S.C. § 355(j)(5)(B)(iv).

The MMA Amendments provide, and this Court has repeatedly held, that a generic filer such as Apotex has standing to bring an action for patent certainty even where the patent holder has voluntarily given up its right to sue on that patent by granting a covenant not to sue where, as here, the patent remains listed in the FDA Orange Book and thereby is delaying the generic filer's ability to get

final FDA approval for its product. *Caraco*, 527 F.3d at 1293; *Dey*, 677 F.3d at 1164. In its analysis (A8) the district court attempted to distinguish Daiichi's disclaimer from the covenant not to sue situation. However, a statutory disclaimer is not meaningfully distinguishable from a covenant not to sue and does not deprive the Court of subject matter jurisdiction in the context of a Hatch-Waxman declaratory judgment action seeking patent certainty.

As long as a patent remains listed in the Orange Book, regardless of whether it has been disclaimed or subjected to a covenant not to sue, it continues to be a barrier to generic approval, and the brand company benefits by having limited, or at times, no generic competition. Thus, taking into account "all the circumstances" as required by *MedImmune*, including the unique circumstances of the Hatch-Waxman framework, the district court should have exercised subject matter jurisdiction and not dismissed Apotex's complaint.

ARGUMENT

The existence of an "actual controversy" sufficient to sustain federal subject matter jurisdiction in a declaratory judgment action is a question of law, reviewed by this Court *de novo*. *Caraco*, 527 F.3d at 1290; *Novartis*, 482 F.3d at 1336.

"In the Hatch–Waxman context, Congress extended declaratory judgment jurisdiction to ANDA paragraph IV disputes, 21 U.S.C. § 355(j)(5)(C), and has

directed federal courts to exercise jurisdiction over these disputes "'to the extent consistent with the Constitution,' 35 U.S.C. § 271(e)(5)." *Dey*, 677 F.3d at 1162.

Under *MedImmune, Inc. v. Genentech, Inc.*, declaratory judgment jurisdiction is created when "the facts alleged, under all the circumstances, show that there is a substantial controversy, between parties having adverse legal interests, of sufficient immediacy and reality to warrant the issuance of a declaratory judgment." 549 U.S. 118, 127 (2007) (quoting *Md. Cas. Co. v. Pac. Coal & Oil Co.*, 312 U.S. 270, 273 (1941)) (internal quotation mark omitted); *Dey*, 677 F.3d at 1162. In applying the "all the circumstances test" of *MedImmune*, this Court has utilized a three-part framework to determine when an action is justiciable under Article III, focusing on whether:(1) the plaintiff has standing, (2) the issues presented are ripe for judicial review, and (3) the case has not been rendered moot. *Caraco*, 527 F.3d at 1291.

Although, Apotex's complaint meets all of these jurisdictional requirements, the district court nevertheless dismissed Apotex's case solely because Daiichi had disclaimed the '703 patent. According to the district court, "[b]ecause Daiichi disclaimed all claims associated with the '703 Patent pursuant to 35 U.S.C. § 253, both Daiichi and Apotex no longer hold any meaningful interest in the now disclaimed patent." (A7.) As demonstrated below, this conclusion was legally erroneous because Daiichi's disclaimer of the '703 patent

did not remove the exclusionary effect that the ’703 patent continues to have by virtue of its listing in the Orange Book.

I. DAIICHI’S DISCLAIMER OF THE ’703 PATENT DOES NOT DEPRIVE THE COURT OF JURISDICTION BECAUSE THAT PATENT STILL HAS PRECLUSIVE EFFECT.

A. THE DISTRICT COURT LEGALLY ERRED IN CONCLUDING THAT DAIICHI’S DISCLAIMER OF THE ’703 PATENT DEPRIVED IT OF JURISDICTION.

The District Court legally erred by dismissing Apotex’s complaint because it erroneously concluded that Daiichi’s statutory disclaimer of the ’703 patent eliminated it as “an independent barrier that deprives Apotex of an opportunity to compete.” (A7.) By focusing solely on the status of the patent in the Patent Office rather than on its continuing exclusionary effect on the market, the district court erroneously held that there was no Article III case or controversy. As this Court explained in *Teva v. Eisai*:

> Neither the statutory disclaimers nor Eisai's covenant-not-to-sue render this declaratory judgment action moot because the DJ patents remain listed in the Orange Book. *Caraco, 527 F.3d at 1296-97*. Thus, regardless of whether Eisai could bring an infringement action with respect to the DJ patents, under the Hatch-Waxman Act Teva still needs a court judgment of noninfringement or invalidity to obtain FDA approval and enter the market. *Id*.

Teva Pharms. USA, Inc. v. Eisai Co., 620 F.3d 1341, 1348 n.3 (Fed. Cir. 2010), *vacated with instructions to dismiss as moot*, 131 S.Ct. 2991 (2011).

While the *Teva v. Eisai* decision is no longer binding precedent because it subsequently was vacated with instructions to dismiss as moot by the Supreme Court because the first filer exclusivity period had already lapsed by the time the certiorari petition was being decided (131 S.Ct. 2991), its reasoning that a disclaimer of a patent that remains listed in the Orange Book does not eliminate the controversy remains compelling here.[3] *See Seattle Children's Hosp. v. Akorn, Inc.*, 2011 WL 6378838, *6 at n.3 (N.D. Ill. Dec. 20, 2011); (A211-20.)

Here, Daiichi's statutory disclaimer of the '703 patent does not eliminate the controversy between Apotex and Daiichi because that patent remains listed in the Orange Book. Regardless of whether Daiichi could bring an infringement action with respect to the '703 patent, under the Hatch-Waxman, framework Apotex still needs a court judgment of noninfringement or invalidity to obtain final FDA marketing approval and enter the market as soon as the '599 patent expires.

[3] The U.S. District Court for the District of Delaware has similarly concluded that a disclaimer of an Orange Book listed patent does not deprive the court of jurisdiction in a declaratory judgment action for patent certainty brought by a second generic filer. *See Bone Care Int'l v. Anchen Pharms.*, Case No. 09-CV-00285 (D.I. 204) (D. Del. Oct. 31, 2011) (A227-30); *Bone Care Int'l v. Sandoz*, Case No. 09-CV-00524 (D.I. 39) (D. Del. Oct. 6, 2011) (reinstating patent declaratory judgment claim on reconsideration of D.I. 29 (Sept. 30, 2010).) (A346-52.)

In its disclaimer analysis, the district court also erroneously relied on language from *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1299 (Fed. Cir. 2011), that "upon entry of a disclaimer under § 253, we treat the patent as though the disclaimed claim(s) had 'never existed.'" This is palpably not true here. If the '703 patent had "never existed," it would not still be listed in the Orange Book. Further, *Genetics* was not a Hatch-Waxman case, but rather involved an interference proceeding under 35 U.S.C. §291. Its holding was expressly limited to the jurisdictional effect of a disclaimer on a §291 action.

> Novartis seeks to enlarge our holding in *Albert* to reach patent expirations. We reject this expansive reading, and we decline to extend *Albert*'s holding beyond the effect of a patent disclaimer in a § 291 action.

Genetics, 655 F.3d at -1298-1299.

Genetics thus says nothing about the jurisdictional effect of a disclaimer on a declaratory judgment action for patent certainty brought pursuant to the Hatch-Waxman Act.

B. LIKE A COVENANT NOT TO SUE, A DISCLAIMER DOES NOT ELIMINATE THE CONTROVERSY OR APOTEX'S INJURY BECAUSE THE DISCLAIMED PATENT REMAINS LISTED IN THE ORANGE BOOK AND CONTINUES TO HAVE EXCLUSIONARY EFFECT.

The district court attempted to distinguish Daiichi's disclaimer from the covenant not to sue situation that this Court has repeatedly held does not eliminate subject matter jurisdiction in the Hatch-Waxman context. (A8.)

However, for purposes of the jurisdictional analysis, a statutory disclaimer is not meaningfully distinguishable from a covenant not to sue. Both preclude infringement liability, but do not eliminate the barrier to regulatory approval caused by Daiichi's listing of the '703 patent in the Orange Book. As the Court in *Caraco* explained: "[t]his controversy is not premised only upon a threat of an infringement suit. A controversy also exists because Forest's actions effectively prevent the FDA from approving Caraco's ANDA and thus exclude Caraco from the drug market." 527 F.3d at 1297.

Thus, while in other contexts perhaps a covenant not to sue or disclaimer might moot a controversy, it does not do so in the Hatch-Waxman context because the Orange Book listed patent continues to have an exclusionary effect.

C. DAIICHI'S REQUEST TO DELIST THE '703 PATENT DOES NOT ABSOLVE IT OF RESPONSIBILITY FOR LISTING THAT PATENT IN THE FIRST PLACE AND DOES NOT ELIMINATE THE CONTROVERSY.

1. Daiichi Continues To Improperly Benefit From The Continued Listing Of Its '703 Patent In The Orange Book.

The district court also erroneously suggests that there is no controversy because Daiichi tried to delist the patent, which remains listed through no "error" of Daiichi's. (A8.)

However, this ignores that Daiichi caused the '703 patent to be listed in the first place and continues to wrongfully benefit from that listing, which significantly limits generic competition. *See Caraco*, 527 F.3d at 1284

("Conversely, NDA holders have a strong incentive to avoid litigation that would trigger the first Paragraph IV ANDA filer's exclusivity period and allow the FDA to approve subsequent Paragraph IV ANDAs 181 days after the triggering event.")

If Daiichi really wanted to surrender all of the exclusionary effects of the '703 patent, it would have agreed to Apotex's proposed consent decree, which would have had the effect of allowing Apotex to get to market on day 1 after the '599 patent expires and causing a forfeiture by Mylan of any first filer exclusivity. 21 U.S.C. § 355(j)(5)(D)(i)(bb)(BB); *see also Caraco*, 527 F.3d at 1294, n.11 ("Although we do not so decide, it appears that if Forest would submit to a consent decree that the drug described in Caraco's ANDA does not infringe the '941 patent, such a decree would redress Caraco's alleged injury-in-fact just as well as any other court judgment. Thus, if Forest's objective in granting the covenant not to sue on the '941 patent was to avoid costly litigation with Caraco, this might be the best approach to resolve the controversy between the parties.") But agreeing to the consent decree would have created competition from multiple generics for Daiichi on day 1, which, according to FDA statistics, can reduce the drug price that American consumers pay by over 40% or more as compared to the price when there is only a single generic on the market. *See, e.g.*, http://www.fda.gov/AboutFDA/centersoffices/officeofmedicalproductsandtobacc

o/cder/ucm129385.htm; *F.T.C. v. Actavis, Inc.*, 133 S.Ct. 2223 at 2234-35 (2013) (discussing the monopoly benefits to the brand company of limiting generic competition).

That Daiichi refused to agree to the consent decree further illustrates the adversity between it and Apotex, and that Daiichi is still benefiting from the '703 patent's continued listing in the FDA Orange Book.

2. The Prohibition Against A NDA Holder Delisting An Orange Book Patent After There Has Been A First Generic Filer Does Not Prevent A Subsequent Generic Filer From Bringing A Declaratory Judgment Action Challenging That Patent.

The district court also expressed uncertainty as to why the FDA had not delisted the '703 patent in response to Daiichi's request to do so. (A7 ("The mere fact that the FDA has failed for some reason to delist Patent '703, despite Daiichi's request, does not create a case or controversy by which Apotex may seek a declaratory judgment regarding a nonexistent patent.").) The district court failed to appreciate that after the D.C. Circuit's decision in *Teva Pharms. USA, Inc. v. Sebelius*, 595 F.3d 1303 (D.C. Cir. 2010), it is settled law that a NDA holder is precluded from delisting a patent after it has been listed and an ANDA has been filed. The rationale behind that *Teva v. Sebelius* decision is that it would skew the Hatch-Waxman incentive system if an NDA holder were permitted to deprive a generic first filer of benefit of its ANDA by simply delisting its patent.

Id. at 1317-18. But this policy which prevents a brand company from delisting a patent does not apply to generic competitors seeking to get their products to market by causing a forfeiture event. The rationale being that if a first ANDA filer is unable to get its product to market fast, a subsequent generic is entitled to cause a forfeiture of any exclusivity. *Dey*, 677 F.3d at 1160.

In the present case, Mylan failed in its challenge to Daiichi's '599 patent and therefore is unable to launch a generic olmesartan product until October 26, 2016 (when Daiichi's pediatric exclusivity on the '599 patent expires) at the earliest.[4] *Matrix*, 619 F.3d at 1357. Therefore, the MMA Amendments incentivize a subsequent ANDA filer like Apotex to file its own challenge to the '703 patent, which if successful, will cause competition from multiple generics on day 1 after the '599 patent expires. This greater competition will benefit the public and is precisely the outcome that the MMA Amendments were intended to create when a first filer failed in its patent challenge and is unable to get its product to market fast.

[4] In its decision the district court incorrectly stated that first Paragraph IV filer is entitled to 180-day exclusivity "regardless" of whether it succeeds in its challenge to the Orange Book listed patents. (A4.) While this might have been true under the old Hatch-Waxman structure, it is no longer true after the MMA Amendments. As discussed *supra*, these Amendments make clear that while Mylan is *eligible* for 180-day exclusivity it also can *forfeit* that exclusivity if it is unable get its product to market fast enough.

There also is no guarantee that Mylan is going to launch its product on day 1 after the '599 patent expires. Nothing in the Hatch-Waxman Act requires Mylan to launch its product on that date and it can choose to launch at some time thereafter thus prolonging Daiichi's monopoly. For example, Mylan could have regulatory or other issues that prevent it from launching on day 1 after the '599 patent expires or it could even enter into an agreement with Daiichi to delay that launch. *See Dey*, 677 F.3d at 1164-65 ("The district court will not lose jurisdiction simply because the period of possible first generic market entry arrives. Even after [first ANDA-filer] Breath is entitled to launch, the possibility remains that Breath will not do so. Breath has not announced plans to launch on August 20, and it is well known that the first generic often elects to delay entry for various reasons, including possible payments from the brand-name manufacturer to delay the launch.") This is all the more reason to allow Apotex to bring its challenge now to ensure generic competition on day 1.

II. CONSIDERING ALL THE CIRCUMSTANCES APOTEX'S DECLARATORY JUDGMENT COMPLAINT SUFFICIENTLY ALLEGES AN ARTICLE III CASE OR CONTROVERSY WITH DAIICHI AND SHOULD NOT HAVE BEEN DISMISSED.

A. APOTEX'S COMPLAINT MEETS ALL JURISDICTIONAL REQUIREMENTS UNDER *MEDIMMUNE*.

This Court repeatedly has applied the *MedImmune* standard to find jurisdiction where, as here, (1) a first ANDA filer has not begun its 180-day

exclusivity period, and (2) a subsequent ANDA filer seeks a declaratory judgment, of noninfringement of a patent, to eliminate a barrier to regulatory approval that exists because that patent remains listed in the Orange Book as a basis for the first ANDA filer's 180-day exclusivity period. *See e.g. Dey*, 677 F.3d at 1158; *Caraco*, 527 F.3d at 1291-92.

Although dressed up in the peculiarities of the Hatch Waxman Act and the unique artificial infringement scheme that it creates under 35 U.S.C. § 271(e)(2), (5), at its heart this is a classic dispute between competitors. Apotex is trying to get its product to market. Daiichi is trying to stop Apotex from getting its product to market and avoid additional generic competition. There can be no doubt that it is Daiichi's patent that is causing the problem and but for its continued listing in the Orange Book we would not be here. Daiichi is still benefiting from the exclusionary effect of its patent and the Court has the power to fix the problems caused by Daiichi's patent by issuing the declaratory judgment that Apotex seeks.

As this Court explained in *Caraco*, the exclusion of non-infringing generic drugs from the market is a judicially cognizable injury-in-fact. 527 F.3d at 1291-92 (explaining that restraint on the free exploitation of non-infringing goods is "exactly the type of injury-in-fact that is sufficient to establish Article III standing under our caselaw." (citing *Red Wing Shoe Co. v. Hockerson-Halberstadt, Inc.*, 148 F.3d 1355, 1360 (Fed. Cir. 1998)).) As a result of the unique Hatch-Waxman

framework, this Court has found the NDA holder's action of listing in the Orange Book the challenged patent is sufficient to satisfy the causation element of the standing analysis. *Caraco*, 527 F.3d at 1292-93. As the *Caraco* Court explained, the generic drug company's injury (i.e., exclusion from the market) is fairly traceable to the defendant's actions because "but-for" the defendant's decision to list a patent in the Orange Book, FDA approval of the generic drug company's ANDA would not have been independently delayed by that patent. *Caraco*, 527 F.3d at 1292 ("Simply put, if Forest had not listed its '712 and in '941 patents in the FDA's Orange Book as valid patents covering the drug described in its NDA for Lexapro (R), then 21 U.S.C. § 355(j)(5)(B)(iv) (2000) would not independently delay Caraco's ANDA from being approved by the FDA. Such but-for causation is sufficient to satisfy the traceability requirement of Article III standing." citing *Duke Power Co. v. Carolina Envtl. Study Group, Inc.*, 438 U.S. 59, 74-78, 81 n.26 (1978)).

This Court also has found sufficient redressability where, as here, a favorable judgment would eliminate an obstacle to a subsequent generic filer bringing its product to market. *Dey*, 677 F.3d at 1164; *Caraco*, 527 F.3d at 1293 ("A favorable judgment in this case would clear the path to FDA approval that Forest's actions would otherwise deny Caraco--namely, using the court-judgment

trigger of 21 U.S.C. § 355(j)(5)(B)(iv)(II) (2000) to activate Ivax's exclusivity period.")

Finally, this Court has had no trouble finding that actions such as Apotex's are ripe and this remains a live controversy. Apotex's filing of its ANDA, which remains pending with FDA, was an act of infringement under 35 U.S.C. § 271(e)(2). When Daiichi did not sue Apotex within 45 days after receiving Apotex's Paragraph IV notice letter, Apotex had a statutory right to file a declaratory judgment action seeking patent certainty that its ANDA product does not infringe the '703 patent, which it is exercising here. 35 U.S.C. § 271(e)(5).

Withholding a declaratory judgment that Apotex's ANDA product does not infringe the '703 patent has the "immediate and substantial impact" of forestalling Apotex's ability to cause a forfeiture event that will enable it to compete with Daiichi and Mylan in the olmesartan market. *Caraco*, 527 F.3d at 1295 ("[I]f Caraco's drug does not infringe Forest's '941 patent, then withholding court consideration of Caraco's declaratory judgment action has the 'immediate and substantial impact' of forestalling Caraco's ability to activate Ivax's exclusivity period through the court-judgment trigger of 21 U.S.C. § 355(j)(5)(B)(iv)(II) (2000).)

B. THIS COURT'S PRE-MMA DECISION IN *JANSSEN* DOES NOT PRECLUDE JURISDICTION HERE.

Daiichi argued below and is likely to argue again here that this Court's analysis in *Janssen Pharm. v. Apotex, Inc.*, 540 F.3d 1353, 1357 (Fed. Cir.2008), compels dismissal here. The district court did not adopt Daiichi's argument and *Janssen* does not support dismissal of Apotex's complaint under the facts of this case. As an initial matter, *Janssen* by its own terms fell under the old statutory scheme that has since been superseded by the MMA Amendments to the Hatch-Waxman Act. Indeed the *Janssen* Court expressly stated that the MMA Amendments at issue here are inapplicable to that case. 540 F.3d 1353 at n. 2 (because a "generic pharmaceutical company…filed the first Paragraph IV ANDA in 2002, before the December 2003 enactment governing the MMA…the **MMA amendments** governing the **commencement and forfeiture of the 180-day exclusivity** period **are inapplicable to this case**." (emphasis added))[5].

As explained above, the MMA Amendments were enacted to clarify provisions of the Hatch-Waxman, which had created "the establishment of a first

[5] While it is true that in *Dey*, this Court has considered and distinguished *Janssen* on other grounds post-MMA Amendments, and suggested that the MMA Amendments did not significantly alter the analysis for purposes of that case, this only indicates that in *Dey* this Court would have found jurisdiction irrespective of which version of the statute was in effect. 677 F.3d at 1160. Regardless, as explained herein, the Court's rationale for denying jurisdiction in *Janssen* does nothing to inhibit or prevent Apotex's exercise of its statutory rights under the MMA Amendments.

filer regime that is not without unintended consequences and perverse incentives." 149 Cong. Rec. S16104 (Dec. 9, 2003) (statement of Sen. Hatch). The MMA Amendments thus expressly created a mechanism for subsequent ANDA filers to challenge non-asserted Orange Book patents and to not just trigger a first filer's exclusivity (as under the old statute), but instead to eliminate the competitive barriers caused by Orange Book listed patents by causing the first filer to forfeit its eligibility for first filer exclusivity if it fails to promptly market its products. *Novartis*, 482 F.3d at 1334 ("We believe there can be a case or controversy sufficient for courts to hear these cases merely because the patents at issue have been listed in the FDA Orange Book, and because the statutory scheme of the Hatch-Waxman Act relies on early resolution of patent disputes. The declaratory judgment provisions in this bill are intended to encourage such early resolution of patent disputes." [quoting 149 Cong. Rec. S15885 (Nov. 25, 2003) (remarks of Sen. Kennedy)].)

As noted above, these "use it, or lose it" exclusivity forfeiture provisions were enacted to avoid situations where, as here, Mylan is a first ANDA filer but not a first successful challenger of all the Orange Book listed patents on which its Paragraph IV certification was based. Because Mylan failed to defeat Daiichi's '599 patent and therefore still cannot market its generic product for several more years, Apotex should be permitted to exercise its statutory rights by challenging

the Orange Book listed patent and triggering the forfeiture provisions of the MMA Amendments so that it will be in a position to compete by getting its generic olmesartan product to market as soon as the '599 patent expires.

Daiichi also has argued that under *Janssen*, Apotex's injury is caused by the statutory scheme and therefore is not a cognizable injury for establishing jurisdiction. The district court did not adopt this argument either. In any event, as noted above, the statutory scheme at issue in *Janssen* did not include the express declaratory judgment provision specifically designed to cause a first filer that delayed launching its product to forfeit its exclusivity. It would be strange logic indeed to interpret the statute that grants subsequent ANDA filers such as Apotex the right to bring a declaratory judgment for patent certainty and cause a first filer that cannot sell its products to forfeit any first-filer exclusivity, to at the same time preclude that very result. As Senator Hatch explained:

> I think in the circumstances when the subsequent challenger has not been sued by the pioneer firm, that the first filer should at least forfeit its 180 days if it is not prepared to go to market in the 75-day grace period the new provision creates. This is good for the consumer and sound policy since the rationale behind the 180-day provision is to create an incentive for challenges to the pioneer's patents, not to create an entitlement to the first applicant to file a patent challenge with the FDA in the Parklawn Building.

149 Cong. Rec. S16105-06 (Dec. 9, 2003) (Remarks of Sen. Hatch).

Here, unlike *Janssen*, Apotex is not just complaining about Mylan's eligibility to 180-day exclusivity as a first filer under the Hatch-Waxman regime. Rather, Apotex is exercising its statutory rights under the MMA to obtain a judgment that the '703 patent is invalid and not infringed, and eliminate that patent as a barrier to Apotex to getting its product to market. While such a judgment also may have the effect of causing Mylan to forfeit its 180-day exclusivity by operation of the statute, this actually is an intended result of the MMA Amendments, which eliminates a first filer's 180-day exclusivity when it fails to bring its product to market fast enough.

CONCLUSION

For the reasons described above, the court should reverse the judgment of the district court and find that there is subject matter jurisdiction over Apotex's declaratory judgment action.

Respectfully Submitted,

Date: May 30, 2014

/s/ Steven E. Feldman

Steven E. Feldman
James P. White
Sherry L. Rollo
HUSCH BLACKWELL LLP
120 South Riverside Plaza • 22nd Floor
Chicago, Illinois 60606
(312) 655-1500

Attorneys for Plaintiff-Appellant
Apotex Inc.

ADDENDUM

IN THE UNITED STATES DISTRICT COURT
FOR THE
NORTHERN DISTRICT OF ILLINOIS

APOTEX, INC, ,

Plaintiff(s),

v.

DAIICHI SANKYO, INC. and DAIICHI SANKYO CO., LTD. ,

Defendant(s).

Case No. 12-cv-9295
Judge Sharon Johnson Coleman

JUDGMENT IN A CIVIL CASE

Judgment is hereby entered (check appropriate box):

☐ in favor of plaintiff(s)
and against defendant(s)
in the amount of $,

which ☐ includes pre–judgment interest.
☐ does not include pre–judgment interest.

Post-judgment interest accrues on that amount at the rate provided by law from the date of this judgment.

Plaintiff(s) shall recover costs from defendant(s).

☒ in favor of defendant(s) DAIICHI SANKYO, INC. and DAIICHI SANKYO CO., LTD.
and against plaintiff(s) APOTEX, INC

.

Defendant(s) shall recover costs from plaintiff(s).

☐ other:

This action was *(check one)*:

☐ tried by a jury with Judge presiding, and the jury has rendered a verdict.
☐ tried by Judge without a jury and the above decision was reached.
☒ decided by Judge Sharon Johnson Coleman on a motion

Date: 1/9/2014

Thomas G. Bruton, Clerk of Court

/s/ Robbie T. Hunt , Deputy Clerk

UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ILLINOIS
EASTERN DIVISION

APOTEX, INC., Plaintiff, v. DAIICHI SANKYO, INC. and DAIICHI SANKYO CO., LTD. Defendants.	)	12-cv-9295 Judge Sharon Johnson Coleman

MEMORANDUM OPINION AND ORDER

The defendants Daiichi Sankyo Co. Ltd. and Daiichi Sankyo, Inc. (collectively "Daiichi") listed United States Patents Nos. 6,878,703 (the "'703 Patent") and 5,616,599 (the "'599 Patent") in connection with their new drug Benicar, consisting of olmesartan medoxomil. Daiichi Sankyo, Co., Ltd. is a Japanese pharmaceutical company and the parent company to Daiichi Sankyo., Inc. This case involves Plaintiff Apotex, Inc.'s ("Apotex") efforts to obtain the Food and Drug Administration's ("FDA") approval to market a generic version of Daiichi's Benicar drug. Apotex seeks a declaratory judgment of noninfringement of the '703 Patent. Pursuant to Fed. R. Civ. P. 12(b)(1), Daiichi moves to dismiss Apotex's amended complaint for lack of subject matter jurisdiction. For the following reasons, Daiichi's motion to dismiss is granted in its entirety.

Background

1. Statutory Framework

The Hatch-Waxman Act (the "Act") governs the FDA's approval process for prescription drugs. The Act was created to "'strike a balance between two competing policy interests: (1) inducing pioneering research and development of new drugs and (2) enabling competitors to bring low-cost, generic copies of those drugs to market.'" *Caraco Pharm. Labs., Ltd. v. Forest Labs., Ltd.*, 527 F.3d 1278, 1282 (Fed. Cir. 2008) (citing *Andrx Pharms., Inc. v. Biovail Corp.*, 276 F.3d 1368, 1371 (Fed. Cir. 2002)). Pursuant to the Act, brand-name (or "pioneering") pharmaceutical companies seeking to market new, previously unapproved drugs are required to file a New Drug Application ("NDA") with the FDA. *Seattle Children's Hosp. v. Akorn, Inc.*, No. 10-CV-5118, 2011 U.S. Dist. LEXIS 145998 at *2 (N.D. Ill. Dec. 20, 2011); *see also* 21

U.S.C. § 355(a), (b). As part of the NDA process, a pioneering drug company must submit information regarding the new drug's safety and efficacy obtained from clinical trials. 21 U.S.C. § 355(b)(1). The pioneering drug company must also provide the FDA with information including "all patents covering its drug or the methods of using the drug with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug.'" *Caraco Pharm. Labs.*, 527 F.3d at 1282 (citing 21 U.S.C. § 355 (b)(1), (c)(2)). The FDA lists these patents provided by the drug company in a publication called the "Approved Drug Products with Therapeutic Equivalence Evaluations," commonly known as the "Orange Book." 21 USC § 355(j)(2)(A)(i). Drugs approved by the FDA are known as "listed drugs." *Id.*

To encourage the development of generic versions of listed drugs, the Hatch-Waxman Act provides for an expedited and far cheaper approval process for generic versions of patented drugs to enter the market. This process is known as the "Abbreviated New Drug Application" ("ANDA"). *Caraco Pharm. Labs.*, 527 F.3d at 1282. Under the ANDA process, generic drug companies are not required to conduct their own independent clinical trials to prove the safety and efficacy of their drugs. 21 U.S.C. § 355(j)(2)(A)(iv). Instead generic drug companies can rely on the research of a pioneering pharmaceutical company so long as the generic drug company demonstrates that its generic drug product is the "bioequivalent" to a NDA listed drug. *Id.* An ANDA applicant must also submit one of four certifications addressing each of the patents listed in the Orange Book that cover the relevant listed drug. 21 U.S.C. §355(j)(2)(A)(vii). Specifically the ANDA filer must certify that either: (I) no patent information has been filed with the FDA; (II) the patent has expired; (III) the patent will expire on a particular date and approval of the ANDA should be deferred until expiration; or (IV) in the opinion of the ANDA applicant, the patent is invalid or will not be infringed by the manufacture, use, or sale of the generic drug. *Seattle Children's Hosp.*, 2011 U.S. Dist. LEXIS 145998 at *3. A certification that an Orange-Book-listed patent is invalid or not infringed is commonly known as a "Paragraph IV" certification. Where an ANDA contains a Paragraph IV certification, the timing of approval depends on two events: (i) whether the holder of the listed patent brings an infringement suit within 45 days of receiving notice of the ANDA filing, and (ii) whether the company seeking approval was the first to file an ANDA with a Paragraph IV certification to the listed patent. *Id.* at *4; *see also* 21 USC 355(j)(5)(B)(iii).

The Hatch-Waxman Act provides that the mere act of filing a Paragraph IV ANDA for a listed drug constitutes an act of patent infringement. *Caraco Pharm. Labs.*, 527 F.3d at 1283. If a patentee or NDA holder does not bring suit within 45 days of receiving notice of a Paragraph IV certification filing, the FDA will approve the ANDA immediately. If the pioneering drug company does bring suit within 45 days, the FDA may not approve the ANDA for 30 months, unless a court decides that the patent(s)-in-suit are invalid or not infringed. *Seattle Children's Hosp.*, 2011 U.S. Dist. LEXIS 145998 at *4. Where a generic company is the first to file an ANDA Paragraph IV certification for a listed patent, the Hatch-Waxman Act grants that company a 180-day period of generic marketing exclusivity during which time the FDA will not approve a later filed Paragraph IV ANDA based on the same NDA. In 2003, Congress enacted the Medicare Prescription Drug, Improvement, and Modernization Act ("MMA") which amended the Hatch-Waxman provisions governing the commencement of the 180-day exclusivity period. *Id.* at *5. After the enactment of the MMA, the exclusivity period can only be triggered by the first-filer's commercial marketing of its generic drug product. However, under the MMA, there is now a forfeiture provision. The first-filer of a Paragraph IV ANDA may forfeit its exclusivity period if a subsequent ANDA filer obtains a final judgment of invalidity or noninfringement. *Id.*

2. *Factual Background*

Daiichi holds an approved NDA for Benicar, a drug used for the treatment of high blood pressure. As part of the process for filing its Benicar NDA, Daiichi listed Patents '599 and '703 in the FDA's Orange Book in connection with its NDA No. 21-286. The first ANDA applicant to file a Paragraph IV certification for Daiichi's '599 and '703 patents was Mylan Laboratories, Ltd. ("Mylan").[1] Accordingly, Mylan is entitled to 180 days of market exclusivity regardless of whether it established that the Orange Book patents were invalid or not. *Janssen Pharmaceutica, N.V. v. Apotex, Inc.*, 540 F.3d 1353, 1356 (Fed. Cir. 2008) (noting that "[a]ll that is required for the first Paragraph IV ANDA filer to receive the 180-day exclusivity period is that it submits a substantially complete ANDA that contains a Paragraph IV Certification"). The start of the 180-day exclusivity period can only be triggered by Mylan's marketing of its generic drug. 21 U.S.C. § 355(j)(5)(B)(iv). If however, a subsequent filer obtains a final judgment of invalidity or

[1] Mylan is presently not a party in this case. Mylan has moved to intervene and has filed its own motion to dismiss should this Court grant its motion to intervene.

noninfringement, Mylan must begin marketing within 75 days or forfeit its exclusivity period. 21 U.S.C. § 355(j)(5)(D)(i)(I)(bb)(AA); *see also Seattle Children's Hosp.*, 2011 U.S. Dist. LEXIS 145998 at *5-6.

After Mylan filed its Paragraph IV ANDA regarding both Patents '703 and '599, Daiichi sued Mylan on July 31, 2006 for infringement of the '599 patent in a district court in New Jersey. Prior to suing Mylan regarding the '599 patent, Daiichi statutorily disclaimed every claim of the '703 patent pursuant to 35 U.S.C. § 253. Eventually the district court found that the '599 patent was valid and that Mylan infringed the '599 patent. Mylan never brought a declaratory judgment action regarding the disclaimed '703 patent. In the instant case, Apotex seeks a final judgment of invalidity or noninfringement regarding the '703 patent in the hopes of compelling Mylan to begin marketing within 75 days or forfeiting its exclusivity period. Daiichi moves to dismiss Apotex's complaint for lack of subject matter jurisdiction. Daiichi argues that there is no case or controversy here because the '703 patent was disclaimed. Apotex argues that despite Daiichi's disclaimer, the '703 patent continues to exclude competition in the market because it remains listed in the FDA's Orange Book.

Legal Standard

Pursuant to Fed. R. Civ. P. 12(b)(1), a court must dismiss any action for which it lacks subject matter jurisdiction. Rule 12(b)(1) motions are premised on either facial or factual attacks on jurisdiction. *Simonian v. Oreck Corp.*, No. 10 C 1224, 2010 U.S. Dist. LEXIS 86832, at *3-4 (N.D. Ill. Aug. 23, 2010). If the defendant makes a factual attack on the plaintiff's assertion of subject matter jurisdiction, it is proper for the court to look beyond the jurisdictional allegations in the complaint and to view whatever evidence has been submitted in response to the motion. *Id.* The plaintiff must then put forth "competent proof" that the court has subject matter jurisdiction. *NLFC, Inc. v. Devcom Mid-America, Inc.*, 45 F.3d 231, 237 (7th Cir. 1995).

Federal courts have subject matter jurisdiction over declaratory judgment actions brought by Paragraph IV ANDA filers to establish noninfringement or invalidity of Orange-Book-listed patents to the extent that they present an Article III case or controversy. *Caraco Pharm. Labs.*, 527 F.3d at 1285; *see also* 31 U.S.C. § 271(e)(5). To determine whether a declaratory judgment action satisfies the Article III case or controversy requirement, the court must inquire as to "whether the facts alleged, under all the circumstances, show that there is a substantial controversy, between parties having adverse legal interests, of sufficient immediacy and reality

to warrant the issuance of a declaratory judgment." *MedImmune, Inc. v. Genentech, Inc.*, 549 U.S. 118, 127 (U.S. 2007). "[A]n action is justiciable under Article III only where (1) the plaintiff has standing, *Lujan v. Defenders of Wildlife*, 504 U.S. 555, 560, 112 S. Ct. 2130, 119 L. Ed. 2d 351 (1992), (2) the issues presented are ripe for judicial review, *Abbott Labs. v. Gardner*, 387 U.S. 136, 149, 87 S. Ct. 1507, 18 L. Ed. 2d 681 (1967), and (3) the case is not rendered moot at any stage of the litigation, *United States Parole Comm'n. v. Geraghty*, 445 U.S. 388, 397, 100 S. Ct. 1202, 63 L. Ed. 2d 479 (1980)." *Caraco Pharm. Labs.,* 527 F.3d at 1291; *see also Seattle Children's Hosp.*, 2011 U.S. Dist. LEXIS 145998, at *13.

In order to have standing, a party must demonstrate: (1) an alleged injury in fact, a harm suffered by the plaintiff that is concrete and actual or imminent; (2) causation, a fairly traceable connection between the plaintiff's injury and the complained-of conduct of the defendant; and (3) redressability, a likelihood that the requested relief will redress the alleged injury. *Caraco Pharm. Labs., Ltd. v. Forest Labs., Ltd.*, 527 F.3d 1278, 1291 (Fed. Cir. 2008). "The Federal Circuit has recognized, in the context of the Hatch-Waxman Act, that the creation of 'an independent barrier to the drug market' by a brand drug company 'that deprives [the generic company] of an economic opportunity to compete' satisfies the injury-in-fact and causation requirements of Article III standing." *Seattle Children's Hosp. v. Akorn, Inc.*, No. 10-CV-5118, 2011 U.S. Dist. LEXIS 145998, at *15 (N.D. Ill. Dec. 20, 2011) (citing *Caraco*, 527 F.3d at 1285 and *Prasco*, 537 F.3d at 1339).

Discussion

Daiichi moves to dismiss Apotex's complaint arguing that there can be no justiciable dispute concerning a disclaimed patent. Apotex concedes that the '703 patent is no longer enforceable, but argues that it continues to exclude competition in the market and continues to have preclusive effect. (Apotex Resp. at 1 and 5). Apotex argues that because a judgment has never been entered stating that the '703 patent is invalid, the '703 patent prevents it from selling its competing generic version of the Benicar drug until the end of Mylan's 180 day exclusivity period.

The Federal Circuit has recognized that prior to the "2003 [MMA] amendments, 'NDA holders employed several methods of delaying the early resolution of patent disputes.'" *Dey Pharma, LP v. Sunovion Pharms., Inc.*, 677 F.3d 1158, 1160 (Fed. Cir. 2012) (citing *Janssen Pharmaceutica, N.V. v. Apotex*, Inc., 540 F.3d 1353, 1357 (Fed. Cir. 2008). In some cases where

NDA patent holders listed multiple patents in the FDA's Orange Book, NDA holders developed a strategy where they would initiate suit on only one of the patents after receiving notice of a Paragraph IV ANDA filing. This would entitle the NDA holder to a 30-month stay before FDA approval of the generic drug. Moreover, even if the one patent sued on was found invalid or not infringed by the generic drug, the ANDA filer would still run the risk of infringing on the other patents implicated, but not sued on by the NDA holder. "To address this problem Congress specified that an ANDA filer who is not sued within 45 days could bring a declaratory judgment action under 28 U.S.C. § 2201 against the NDA holder." *Dey Pharma*, 677 F.3d at 1160-1161 (citing 21 U.S.C. § 355(j)(5)(C)). These amendments also protect subsequent ANDA filers' interest in the early resolution of patent rights due to the 180-day exclusivity period afforded successful first ANDA filers. "If the first ANDA filer 'parked' its 180-day exclusivity under an agreement with the brand-name company, a subsequent ANDA filer could independently trigger the first filer's exclusivity period through a declaratory judgment action leading to a final judgment of invalidity or noninfringement, thereby accelerating the second ANDA filer's ability to market its drug." *Dey Pharma*, 677 F.3d at 1160-1161.

Here, Patent '703 does not create an independent barrier that deprives Apotex of an economic opportunity to compete. Because Daiichi disclaimed all claims associated with the '703 Patent pursuant to 35 U.S.C. § 253, both Daiichi and Apotex no longer hold any meaningful interest in the now disclaimed patent. "Disclaiming particular claims under § 253 'effectively eliminate[s] those claims from the original patent.'" *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1299 (Fed. Cir. 2011) (*citing Vectra Fitness, Inc. v. TNWK Corp.*, 162 F.3d 1379, 1383 (Fed. Cir. 1998)). "In other words, upon entry of a disclaimer under § 253, we treat the patent as though the disclaimed claim(s) had 'never existed.'" *Genetics Inst.*, 655 F.3d at 1299; *see also Guinn v. Kopf*, 96 F.3d 1419, 1422 (Fed. Cir. 1996). Apotex concedes that the '703 patent was statutorily disclaimed and does not dispute the effects of such a disclaimer. Nevertheless, Apotex argues that this Court must still decide whether its generic drug infringes on the non-existent '703 patent because the patent remains listed in the Orange Book. Daiichi, however, requested that the FDA delist the '703 Patent on July 11, 2006. It is unclear why the FDA has yet to actually remove the patent from the Orange Book.

Apotex relies on *Caraco Pharm. Labs.*, 527 F.3d 1278, to support its argument that there is jurisdiction where a first ANDA filer has not begun its exclusivity period and a subsequent

ANDA filer seeks a declaratory judgment of noninfringement to eliminate an independent barrier to regulatory approval. *Caraco*, however, is distinguishable from the case at hand by the important fact that the patent at issue in that case was never disclaimed. The Federal Circuit held that by preventing the FDA from approving ANDAs of generic drug manufacturers, the NDA holder was effectively excluding Caraco from offering what it claimed to be a non-infringing generic drug. Unlike *Caraco*, there is no such exclusion in the instant case. Daiichi is not preventing the FDA from approving Apotex's ANDA through any delay tactics or strategies similar to the NDA holder's covenant not to sue in *Caraco*. Moreover, all parties acknowledge that Daiichi can never assert the '703 patent against any ANDA filer or any entity as the patent no longer exists by virtue of Daiichi's disclaimer of all claims associated with the patent. The mere fact that the FDA has failed for some reason to delist Patent '703, despite Daiichi's request, does not create a case or controversy by which Apotex may seek a declaratory judgment regarding a nonexistent patent. Daiichi disclaimed Patent '703 and properly requested that the Orange Book be updated to reflect Daiichi's disclaimer. Although in *Seattle Children's Hosp.*, 2011 U.S. Dist. LEXIS 145998, the court held that notwithstanding an NDA holders unilateral covenant not to sue, a case or controversy continued to exist between the parties because of the continued listing of the patent in the FDA's Orange Book; in that case, again, the listed patent was never disclaimed. Accordingly, in that case, the patent actually served as an independent barrier to the approval of the defendant's ANDA. Here, the '703 patent continues to be listed, by no error on Daiichi's part, even though the patent was disclaimed. This is insufficient to meet the case and controversy standing requirements under Article III.

Conclusion

For the foregoing reasons, Daiichi's motion to dismiss is granted in its entirety. Given this Court's ruling granting Daiichi's motion to dismiss, non-party Mylan's motions are moot.

IT IS SO ORDERED.

Date: January 9, 2014

Sharon Johnson Coleman
United States District Judge

US006878703B2

(12) **United States Patent**
Sada et al.

(10) **Patent No.: US 6,878,703 B2**
(45) **Date of Patent: Apr. 12, 2005**

(54) **PHARMACEUTICAL COMPOSITION**

(75) Inventors: **Toshio Sada**, Tokyo (JP); **Makoto Mizuno**, Funabashi (JP)

(73) Assignee: **Sankyo Company, Limited**, Tokyo (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/442,874**

(22) Filed: **May 20, 2003**

(65) **Prior Publication Data**

US 2004/0002529 A1 Jan. 1, 2004

Related U.S. Application Data

(63) Continuation of application No. PCT/JP01/10095, filed on Nov. 19, 2001.

(30) **Foreign Application Priority Data**

Nov. 21, 2000 (JP) 2000-354327
May 31, 2001 (JP) 2001-164009

(51) **Int. Cl.**[7] **A61K 31/54**; A61K 31/41
(52) **U.S. Cl.** **514/223.5**; 514/381
(58) **Field of Search** 514/223.5, 382, 514/381

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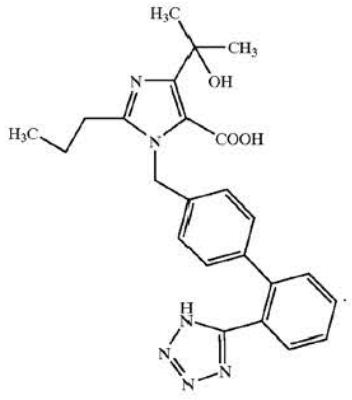
Primary Examiner—Raymond J. Henley, III
(74) *Attorney, Agent, or Firm*—Frishauf, Holtz, Goodman & Chick, P.C.

(57) **ABSTRACT**

A pharmaceutical composition comprises an angiotensin II receptor antagonist selected from among compounds having the following formula (I), a pharmacologically acceptable salt thereof, a pharmacologically acceptable ester thereof and a pharmacologically acceptable salt of such ester, and one or more diuretics:

(I)



The pharmaceutical composition of the present invention has an excellent hypotensive effect and low toxicity, and therefore is useful as a medicament for preventing or treating hypertension or heart disease.

15 Claims, No Drawings

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PHARMACEUTICAL COMPOSITION

CROSS-REFERENCE TO RELATED APPLICATION

This application is a Continuation application of International application No. PCT/JP01/10095, filed Nov. 19, 2001, the entire contents of which are hereby incorporated by reference herein.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a pharmaceutical composition containing a specific angiotensin II receptor antagonist and one or more diuretics as the active ingredients (particularly a pharmaceutical composition for preventing or treating hypertension), the use of a specific angiotensin II receptor antagonist and one or more diuretics for manufacturing the pharmaceutical composition (particularly a pharmaceutical composition for preventing or treating hypertension), and a method for preventing or treating (particularly treating) diseases (particularly hypertension) by the administration of a pharmaceutical composition to warm-blooded animals (particularly humans) comprising effective doses of a specific angiotensin II receptor antagonist and one or more diuretics.

2. Background Information

It is known that co-administration of an angiotensin II receptor antagonist and a diuretic is an effective therapy for the prevention or treatment of hypertension (particularly treatment). These pharmaceutical compositions are described, for example, in WO89/6233, Japanese Patent Application Kokai No. Hei 3-27362 and the like.

However, the effects of a pharmaceutical composition containing a specific angiotensin II receptor antagonist, such as CS-866 ((5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[2'-(1H-tetrazol-5-yl) biphenyl-4-ylmethyl]imidazol-5-carboxylate) (U.S. Pat. No. 5,616,599)), and a diuretic remain unknown.

SUMMARY OF THE INVENTION

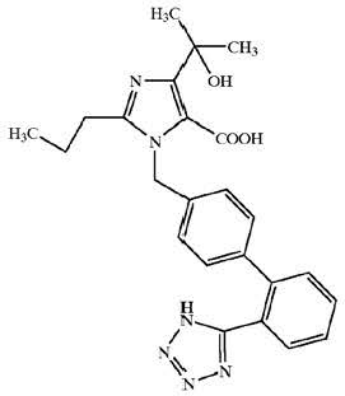
Considering that prevention and/or treatment of hypertension are important, the present inventors investigated combinations of various drugs and found that a pharmaceutical composition containing a specific angiotensin II receptor antagonist, such as CS-866, and one or more diuretics exerts excellent anti-hypertensive effects and hence may be useful as a preventative and/or therapeutic agent for hypertension.

The present invention provides a pharmaceutical composition containing a specific angiotensin II receptor antagonist and one or more diuretics as the active ingredients (particularly pharmaceutical compositions for preventing or treating hypertension), the use of a specific angiotensin II receptor antagonist and one or more diuretics for manufacturing the pharmaceutical compositions (particularly pharmaceutical compositions for preventing or treating hypertension), a method for preventing or treating (particularly treating) diseases (particularly hypertension) by the administration of a specific angiotensin II receptor antagonist and one or more diuretics to warm-blooded animals (particularly humans) at effective doses, and a pharmaceutical composition for administering simultaneously or sequentially a specific angiotensin II receptor antagonist and one or more diuretics for preventing or treating hypertension.

DETAILED DESCRIPTION OF THE INVENTION

The active ingredients of the pharmaceutical composition of this invention include an angiotensin II receptor antagonist selected from the group consisting of a compound having the following formula (I), pharmacologically acceptable salts thereof, pharmacologically acceptable esters thereof and pharmacologically acceptable salts of said esters; and one or more diuretics.

(I)



The compound of formula (I), a salt thereof and the like are known compounds, for example, described in the specification of Japanese Patent Application Kokai No. Hei 5-78328 etc. and the chemical name of the compound of formula (I) is 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]imidazol-5-carboxylic acid.

The "pharmacologically acceptable salt" of the compound of formula (I), which is an active ingredient of this invention, includes an alkali metal salt such as sodium salt, potassium salt or lithium salt; an alkaline earth metal salt such as calcium salt or magnesium salt; a metal salt such as aluminum salt, iron salt, zinc salt, copper salt, nickel salt or cobalt salt; or an amine salt such as ammonium salt, t-octylamine salt, dibenzylamine salt, morpholine salt, glucosamine salt, phenylglycine alkyl ester salt, ethylenediamine salt, N-methylglucamine salt, guanidine salt, diethylamine salt, triethylamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, chloroprocaine salt, procaine salt, diethanolamine salt, N-benzylphenethylamine salt, piperazine salt, tetramethylammonium salt or tris (hydroxymethyl)aminomethane salt. An alkali metal salt is preferable and the sodium salt is particularly preferable.

The "pharmacologically acceptable ester" of the compound of formula (I), which is an active ingredient of this invention, is a compound esterified at the carboxyl moiety of the compound of formula (I). A group forming said ester is a group which can be cleaved by a biological process such as hydrolysis in vivo. Such groups include, for example, a (C_1–C_4)alkoxy-(C_1–C_4)alkyl group such as methoxymethyl, 1-ethoxyethyl, 1-methyl-1-methoxyethyl, 1-(isopropoxy) ethyl, 2-methoxyethyl, 2-ethoxyethyl, 1,1-dimethyl-1-methoxymethyl, ethoxymethyl, propoxymethyl, isopropoxymethyl, butoxymethyl or t-butoxymethyl; a (C_1–C_4)alkoxylated (C_1–C_4)alkoxy-(C_1–C_4)alkyl group such as 2-methoxyethoxymethyl; a (C_6–C_{10})aryloxy-(C_1–C_4)alkyl group such as phenoxymethyl; a halogenated (C_1–C_4)alkoxy-(C_1–C_4)alkyl group such as 2,2,2-

trichloroethoxymethyl or bis(2-chloroethoxy)methyl; a (C_1–C_4)alkoxycarbonyl-(C_1–C_4)alkyl group such as methoxycarbonylmethyl; a cyano-(C_1–C_4)alkyl group such as cyanomethyl or 2-cyanoethyl; a (C_1–C_4)alkylthiomethyl group such as methylthiomethyl or ethylthiomethyl; a (C_6–C_{10})arylthiomethyl such as phenylthiomethyl or naphthylthiomethyl; a (C_1–C_4)alkylsulfonyl-(C_1–C_4) lower alkyl group, which may be optionally substituted with a halogen atom(s), such as 2-methanesulfonylethyl or 2-trifluoromethanesulfonylethyl; a (C_6–C_{10})arylsulfonyl-(C_1–C_4)alkyl group such as 2-benzenesulfonylethyl or 2-toluenesulfonylethyl; an aliphatic (C_1–C_7)acyloxy-(C_1–C_4)alkyl group such as formyloxymethyl, acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl, valeryloxymethyl, isovaleryloxymethyl, hexanoyloxymethyl, 1-formyloxyethyl, 1-acetoxyethyl, 1-propionyloxyethyl, 1-butyryloxyethyl, 1-pivaloyloxyethyl, 1-valeryloxyethyl, 1-isovaleryloxyethyl, 1-hexanoyloxyethyl, 2-formyloxyethyl, 2-acetoxyethyl, 2-propionyloxyethyl, 2-butyryloxyethyl, 2-pivaloyloxyethyl, 2-valeryloxyethyl, 2-isovaleryloxyethyl, 2-hexanoyloxyethyl, 1-formyloxypropyl, 1-acetoxypropyl, 1-propionyloxypropyl, 1-butyryloxypropyl, 1-pivaloyloxypropyl, 1-valeryloxypropyl, 1-isovaleryloxypropyl, 1-hexanoyloxypropyl, 1-acetoxybutyl, 1-propionyloxybutyl, 1-butyryloxybutyl, 1-pivaloyloxybutyl, 1-acetoxypentyl, 1-propionyloxypentyl, 1-butyryloxypentyl, 1-pivaloyloxypentyl, or 1-pivaloyloxyhexyl; a (C_5–C_6)cycloalkylcarbonyloxy-(C_1–C_4)alkyl group such as cyclopentylcarbonyloxymethyl, cyclohexylcarbonyloxymethyl, 1-cyclopentylcarbonyloxyethyl, 1-cyclohexylcarbonyloxyethyl, 1-cyclopentylcarbonyloxypropyl, 1-cyclohexylcarbonyloxypropyl, 1-cyclopentylcarbonyloxybutyl or 1-cyclohexylcarbonyloxybutyl; a (C_6–C_{10}) arylcarbonyloxy-(C_1C_4)alkyl group such as benzoyloxymethyl; a (C_1–C_6)alkoxycarbonyloxy-(C_1–C_4)alkyl group such as methoxycarbonyloxymethyl, 1-(methoxycarbonyloxy)ethyl, 1-(methoxycarbonyloxy)propyl, 1-(methoxycarbonyloxy)butyl, 1-(methoxycarbonyloxy)pentyl, 1-(methoxycarbonyloxy)hexyl, ethoxycarbonyloxymethyl, 1-(ethoxycarbonyloxy)ethyl, 1-(ethoxycarbonyloxy)propyl, 1-(ethoxycarbonyloxy)butyl, 1-(ethoxycarbonyloxy)pentyl, 1-(ethoxycarbonyloxy)hexyl, propoxycarbonyloxymethyl, 1-(propoxycarbonyloxy)ethyl, 1-(propoxycarbonyloxy)propyl, 1-(propoxycarbonyloxy)butyl, isopropoxycarbonyloxymethyl, 1-(isopropoxycarbonyloxy)ethyl, 1-(isopropoxycarbonyloxy)butyl, butoxycarbonyloxymethyl, 1-(butoxycarbonyloxy)ethyl, 1-(butoxycarbonyloxy)propyl, 1-(butoxycarbonyloxy)butyl, isobutoxycarbonyloxymethyl, 1-(isobutoxycarbonyloxy)ethyl, 1-(isobutoxycarbonyloxy)propyl, 1-(isobutoxycarbonyloxy)butyl, t-butoxycarbonyloxymethyl, 1-(t-butoxycarbonyloxy)ethyl, pentyloxycarbonyloxymethyl, 1-(pentyloxycarbonyloxy)ethyl, 1-(pentyloxycarbonyloxy)propyl, hexyloxycarbonyloxymethyl, 1-(hexyloxycarbonyloxy)ethyl or 1-(hexyloxycarbonyloxy)propyl; a (C_5–C_6)cycloalkyloxycarbonyloxy-(C_1–C_4)alkyl group such as cyclopentyloxycarbonyloxymethyl, 1-(cyclopentyloxycarbonyloxy)ethyl, 1-(cyclopentyloxycarbonyloxy)propyl, 1-(cyclopentyloxycarbonyloxy)butyl, cyclohexyloxycarbonyloxymethyl, 1-(cyclohexyloxycarbonyloxy)ethyl, 1-(cyclohexyloxycarbonyloxy)propyl, or 1-(cyclohexyloxycarbonyloxy)butyl; a [5-(C_1–C_4)alkyl-2-oxo-1,3-dioxolen-4-yl]methyl group such as (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl, (5-ethyl-2-oxo-1,3-dioxolen-4-yl)methyl, (5-propyl-2-oxo-1,3-dioxolen-4-yl)methyl, (5-isopropyl-2-oxo-1,3-dioxolen-4-yl)methyl, (5-butyl-2-oxo-1,3-dioxolen-4-yl)methyl; [5-(phenyl, which may be optionally substituted with a (C_1–C_4)alkyl, (C_1–C_4)alkoxy group(s) or halogen atom(s))-2-oxo-1,3-dioxolen-4-yl] methyl group such as (5-phenyl-2-oxo-1,3-dioxolen-4-yl) methyl, [5-(4-methylphenyl)-2-oxo-1,3-dioxolen-4-yl] methyl, [5-(4-methoxyphenyl)-2-oxo-1,3-dioxolen-4-yl] methyl, [5-(4-fluorophenyl)-2-oxo-1,3-dioxolen-4-yl] methyl, [5-(4-chlorophenyl)-2-oxo-1,3-dioxolen-4-yl] methyl; or a phthalidyl group, which may be optionally substituted with a (C_1–C_4)alkyl or (C_1–C_4)alkoxy group(s), such as phthalidyl, dimethylphthalidyl or dimethoxyphthalidyl. Preferred ester groups are a pivaloyloxymethyl group, phthalidyl group or (5-methyl-2-oxo-1,3-dioxolen-4-yl) methyl group and the more preferred ester group is a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl group.

The "pharmacologically acceptable salt of the pharmacologically acceptable ester" of the compound of formula (I), which is an active ingredient of this invention, includes a pharmacologically acceptable salt of the "pharmacologically acceptable ester" described above, for example, a hydrohalogenic acid salt such as hydrofluoride, hydrochloride, hydrobromide or hydroiodide; nitrate; perchlorate; sulfate; phosphate; a C_1–C_4 alkanesulfonic acid salt, which may be optionally substituted with a halogen atom(s) such as methanesulfonate, trifluoromethanesulfonate or ethanesulfonate; a C_6–C_{10} arylsulfonic acid salt, which may be optionally substituted with a C_1–C_4 alkyl group(s), such as benzenesulfonate or p-toluenesulfonate; a C_1–C_6 aliphatic acid salt such as acetate, malate, fumarate, succinate, citrate, tartrate, oxalate or maleate; or an amino acid salt such as a glycine salt, lysine salt, alginine salt, ornitine salt, glutamic acid salt or aspartic acid salt. Preferred salts are hydrochloride, nitrate, sulfate or phosphate and the particularly preferred salt is hydrochloride.

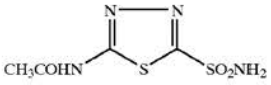
The angiotensin II receptor antagonist, which is an active ingredient of this invention, is preferably the compound of formula (I) or a pharmacologically acceptable ester thereof, more preferably a pharmacologically acceptable ester of the compound of formula (I), and still more preferably the pivaloyloxymethyl, phthalidyl or (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl ester of compound of formula (I). The most preferred compound is (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]imidazol-5-carboxylate (CS-866).

The compound of formula (I), which is an active ingredient of this invention, may absorb water or an organic solvent to form a hydrate or a solvate and the present invention encompasses such hydrates and solvates.

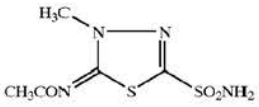
The diuretics, which are another active ingredient of this invention, are known compounds and, for example, include sulfonamide compounds such as acetazolamide, methazolamide, ethoxzolamide, clofenamide, dichlorphenamide, disulfamide, mefruside, chlorthalidone, quinethazone, furosemide, clopamide, tripamide, indapamide, chlorexolone, metolazone, xipamide, bumetanide, piretanide and X-54; thiazide compounds such as hydrochlorothiazide, methylclothiazide, benzylhydrochlorothiazide, trichloromethiazide, cyclopenthiazide, polythiazide, ethiazide, cyclothiazide, bendroflumethiazide, and hydroflumethiazide; phenoxyacetic acid compounds such as ethacrynic acid, tienilic acid, indacrinone and quincarbate; triamterene; amiloride; spironolactone; potassium canrenoate; torasemide; MK-447; and traxanox sodium which have been disclosed in U.S. Pat. No. 2,554,816, U.S. Pat. No. 2,980,679, U.S. Pat. No. 2,783,241, GB 795,174, *J. Chem. Soc.*, 1125 (1928),

U.S. Pat. No. 2,835,702, GB 851,287, U.S. Pat. No. 3,356,692, U.S. Pat. No. 3,055,904, U.S. Pat. No. 2,976,289, U.S. Pat. No. 3,058,882, *Helv. Chim. Acta,* 45, 2316 (1962), *Pharmacometrics,* 21, 607 (1982), U.S. Pat. No. 3,183,243, U.S. Pat. No. 3,360,518, U.S. Pat. No. 3,567,777, U.S. Pat. No. 3,634,583, U.S. Pat. No. 3,025,292, *J. Am. Chem. Soc.,* 82, 1132 (1960), U.S. Pat. No. 3,108,097, *Experientia,* 16, 113 (1960), *J. Org. Chem.,* 26, 2814 (1961), U.S. Pat. No. 3,009,911, U.S. Pat. No. 3,265,573, U.S. Pat. No. 3,254,076, U.S. Pat. No. 3,255,241, U.S. Pat. No. 3,758,506, BE 639,386 and U.S. Pat. No. 3,163,645. The preferred diuretic is a thiazide compound and the more preferred one is hydrochlorothiazide.

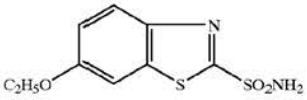
The planar chemical formulae of typical diuretics are shown below:



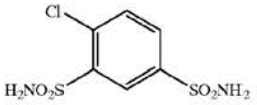
Acetazolamide



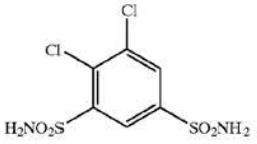
Methazolamide



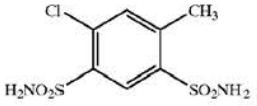
Ethoxzolamide



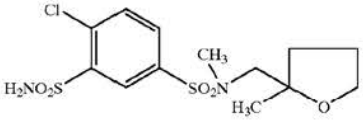
Clofenamide



Dichlorphenamide

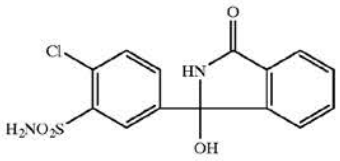


Disulfamide

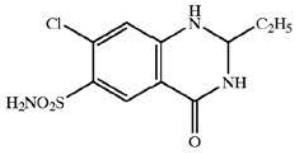


Mefruside

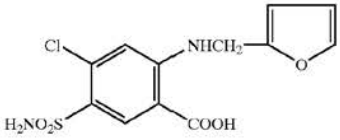
-continued



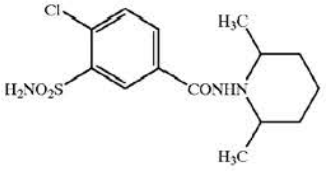
Chlorthalidone



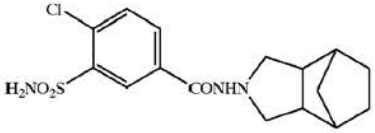
Quinethazone



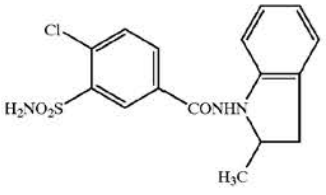
Furosemide



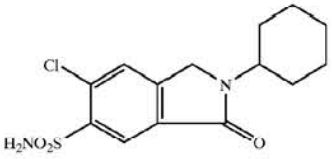
Clopamide



Tripamide

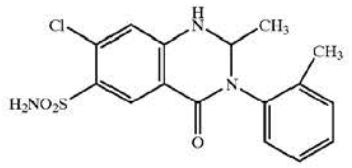


Indapamide

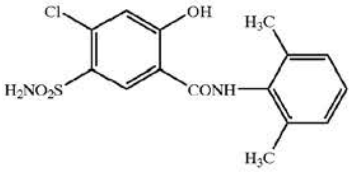


Clorexolone

-continued

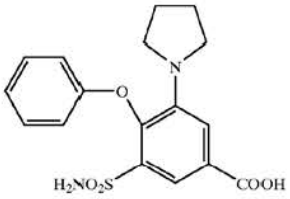


Metolazone

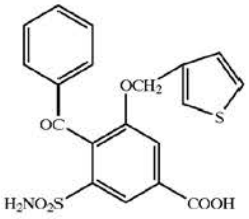


Xipamide

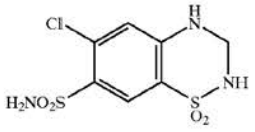
Bumetanide



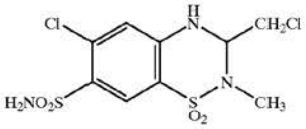
Piretanide



X-54

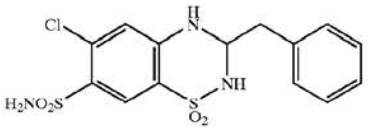


Hydrochlorothiazide

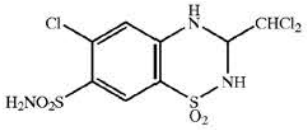


Methylclothiazide

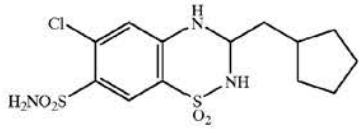
-continued



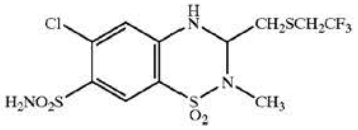
Benzylhydrochlorothiazide



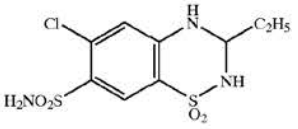
Trichloromethiazide



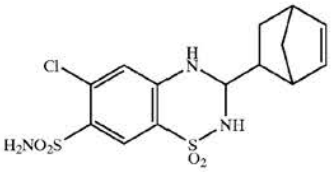
Cyclopenthiazide



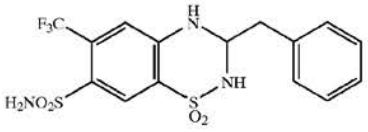
Polythiazide



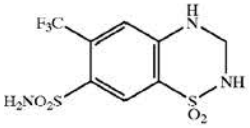
Ethiazide



Cyclothiazide

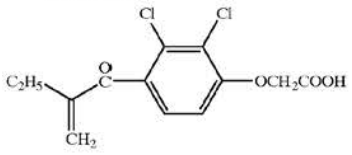


Bendroflumethiazide

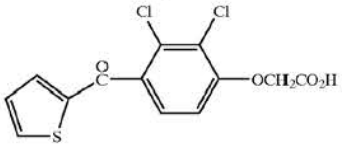


Hydroflumethiazide

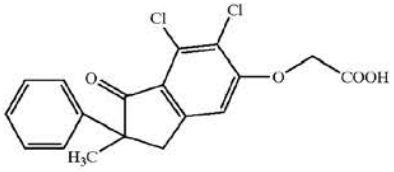
-continued



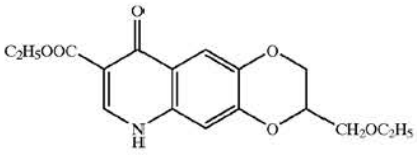
Ethacrynic acid



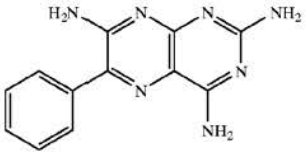
Tienilic acid



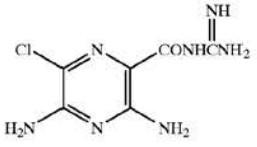
Indacrinone



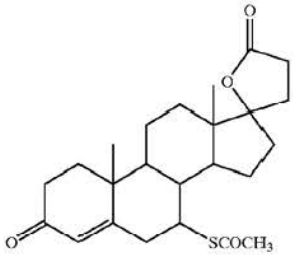
Quinearbate



Triamterene

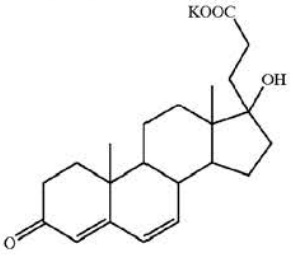


Amiloride

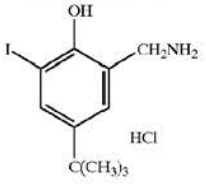


Spironolactone

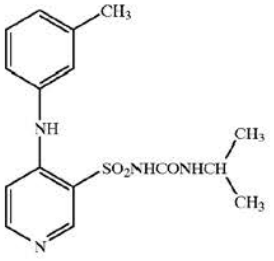
-continued



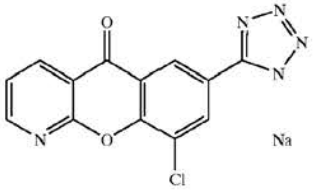
Potassium canrenoate



MK-447



Torasemide



Traxanox sodium

The compound name of hydrochlorothiazide is 6-chloro-3,4-dihydro-2H-1,2,4,-benzothiadiazin-7-sulfonamide 1,1-dioxide. The hydrochlorothiazide of this invention includes pharmacologically acceptable salts thereof, for example, a hydrohalogenic acid salt such as hydrofluoride, hydrochloride, hydrobromide or hydroiodide; nitrate; perchlorate; sulfate; phosphate; a C_1–C_4 alkanesulfonic acid salt, which may be optionally substituted with a halogen atom(s) such as methanesulfonate, trifluoromethanesulfonate or ethanesulfonate; a C_6–C_{10} arylsulfonic acid salt, which may be optionally substituted with a C_1–C_4 alkyl group(s), such as benzenesulfonate or p-toluenesulfonate; a C_1–C_6 aliphatic acid salt such as acetate, malate, fumarate, succinate, citrate, tartrate, oxalate or maleate; or an amino acid salt such as the glycine salt, lysine salt, alginine salt, ornitine salt, glutamic acid salt or aspartic acid salt. The preferred salts are the hydrochloride, nitrate, sulfate or phosphate and the particularly preferred salt is hydrochloride.

When the diuretic described hereinbefore has an asymmetric carbon(s), the present invention encompasses individual optical isomers and mixtures thereof. The present invention also encompasses hydrates of the compound described hereinbefore.

The diuretic of this invention is selected from one or more compounds described hereinbefore and preferably one diuretic agent is selected, which is used in combination with an angiotensin II receptor antagonist such as CS-866.

Preferred pharmaceutical compositions of this invention are:

(1) a pharmaceutical composition wherein the diuretic is a sulfonamide compound, a phenoxyacetic acid compound or a thiazide compound;

(2) a pharmaceutical composition wherein the diuretic is a thiazide compound;

(3) a pharmaceutical composition wherein the diuretic is selected from the group consisting of hydrochlorothiazide, methylclothiazide, benzylhydrochlorothiazide, trichloromethiazide, cyclopenthiazide, polythiazide, ethiazide, cyclothiazide, bendroflumethiazide and hydroflumethiazide; or

(4) a pharmaceutical composition wherein the diuretic is hydrochlorothiazide.

Since the present invention, i.e., pharmaceutical compositions containing a specific angiotensin II receptor antagonist, such as CS-866, and one or more diuretics, exerts excellent antihypertensive actions and has low toxicities, the pharmaceutical compositions are useful as remedies, i.e., preferably preventative or therapeutic agents for hypertension, heart diseases (angina pectoris, cardiac failure, cardiac hypertrophy), vascular disorders (arteriosclerosis, post-PTCA restenosis, peripheral vascular disorders), renal diseases (diabetic nephropathy, glomerular nephritis, nephrosclerosis); more preferably preventative and/or therapeutic agents (particularly therapeutic agents) for hypertension or heart diseases; and most preferably preventative or therapeutic agents (particularly therapeutic agents) for hypertension]. The remedies described above are preferably applied to warm-blooded animals, especially to humans.

According to the present invention, the specific angiotensin II receptor antagonist such as CS-866 and diuretics exert better therapeutic efficacy by combined administration rather than when used separately. In addition, these agents exert excellent efficacy when administered to the same warm-blooded animal at different times. It is speculated that when the 2 groups of compounds employed in the present invention are absorbed in warm-blooded animals, they switch on the signals at their respective receptors to cause their pharmacological actions. Hence, even when their plasma concen-trations decrease below the threshold plasma levels to cause each drug's effects, the switches located at their receptors have already been turned on and so the preventative or therapeutic effects on hypertension caused by the first drug are seen. The effects of the compound that is administered later are superimposed on those of the former drug. Thus the actions of these 2 agents are additive and excellent effects can be observed. Since it is clinically convenient if these 2 agents are administered at the same time, the specific angiotensin II receptor antagonist, such as CS-866, and the diuretics can be administered at the same time as a single pharmaceutical composition. In the case that these agents cannot adequately be mixed physically from formulation techniques, each compound may be separately administered at the same time. Furthermore, as described above, since these 2 groups of agents do not necessarily have

to be administered at the same time to get excellent therapeutic efficacy, the compounds may be administered at appropriate intervals. The maximum acceptable time interval to administer these 2 groups of compounds to obtain excellent treatment or preventative efficacy can be confirmed clinically or preclinically.

The administration route of specific angiotensin II receptor antagonists, such as CS-866, and diuretics is generally oral. Thus these 2 groups of compounds can be prepared as separate single formulations of each or as a single formulation by physically mixing these 2 groups of compounds. Administration formulations are, for instance, powder, granules, tablets, capsules, etc. The free compounds or pharmacologically acceptable salts or esters thereof are mixed with constituents, diluents, etc., and prepared according to conventional preparation techniques as described below.

Namely, preparations as described above are manufactured by conventionally known methods using additive agents, i.e., carriers such as diluents (for instance, organic diluents including sugar derivatives such as lactose, sucrose, glucose, mannitol, sorbitol; starch derivatives such as cornstarch, potatostarch, α-starch, and dextrin; cellulose derivatives such as crystalline cellulose; gum arabic; dextran; pullulan; and inorganic diluents including silicate derivatives such as light anhydrous silicic acid, synthetic aluminum silicate, calcium silicate, magnesium aluminometasilicate; phosphate derivatives such as calcium hydrogenphosphate; carbonates such as calcium carbonate; and sulfate derivatives such as calcium sulfate), lubricants (for instance, metallic salts of stearic acid such as stearic acid, calcium stearate, magnesium stearate; talc; waxes such as beeswax, spermaceti; boric acid; adipic acid; sulfates such as sodium sulfate; glycol; fumaric acid; sodium benzoate; DL-leucine; laurylsulphates such as sodium lauryl sulfate, magnesium lauryl sulfate; silicates such as anhydrous silicic acid, silicic acid hydrates; and starch derivatives described above can be listed), binders (for instance, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, macrogol, and similar diluents described above), disintegrators (for instance, cellulose derivatives such as low-substituted hydroxypropylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, and internally bridged-sodium carboxymethylcellulose; chemically modified starch/cellulose derivatives such as carboxymethylstarch, sodium carboxymethylstarch, bridged polyvinylpyrrolidone; and starch derivatives described above), demulsifiers (for instance, colloidal clay such as bentonite and veegum; metal hydrates such as magnesium hydroxide, aluminum hydroxide; anionic surfactants such as sodium lauryl sulfate, calcium stearate; cationic surfactants such as benzalkonium chloride; and non-ionic surfactants such as polyoxyethylenealkyl ether, and polyoxyethylene sorbitan fatty acid ester, and sucrose esters fatty acids), stabilizers (for instance, parahydroxybenzoates such as methylparaben and propylparaben; alcohols such as chlorobutanol, benzylalcohol, phenylethylalcohol; benzalkonium chloride; phenols such as phenol and cresol; thimerosal; dehydroacetic acid; and sorbic acid), flavors (for instance, sweeteners, acidifiers, and conventionally used flavors), etc.

The dose and rate of administration of the specific angiotensin II receptor antagonist, such as CS-866, and diuretics depend upon various factors such as the drugs' activities, symptoms, age, and body weight of the patients. However, generally speaking, the adult dosage (mg dose/time) of the specific angiotensin II receptor antagonist and diuretics is 0.5 to 1,000 mg (preferably 1 to 100 mg) and about 0.05 to

1,500 mg (preferably 5 to 300 mg), respectively. Compounds are administered once or several times per day, depending upon the symptoms of the patients.

Dosing ratios of the drugs in the 2 categories may also be varied. However, generally speaking, the rates of the specific angiotensin II receptor antagonist, such as CS-866, and diuretics are 1:200 to 200:1 as their weight ratios.

In the present invention, the specific angiotensin II receptor antagonist, such as CS-866, and diuretics are simultaneously administered, or separately or sequentially administered at the doses described above.

The present invention is described in more detail by way of the following Examples. However, the present invention is not limited to these examples.

TEST EXAMPLE 1

Hypotensive Effects Elicited by Co-Administration of CS-866 and Hydrochlorothiazide

Twenty-eight male spontaneously hypertensive rats aged 20 weeks (SHRs, SPF grade, purchased from Hoshino Laboratory Animals) were used. A transmitter of a telemeter (TA11PA-C40, DATA SCIENCES Inc.) was implanted in each SHR for recording blood pressure. After recovery from the surgical operations, blood pressure was monitored in the rats from the age of 24 weeks. The rats were orally given 0.5% carboxymethylcellulose solution (CMC, 2 ml/kg) for 7 successive days (once daily) by gavage. They were divided into 4 groups (7 SHRs per group) so as to give equally averaged blood pressure levels in the groups based on the blood pressure recorded on the 5th and 6th days after the CMC solution was initiated. The rats were orally treated with 0.5% CMC solution (2 ml/kg, control group) or test substance suspended in 0.5% CMC solution (2 ml/kg) for 14 successive days (once daily). Blood pressure was monitored 1 day prior to the drug administration and on the 7th and 14th days after the drug was initiated. The group composition, test substances, doses and blood pressure (the 24 hour mean blood pressure±standard error on the respective monitoring days) are summarized in Tables 1 and 2.

The test substances were hydrochlorothiazide (HCTZ), CS-866, and HCTZ and CS-866.HCTZ was prepared so as to be 10 mg/2 ml of final concentration with 0.5% CMC solution. CS-866 was suspended in 0.5% CMC solution so as to be at a final concentration of 1 mg/2 ml. CS-866 and HCTZ solution was prepared so as to be at a final concentration of [10 mg (HCTZ)+1 mg (CS-866)]/2 ml with 0.5% CMC solution.

TABLE 1

Group composition and administration of the test substance	
Group 1 Control	0.5% CMC solution
Group 2 HCTZ	HCTZ (10 mg/kg)
Group 3 CS-866	CS-866 (1 mg/kg)
Group 4 HCTZ and CS-866	HCTZ (10 mg/kg) + CS-866 (1 mg/kg)

TABLE 2

Blood pressure levels

	Group 1	Group 2	Group 3	Group 4
1 day before administration	167 ± 6	165 ± 6	167 ± 6	165 ± 4
7th day after administration	163 ± 6	152 ± 6	147 ± 4	132 ± 4
14th day after administration	166 ± 7	156 ± 6	148 ± 4	134 ± 4

As summarized in Table 2, co-administration of CS-866 and HCTZ (Group 4) showed a more excellent hypotensive action than those elicited by each of the agents CS-866 and HCTZ alone (Group 2 or 3).

Preparation Example 1

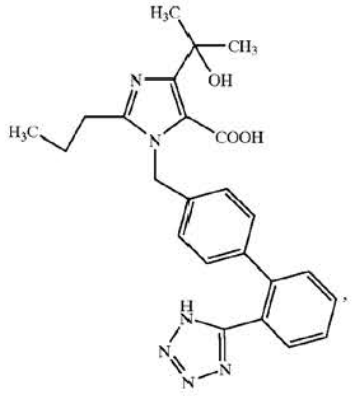
Tablets	
CS-866	10.0 mg
Hydrochlorothiazide	12.5 mg
Lactose	275.5 mg
Cornstarch	50.0 mg
Magnesium stearate	2.0 mg
Total	350 mg

The powders described above are mixed well, and tableted with a tableting machine to prepare a tablet containing 350 mg. The tablets can be sugar coated if desired.

What is claimed is:

1. A method for treating hypertension comprising administering to a warm-blooded animal in need thereof a pharmaceutically effective amount of each of (i) an angiotensin II receptor antagonist selected from the group consisting of a compound having the following formula (I):

(I)



a pharmacologically acceptable salt thereof, a pharmacologically acceptable ester thereof and a pharmacologically acceptable salt of said ester thereof, and (ii) a diuretic which is hydrochlorothiazide.

2. The method according to claim 1, wherein the warm-blooded animal is a human.

3. The method according to claim 2, wherein the angiotensin II receptor antagonist is the compound of the formula (I) or a pharmacologically acceptable ester hereof.

4. The method according to claim 2, wherein the angiotensin II receptor antagonist is a pharmacologically acceptable ester of the compound of the formula (I).

5. The method according to claim 2, wherein the angiotensin II receptor antagonist is the pivaloyloxymethyl ester, phthalidyl ester, or (5-methyl-2-oxo-1,3-dioxolen-4-yl) methyl ester of the compound of the formula (I).

6. The method according to claim 2, wherein the angiotensin II receptor antagonist is the (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl ester of the compound of th formula (I).

7. The method according to claim 2, wherein the diuretic further comprises one or more diuretics selected from the

group consisting of methylclothiazide, benzylhydrochlorothiazide, trichlormethiazide, cyclopenthiazide, polythiazide, ethiazide, cyclothiazide, bendroflumethiazide and hydroflumethiazide.

8. The method according to claim **2**, wherein a weight ratio of amounts of the compound of the formula (I) to the diuretic is 1:200 to 200:1.

9. The method according to claim **3**, wherein a weight ratio of amounts of the compound of the formula (I) to the diuretic is 1:200 to 200:1.

10. The method according to claim **5**, wherein a weight ratio of amounts of the compound of the formula (I) to the diuretic is 1:200 to 200:1.

11. The method according to claim **2**, wherein the compound of the formula (I) is administered at least once a day in an amount of 0.5 to 1,000 mg and the diuretic is administered at least once a day in an amount of 0.05 to 1,500 mg.

12. The method according to claim **2**, wherein the compound of the formula (I) is administered at least once a day in an amount of 1 to 100 mg and the diuretic is administered at least once a day in an amount of 5 to 300 mg.

13. The method according to claim **6**, wherein a weight ratio of amounts of the compound of the formula (I) to the diuretic is 1:200 to 200:1.

14. The method according to claim **6**, wherein the compound of the formula (I) is administered at least once a day in an amount of 0.5 to 1,000 mg and the diuretic is administered at least once a day in an amount of 0.05 to 1,500 mg.

15. The method according to claim **6**, wherein the compound of the formula (I) is administered at least once a day in an amount of 1 to 100 mg and the diuretic is administered at least once a day in an amount of 5 to 300 mg.

* * * * *

United States Court of Appeals
for the Federal Circuit

Apotex Inc. v. Daiichi Sankyo, Inc., 2014-1282, -1291

CERTIFICATE OF SERVICE

I, John C. Kruesi, Jr, being duly sworn according to law and being over the age of 18, upon my oath depose and say that:

Counsel Press was retained by HUSCH BLACKWELL LLP, Attorneys for Appellant to print this document. I am an employee of Counsel Press.

On **May 30, 2014** counsel has authorized me to electronically file the foregoing **Brief for Plaintiff-Appellant** with the Clerk of Court using the CM/ECF System, which will serve via e-mail notice of such filing to all counsel registered as CM/ECF users, including any of the following:

Dominick A. Conde
(Principal Counsel)
Charles A. Ginnings
Nina Shreve
Fitzpatrick, Cella, Harper & Scinto
1290 Avenue of the Americas
New York, NY 10104
212-218-2255
dconde@fchs.com
caginnings@fchs.com
nschreve@fchs.com
Counsel for Appellees

Michael Shumsky
(Principal Counsel)
John K. Crisham
Steven S. Schwartz
Kirkland & Ellis LLP
655 15th Street, N.W.
Suite 1200
Washington, DC 20005
202-879-5228
mshumsky@kirkland.com
jcrisham@kirkland.com
stephen.schwartz@kirkland.com
Counsel for Movant Cross-Appellant

Paper copies will also be mailed to the above principal counsel at the time paper copies are sent to the Court.

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May 30, 2014

/s/ John C. Kruesi, Jr.
John C. Kruesi, Jr.
Counsel Press

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Undersigned counsel certifies that:

This brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7)(B). The brief contains **7,335** words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii) and Federal Circuit Rule 32(b).

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Date: May 30, 2014

/s/ Steven E. Feldman
Steven E. Feldman
Attorney for Plaintiff-Appellant
Apotex Inc.