IN THE UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF WEST VIRGINIA

AUG 2 2000

MYLAN PHARMACEUTICALS INC.,

Plaintiff,

v.

GENEVA PHARMACEUTICALS, INC. and NORVARTIS CORPORATION,

Defendants.

Civil Action No. 1:00CV142

COMPLAINT FOR DECLARATORY JUDGMENT

Plaintiff, Mylan Pharmaceuticals Inc., by and through its undersigned counsel, files this Complaint for Declaratory Judgment against Defendants, Geneva Pharmaceuticals, Inc. and Novartis Corporation, (collectively referred to herein as "Defendants" or "Geneva") averring as follows:

NATURE OF THE ACTION

1. This is an action for a declaratory judgment pursuant to 28 U.S.C. §§ 2201 and 2202. This action arises under the Patent Laws of the United States, in particular 35 U.S.C. §§ 102, 103, 112 and 271.

THE PARTIES

2. Mylan Pharmaceuticals Inc. is a corporation organized and existing under the laws of the State of West Virginia and has its principal place of business at 781 Chestnut Ridge Road, Morgantown, West Virginia. Mylan has long been engaged in the research, development, manufacturing, and distribution of generic pharmaceutical products.

3. Upon information and belief, Geneva Pharmaceuticals, Inc. is a corporation organized under the laws of the State of Colorado, having an office and principal place of business at 2555 W. Midway Blvd., Broomfield, Colorado 80020-1632. Upon information and belief, Geneva

Pharmaceuticals, Inc. is a subsidiary of Novartis Corporation and is a licensee under U.S. Patent 6,110,493 (the "'493 patent") entitled "Terazosin capsules". A copy of the '493 patent is attached as Exhibit A.

4. Upon information and belief, Novartis Corporation ("Novartis"), is a corporation organized and existing under the laws of the New York, having a place of business at 564 Morris Avenue, Summit, New Jersey, 07901-1027.

JURISDICTION AND VENUE

5. This court has jurisdiction over the subject matter of this action under 28 U.S.C. § 1338(a).

6. Venue is proper in this district court pursuant to 28 U.S.C. §§ 1391(b) and (c).

7. Upon information and belief, this Court has personal jurisdiction over Defendants.

COUNT 1: DECLARATORY JUDGMENT OF PATENT INVALIDITY AND NON-INFRINGEMENT

8. Mylan repeats and realleges the allegations of paragraphs 1-7 as if set forth herein.

9. Mylan filed an abbreviated new drug application ("ANDA") under Section 505(j) of the Federal Food, Drug and Cosmetic Act seeking approval to engage in the commercial manufacture, use and sale of its pharmaceutical formulation containing terazosin hydrochloride as a generic version of a product marketed by Abbott Laboratories Inc. under the trademark, HYTRIN®.

10. On February 13, 2000, the United States Food and Drug Administration ("FDA") granted final approval to Mylan's ANDA No. 75-140 to market its terazosin hydrochloride product. Mylan has begun marketing its terazosin hydrochloride product.

11. Geneva has placed Mylan in reasonable apprehension that it will be sued for the alleged infringement of the '493 patent for sale of its terazosin hydrochloride product. To wit:

(a) Geneva is a licensee under U.S. Patent 5,952,003 (the "'003 patent") entitled Terazosin Capsules.

(b) In a brief filed with the U.S. District Court for the District of Columbia, Geneva has stated, "[o]bviously, if Mylan were to attempt to infringe Geneva's ['003] patent by launching terazosin capsules without obtaining Geneva's approval, Geneva would be required to seek relief to prevent such a launch."

(c) On January 18, 2000, Mylan filed a Complaint for Declaratory Judgment in this court -- Mylan Pharmaceuticals Inc. v. Geneva Pharmaceuticals Inc. and Novartis Corporation -- based upon Geneva's threats to sue Mylan for infringement of the '003 patent.

(d) On March 21, 2000, Defendants executed a covenant not to sue Mylan on the '003 patent and filed a Motion to Dismiss based upon the covenant not to sue. In oral argument before Judge Maxwell, Defendants acknowledged that a divisional of the '003 patent was pending issuance and that they would sue Mylan for infringement of the patent to be issued if settlement between the parties cannot be reached. TR. 11.

(e) In an Order dated June 7, 2000, Judge Maxwell dismissed Mylan's declaratory judgment action because, based upon Geneva's covenant not to sue, there was no longer a case or controversy. A copy of Judge Maxwell's Order and that portion of the transcript of the May 31, 2000 proceeding before Judge Maxwell in which he sets forth the basis for his ruling are attached as Exhibit B.

(f) The '493 patent which issued on August 29, 2000, is the patent Defendants were referring to in oral argument before Judge Maxwell.

12. Geneva's threats have placed Mylan in apprehension of being sued by Geneva for infringement of the '493 patent for sale of Mylan's terazosin hydrochloride product.

13. There is a substantial and continuing controversy between Mylan and Geneva as to Geneva's assertion of its intention to enforce the '493 patent against Mylan.

14. The claims of the '493 patent are invalid and/or not infringed by any product produced by Mylan..

WHEREFORE, Mylan respectfully request that this Court enter the following relief:

A. a declaratory judgment that Mylan is not liable for infringement of the '493 patent;

B. a declaratory judgment that the '493 patent is invalid;

C. a judgment in favor of Mylan for its attorneys fees, costs, and expenses in this action; and

D. a judgment in favor of Mylan for such further necessary proper relief as this Court may deem just.

A trial by jury is requested on all matters and issues so triable.

Dated: August 29, 2000

Respectfully submitted,

By: _____

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EX. A

US PATENT & TRADEMARK OFFICE
PATENT FULL TEXT AND IMAGE DATABASE

United States Patent
Guentensberger , et al.
6,110,493
August 29, 2000

Terazosin capsules

Abstract

A capsule dosage form containing solid form of terazosin in a solid carrier is disclosed. The capsule dosage form is stable under accelerated stability conditions and therapeutically equivalent to known liquid-filled terazosin capsules.

Inventors: **Guentensberger; Jeffrey W.** (Northglenn, CO); **Pelloni; Christopher L.** (Louisville, CO)
Assignee: **Novartis Corporation** (Summit, NJ)
Appl. No.: **313613**
Filed: **May 18, 1999**

U.S. Class: **424/451**; 424/456
Intern'l Class: A61K 009/48
Field of Search: 424/451,489,490,456 514/254 544/291

References Cited [Referenced By]

4092315	May., 1978	Biancee	544/291.
4112097	Sep., 1978	Uinn et al.	424/257.
4251532	Feb., 1981	Roteman	424/251.
5122514	Jun., 1992	Boger et al.	514/19.
5212176	May., 1993	Kymil et al.	514/254.
5294615	Mar., 1994	Meyer et al.	54/254.
5362730	Nov., 1994	Bauer et al.	544/291.
5412095	May., 1995	Merley et al.	544/291.
5504207	Apr., 1996	Mannine et al.	544/291.
5587377	Dec., 1996	Patel et al.	514/254.
5952003	Sep., 1999	Guentensberger et al.	424/451.
5959108	Sep., 1999	Bauer et al.	544/291.

Foreign Patent Documents

WO 93/19758	Oct., 1993	WO.

Other References

Hytrin monograph P.D.R. 46th Ed. (1992) pp. 529-531.
Hytrin monograph, P.D.R. 50th Ed. (1996) pp. 430-433.
Merck Index, 11th Ed. (1989) entry 9084.
Information Obtained Under the Freedom of Information Act relating to NDA-057 (1988).
U.S. Pharmacopcial Convention, Inc., 23, p. 1791-1793 (1995).
Sucker, et al., Pharmazeutiside Technologie, p. 320-322, Thieme Verlag Stuttgart (1991).
Information obtained under The Freedom of Information Act relating to NDA 20-347 (Dec. 1994).

Primary Examiner: Page; Thurman K.
Assistant Examiner: Benston, Jr.; William E.
Attorney, Agent or Firm: Dohmann; George R.

Parent Case Text

This application is a division of Ser. No. 08/691,907 filed Aug. 1, 1996 now U.S. Pat. No. 5,952,003.

Claims

1. A pharmaceutical solid-filled capsule dosage form containing a fill which consists of a pharmaceutically effective amount of anhydrous terazosin hydrochloride, and a solid carrier, which solid-filled capsule dosage form is therapeutically equivalent to a reference liquid-filled terazosin hydrochloride capsule which is the subject of FDA-approved New Drug Application N20347 comprising an equivalent amount of terazosin and a non-aqueous liquid carrier, and which solid-filled capsule dosage form has an average dissolution at 30 minutes measured according to U.S.P. Method II at 50 r.p.m. in water of at least 85 percent of the label amount with no individual capsule below 80 percent of the label amount after being maintained in a high density polyethylene bottle closed with a screw cap at about 40.degree. C. and 85 percent relative humidity for twelve weeks.

2. A capsule dosage form of claim 1 wherein the average dissolution at 30 minutes is at least 90 percent of the label amount with no individual capsule below 80 percent of the label amount.

3. A capsule dosage form of claim 1 wherein the average dissolution at 30 minutes is at least 95 percent of an initial average dissolution.

4. A dosage form of claim 1 wherein the solid carrier comprises (a) from 70 to 100 percent by weight of a diluent; (b) from 0 to 20 percent by weight of a disintegrant; and (c) 0 to 10 percent by weight of a lubricant.

5. A dosage form of claim 4 wherein the solid carrier comprises (a) from 85 to 97 percent by weight of a diluent; (b) from 1 to 10 percent by weight of a disintegrant; and (c) 0.2 to 5 percent by weight of a lubricant.

6. A dosage form of claim 4 wherein the solid carrier comprises (a) from 90 to 97 percent by weight of a diluent; (b) from 1 to 5 percent by weight of a disintegrant; and (c) 0.5 to 2 percent by weight of a lubricant.

7. A dosage form of claim 4 wherein the diluent is a monosaccharide, a disaccharide or a polysaccharide.

8. A capsule dosage form of claim 5 wherein the average dissolution at 30 minutes is at least 90 percent of the label amount with no individual capsule below 80 percent of the label amount.

9. A capsule dosage form of claim 6 wherein the average dissolution at 30 minutes is at least 95 percent of an initial average dissolution.

10. A capsule dosage form according to claim 1 which is a hard gelatin capsule.

11. A capsule dosage form of claim 10 wherein the solid carrier comprises microcrystalline cellulose.

12. A capsule dosage form of claim 11 wherein the average dissolution at 30 minutes is at least 90 percent of an initial average dissolution.

13. A capsule dosage form of claim 12 wherein the average dissolution at 30 minutes is at least 95 percent of an initial average dissolution.

Description

SUMMARY

Terazosin is administered to subjects in filled gelatin capsules containing a solid fill. The capsules are bioequivalent to a reference liquid-filled terazosin capsule dosage form, but have an advantageous shelf life and are simpler to manufacture.

BACKGROUND

Terazosin, especially in its salt forms, is a well-known medicament which is useful in the treatment of hypertension and benign prostatic hyperplasia. For example, U.S. Pat. No. 4,026,894 discloses the hydrochloride salt of terazosin as well as its use in pharmaceutical formulations used for the treatment of hypertension, and U.S. Pat. No. 4,251,532 discloses the compound terazosin hydrochloride dihydrate and its use as a pharmaceutical active ingredient.

The U.S. Food and Drug Administration (FDA) first approved terazosin hydrochloride dihydrate for sale in the United States in 1987 as a tablet formulation which was marketed by Abbott Laboratories under

the tradename HYTRIN.

U.S. Pat. No. 5,294,615 describes a soft gelatin capsule dosage form containing terazosin hydrochloride in a non-aqueous liquid carrier and indicates that polyethylene glycol is a preferred non-aqueous liquid carrier. In 1994, the FDA approved a soft gelatin capsule formulation containing the active ingredient suspended in a non-aqueous liquid carrier composed primarily of polyethylene glycol with some glycerine present.

The present invention relates to the surprising discovery that a stable, therapeutic equivalent of known liquid-filled capsule dosage forms of terazosin hydrochloride is prepared simply and effectively by replacing the liquid carrier with a solid carrier. Thus, the present invention relates to solid-filled terazosin hydrochloride capsules which are stable under accelerated conditions and which are therapeutic equivalents of the liquid-filled capsule dosage forms.

As therapeutic equivalents, the inventive solid-filled terazosin hydrochloride capsules are surprisingly bioequivalent to the FDA approved liquid-filled terazosin hydrochloride capsules. It is a great advantage that the inventive formulations are bioequivalent to the FDA approved liquid-filled terazosin hydrochloride capsules because the inventive formulations can be marketed as generic equivalents of the approved product without performing new safety and efficacy studies, which add considerably to the cost of obtaining FDA approval to market a drug product.

DETAILED DESCRIPTION

The present invention relates to a pharmaceutical capsule dosage form which comprises a pharmaceutically effective amount of terazosin in the form of a solid pharmaceutically acceptable salt, or solvate thereof, and a solid carrier, which capsule dosage form is bioequivalent to a reference terazosin capsule, which reference terazosin capsule is a liquid-filled capsule comprising an equivalent amount of terazosin and a non-aqueous liquid carrier. Thus, the present invention relates to an improved, pharmaceutical capsule dosage form containing terazosin, in the form of a salt or solvate thereof, which dosage form is bioequivalent to a liquid-filled terazosin capsule comprising an equivalent amount of terazosin and a non-aqueous liquid carrier, wherein the improvement consists essentially of replacing the non-aqueous liquid carrier with a pharmaceutically acceptable carrier which is a solid at 25.degree. C.

In particular, the present invention relates to a pharmaceutical capsule dosage form which is stable under accelerated stability conditions. Accordingly, the present invention relates to a stable pharmaceutical solid-filled capsule dosage form which comprises a pharmaceutically effective amount of terazosin in the form of a solid pharmaceutically acceptable salt, or solvate thereof, and a solid carrier, which solid-filled capsule dosage form is therapeutically equivalent to a reference liquid-filled terazosin capsule comprising an equivalent amount of terazosin and a non-aqueous liquid carrier, and which solid-filled capsule dosage form has an average dissolution at 30 minutes measured according to U.S.P. Method II at 50 r.p.m. in water of at least 85 percent of the label amount with no individual capsule below 80 percent of the label amount after being maintained in a high density polyethylene bottle closed with a screw cap at about 40.degree. C. and 85 percent relative humidity for twelve weeks.

Pharmaceutical capsule dosage forms are well-known in the art. In general, a capsule dosage form consists essentially of a shell and a fill, which is encapsulated by the shell and contains the active ingredient, in this case terazosin in the form of a salt or solvate, as well as carrier. The shell is usually primarily composed of gelatin and can contain additional ingredients such as a plasticizer, like glycerine, sorbitol or propylene glycol, an opacifier, a coloring agent, a flavoring agent and/or a preservative. Generally, capsule shells are classified as either soft elastic capsules, such as those described in U.S. Pat. No. 5,294,615 which have a plasticizer, or hard capsule shells, which generally do not contain any appreciable amount of a plasticizer. Preferably, the inventive dosage forms have a hard capsule shell due to the relative ease of manufacture.

In this application, when referring to a solid-filled capsule dosage form, "stable" means that the capsule dosage form has an expiration date which permits it to be sold for a period of at least two years from its manufacture.

A pharmaceutically effective amount of terazosin is an amount which is appropriate in a dosage form useful to treat hypertension or benign prostate hyperplasia. In general, from 1 to 15 mg of terazosin is a pharmaceutically effective amount. Currently, terazosin hydrochloride is marketed in dosage forms containing 1, 2, 5, and 10 mg equivalent of terazosin.

Solid pharmaceutically acceptable salts and solvates of terazosin include any non-toxic acid addition salt which is water-soluble and solid at room temperature, in particular the hydrochloride salt in anhydrous form, including polymorphic forms and mixtures thereof, or as a non-toxic solvate, such as terazosin hydrochloride dihydrate.

In this application, the expression "therapeutically equivalent to a reference liquid-filled terazosin capsule" is intended to mean that the inventive capsule dosage form is a generic equivalent of the reference liquid-filled terazosin capsule and as such is rated an AB therapeutic equivalent of the reference liquid-filled capsule by the FDA whereby actual or potential bioequivalence problems have been resolved with adequate in vivo and/or in vitro evidence supporting bioequivalence. Accordingly, the solid-filled capsule dosage form is the subject of an Abbreviated New Drug Application (ANDA) filed under section 505(j) of the Food Drug and Cosmetic Act (FDCA) (21 U.S.C. 355(j)) which contains a bioequivalence study wherein the reference drug is a liquid-filled terazosin capsule containing the active ingredient dissolved or suspended in a non-aqueous liquid carrier as the fill.

The expression "bioequivalent" or "bioequivalence" is a term of art and is intended to be defined in accordance with Approved Drug Products with Therapeutic Equivalence Evaluations, 15th Edition, pages vii-xvii, which is published by the U.S. Department of Health and Human Services, and is commonly known as the "Orange Book". Bioequivalence of different formulations of the same drug substance involves equivalence with respect to the rate and extent of drug absorption. The extent and rate of absorption of the test formulation is compared to a reference formulation in order to determine whether the two formulations are bioequivalent. The standard bioequivalence study is conducted in crossover fashion by extensive testing which includes administering single doses of the test and reference drugs to a number of volunteers, usually 12 to 24 healthy normal adults, and then measuring the blood or plasma levels of the drug over time. The pharmacokinetic characteristics of the concentration-time curve, such as the maximum observed plasma concentration (C.sub.max), the time to reach C.sub.max, and the area under the plasma concentration versus time curve (AUC), are examined by statistical procedures which are well-established in the field of pharmacokinetics. Two formulations whose rate and extent of absorption differ by -20%/+25% or less are generally considered to be bioequivalent. Detailed guidelines for establishing the bioequivalence of a formulation with a reference formulation have been published by the FDA Office of Generic Drugs, Division of Bioequivalence.

The expression "solid carrier" means that the overall physical form of the filling of the capsule is in solid form at room temperature. Generally, the filling is a powder which has been formed into a capsule-shaped slug at low compression.

The expression "liquid-filled" means that the overall physical form of the filling is a liquid at room temperature. The expression "liquid-filled" is intended to include suspensions or mixtures of liquids and solids which have the overall characteristics of a liquid.

An "equivalent amount of terazosin" means the same amount of terazosin base. Thus, by weight, it requires less anhydrous terazosin hydrochloride than terazosin hydrochloride dihydrate to have an equivalent amount of terazosin. Generally, the inventive capsules have an equivalent amount of terazosin of 1 mg, 2 mg, 5 mg or 10 mg.

The expression "non-aqueous liquid carrier" is defined according to U.S. Pat. No. 5,294,615, which is here incorporated by reference. In general, liquid carriers containing a major portion a liquid polyethylene glycol, for example, those having a molecular weight between about 200 and about 600, alone or combined with additives, like a viscosity-building agent or glycerine, are described as suitable non-aqueous liquid carriers.

The present solid-filled capsule dosage form is stable based on accelerated stability studies. Accelerated stability studies are well-known in the pharmaceutical formulation sciences. In general, the capsules are maintained at about 40.degree. C. and 85 percent relative humidity for up to twelve weeks in a high density polyethylene (HDPE) bottle closed with a screw cap and the release rate of the capsule is measured by in vitro dissolution testing. Since accelerated stability studies are generally predictive of the stability of a formulation under normal conditions, for example, by use of the Arrhenius rate equation, such studies are used to determine the appropriate expiration dating for the formulation. If the formulation performs well in accelerated stability studies, no further testing is usually required to establish an advantageous expiration period. If the dissolution slows significantly after storage, the accelerated stability study does not support an advantageous expiration period. In general, it is a great advantage if an expiration period of at least 24 months is established by an accelerated stability study.

In general, the average dissolution at 30 minutes measured according to U.S.P. Method II at 50 r.p.m. in water for 6 randomly selected capsules of the present invention, which capsules were maintained at about 40.degree. C. and 85 percent relative humidity for twelve weeks in a high density polyethylene (HDPE) bottle closed with a screw cap, is at least 85 percent of the label amount, with no individual capsule below 80 percent of the label amount, the label amount being the amount of terazosin base listed on the label, for example, a 5 mg capsule has a label amount of 5 mg of terazosin. Preferably, the average dissolution at 30 minutes is at least 90 percent of the label amount with no individual capsule below 80, preferably 85, percent of the label amount. Most preferably, the average dissolution at 30 minutes is at least 90, preferably 95, percent of an initial dissolution; the initial dissolution being the result obtained by testing capsules from the same lot under identical conditions; except that the initially tested capsules are not subjected to accelerated stability conditions. Thus, the average dissolution of the inventive capsule dosage form remains virtually constant over time, even after being stored under accelerated conditions for 12 weeks.

Capsules showing the results described above in accelerated stability studies are generally expected to be stable under normal conditions for at least two years.

The present solid-filled capsules are bioequivalent to a reference liquid-filled terazosin capsule comprising an equivalent amount of terazosin and a non-aqueous liquid carrier. Preferably, the liquid carrier comprises a major portion, such as 80 to 100% by weight, of a liquid polyethylene glycol, such as is described in U.S. Pat. No. 5,294,615, especially wherein the liquid carrier further comprises a minor amount, such as from 1 to 4 weight-percent, of glycerine. Most preferably, the reference liquid-filled terazosin capsule is a terazosin hydrochloride capsule which is the subject of a New Drug Application which is approved by the U.S. Food and Drug Administration, especially New Drug Application number N20347, which was approved on Dec. 14, 1994.

In general, the solid carrier is composed of a solid diluent along with other optional ingredients such as a disintegrant, a lubricant, a binder or a surfactant. A solid carrier used in the inventive formulations is typically composed of (a) from 70 to 100 percent by weight of a diluent; and optionally an effective disintegration-producing amount of a disintegrant and/or an effective lubricating amount of a lubricant. For example a typical formulation contains (a) from 70 to 100 percent by weight of a diluent, (b) from 0 to 30 percent by weight of a disintegrant; and (c) 0 to 10 percent by weight of a lubricant. Preferably, the solid carrier contains (a) from 85 to 97 percent by weight of a diluent; (b) from 1 to 10 percent by weight of a disintegrant; and (c) 0.2 to 5 percent by weight of a lubricant. Most preferably, the solid carrier contains (a) from 90 to 97 percent by weight of a diluent; (b) from 1 to 5 percent by weight of a disintegrant; and (c) 0.5 to 2 percent by weight of a lubricant.

Any pharmaceutically acceptable solid diluent which is non-toxic, inert, both to the active ingredient and to the capsule shelf, and compressible is useful in the solid carrier. Preferably, the diluent is readily wetted by or dissolved in an aqueous medium. In general, the diluent is a non-toxic, inert monosaccharide, disaccharide, polysaccharide, solid fatty acid, solid triglyceride, or solid phosphate, carbonate, silicate, sulfate or chloride salt. Suitable saccharide diluents include anhydrous or hydrated lactose, microcrystalline cellulose, sucrose, dextrose, sorbitol, manitol, and starch. Suitable inorganic diluents include dibasic calcium phosphate, calcium sulfate, kaolin, magnesium carbonate, magnesium oxide, talc, potassium chloride and sodium chloride and/or hydrates thereof.

Disintegrants and lubricants are well-known in the pharmaceutical sciences. Suitable disintegrants include starch, croscarmellose sodium, crospovidone, sodium starch glycolate, croscarmellose calcium, microcrystalline cellulose and polacralin potassium, and the like. Suitable lubricants include magnesium stearate, sodium stearyl fumarate, hydrogenated vegetable oil, hydrogenated castor oil, hydrogenated cottonseed oil, stearic acid and calcium stearate, and the like.

It is possible for certain ingredients to serve more than one function in the formulation, for example, microcrystalline cellulose and starch each function as both diluent and as a disintegrant.

In addition to the diluent, disintegrant and lubricant, solid carriers according to the present invention can also include a binder, such as povidone, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, ethylcellulose and sodium alginate, as well as other pharmaceutical excipients, such as glidants and surfactants, like talc, colloidal silicon dioxide, polyethylene glycol, sodium lauryl sulfate, polysorbate, docusate sodium.

It is important for the solid carrier to contain only excipients which are inert to both the active ingredient and to the capsule shell. With regard to the capsule shell, inert excipients are those which do not promote cross-linking in the capsule shell. Such cross-linking producing excipients are well-known in the pharmaceutical formulation sciences and are generally those which degrade by releasing formaldehyde. Thus, the inert solid carrier is a non-formaldehyde-releasing solid carrier.

The present invention further relates to a method of administering a therapeutically effective amount of terazosin to a human subject, which comprises producing a plasma concentration of terazosin in the subject having both a maximum concentration (C.sub.max) and an area under a plasma-concentration vs. time curve (AUC) within the range from -20% to +25% of that produced by a reference liquid-filled terazosin capsule, which contains an equivalent amount of terazosin in a non-aqueous liquid carrier, by administering a solid-filled capsule dosage form which consists essentially of a pharmaceutically effective amount of terazosin in the form of a solid pharmaceutically acceptable salt, or solvate thereof, and a solid carrier to the subject; especially wherein the reference capsule is the subject of approved New Drug Application number N20347. Preferably, the terazosin is present in the form of anhydrous terazosin hydrochloride or terazosin hydrochloride dihydrate.

In addition, the present invention relates to a method of formulating a stable therapeutic equivalent of a reference liquid-filled terazosin capsule, which comprises the steps of

(a) preparing a solid-filled capsule dosage form consisting essentially of a pharmaceutically effective amount of terazosin in the form of a solid pharmaceutically acceptable salt, or solvate thereof, and a solid carrier, which solid-filled capsule dosage form has an average dissolution at 30 minutes measured according to U.S.P. Method II at 50 r.p.m. in water of at least 85 percent of the label amount with no individual capsule below 80 percent of the label amount after being maintained in a high density polyethylene bottle closed with a screw cap at about 40.degree. C. and 85 percent relative humidity for twelve weeks; and

(b) establishing that the solid-filled capsule dosage form is a therapeutic equivalent of the reference liquid-filled terazosin capsule by conducting a bioequivalence study which demonstrates that administration of the solid-filled capsule dosage form to a human subject produces both a maximum concentration (C.sub.max) and an area under a plasma-concentration vs. time curve (AUC) within the range from -20% to +25% of that produced by the reference liquid-filled terazosin capsule.

The following examples further illustrate, but do not limit, the present invention.

EXAMPLE 1

Capsules containing 5 mg of terazosin were prepared by blending the following ingredients according to standard methods and encapsulating the formulation in #3 gelatin capsules.

Ingredient	mg/dose
Terazosin HCl Anhydrous	5.471
Lactose Monohydrate, NF	174.529
Microcrystalline Cellulose, NF	28.000
Crospovidone, NF	14.000
Magnesium Stearate, NF	3.000
Total Capsule Fill Weight	225.000

The rate and extent of terazosin absorption under fasting conditions of the capsules described above was compared with the rate and extent of terazosin absorption of the FDA-approved terazosin hydrochloride capsule containing the equivalent amount of terazosin base (approved on Dec. 14, 1994 under application N20347 and sold by Abbott Laboratories under the tradename HYTRIN Capsules, 5 mg) measured under identical conditions in a single dose, randomized, two-period, two-treatment, two-sequence crossover study in a group of healthy adult male volunteers. The study demonstrates that the above-described capsule formulation is bioequivalent to the liquid-filled FDA-approved capsule containing the equivalent amount of terazosin base in accordance with Guidance Statistical Procedures for Bioequivalence Studies Using a Standard Two Treatment Crossover Design prepared by the FDA Division of Bioequivalence because it meets the log transformed confidence intervals of 0.8-1.25 for both AUC and C.sub.max. In vitro studies further demonstrate that capsules similar to those described above containing 1 mg, 2 mg and 10 mg of terazosin base are also biocquivalent to with the FDA-approved terazosin hydrochloride capsule containing the equivalent amount of terazosin base. The 1 mg, 2 mg and 10 mg capsules contain the above ingredients in the amounts stated above, but adjust the amount of terazosin and lactose monohydrate according to the formula terazosin HCl+lactose monohydrate.apprxeq.180 mg.

EXAMPLE 2

Capsules prepared according to Example 1 were subjected to an accelerated stability study wherein HDPE bottles containing 100 or 1000 capsules were closed with a screw cap and stored at 40.degree. C. and 85% relative humidity for a period of from 1 to 12 weeks. After the storage period, a sample of capsules was subjected to dissolution testing according to U.S.P. Method II (paddles) at 50 rpm in 900 ml of water for 30 minutes. The average results are reported in the following table.

TABLE 1

Accelerated Stability
Dissolution Test (% of label - average of 6 capsules)

	1 mg		2 mg		5 mg		10 mg	
bottle count	100	1000	100	1000	100	1000	100	1000
Initial	102	102	100	100	100	100	99	99
4 week	105	105	98	98	99	101	98	99
8 week	99	100	100	98	100	100	100	98
12 week	99	99	100	101	100	101	98	98

No individual capsule showed a dissolution below 95% at 4 weeks, 91% at 8 weeks, and 88% at 12 weeks.

The accelerated stability study supports a two year expiration date for the solid-filled capsules described above.

EXAMPLE 3

The following formulations for capsules containing terazosin hydrochloride equivalent to 5 mg of terazosin are prepared by blending the ingredients according to standard methods. Capsules containing 1 mg, 2 mg and 10 mg of terazosin are prepared by encapsulating a proportional amount of the capsule fill.

Ingredient	mg/dose
1A.	
Terazosin HCl Anhydrous	5.471
Lactose Monohydrate, NF	88.529
Microcrystalline Cellulose, NF	89.000
Crospovidone, NF	14.000
Magnesium Stearate, NF	3.000
Total Capsule Fill Weight	200.000
1B.	
Terazosin HCl Anhydrous	5.471
Microcrystalline Cellulose, NF	167.529
Crospovidone, NF	14.000
Magnesium Stearate, NF	3.000
Total Capsule Fill Weight	190.000
1C.	
Terazosin HCl Anhydrous	5.471
Lactose Monohydrate, NF	174.529
Microcrystalline Cellulose, NF	28.000
Sodium Starch Glycolate, NF	14.000
Magnesium Stearate, NF	3.000
Total Capsule Fill Weight	225.000
1D.	
Terazosin HCl Anhydrous	5.471
Lactose Monohydrate, NF	174.529
Microcrystalline Cellulose, NF	28.000
Croscarmellose Sodium, NF	14.000
Magnesium Stearate, NF	3.000
Total Capsule Fill Weight	225.000
1E.	
Terazosin HCl Anhydrous	5.471
Lactose Monohydrate, NF	170.529
Microcrystalline Cellulose, NF	28.000
Crospovidone, NF	14.000
Colloidal Silicon Dioxide, NF	2.000
Talc USP	2.000
Magnesium Stearate, NF	3.000
Total Capsule Fill Weight	225.000
1F.	
Terazosin HCl Anhydrous	5.471
Corn Starch, NF, Pregelatinized	174.529

Microcrystalline Cellulose, NF 28.000
Crospovidone, NF 14.000
Magnesium Stearate, NF 3.000
Total Capsule Fill Weight 225.000

1G.
Terazosin HCl Anhydrous 5.471
Lactose Monohydrate, NF 172.529
Microcrystalline Cellulose, NF 28.000
Crospovidone, NF 14.000
Sodium Stearyl Fumarate, NF 5.000
Total Capsule Fill Weight 225.000

1H.
Terazosin HCl Anhydrous 5.471
Dibasic Calcium Phosphate USP 199.529
Microcrystalline Cellulose, NF 28.000
Crospovidone, NF 14.000
Magnesium Stearate, NF 3.000
Total Capsule Fill Weight 250.000

1I.
Terazosin HCl Anhydrous 5.471
Lactose Monohydrate, NF 194.529
Hydroxypropyl Methylcellulose 8.000
Crospovidone, NF 14.000
Magnesium Stearate, NF 3.000
Total Capsule Fill Weight 225.000

1J.
Terazosin HCl Anhydrous 5.471
Lactose Monohydrate, NF 197.529
Povidone USP 5.000
Crospovidone, NF 14.000
Magnesium Stearate, NF 3.000
Total Capsule Fill Weight 225.000

1K.
Terazosin HCl Anhydrous 5.471
Lactose Monohydrate, NF 170.529
Microcrystalline Cellulose, NF 28.000
Crospovidone, NF 14.000
Sodium Lauryl Sulfate USP 2.000
Polyethylene Glycol, NF 2.000
Hydrogenated Vegetable Oil NF 3.000
Total Capsule Fill Weight 225.000

1L.
Terazosin HCl Anhydrous 5.471
Compressible, Sugar, NF 194.529
Microcrystalline Cellulose, NF 28.000
Crospovidone, NF 14.000
Magnesium Stearate, NF 3.000
Total Capsule Fill Weight 245.000

1M.
Terazosin HCl Anhydrous 5.471
Compressible Sugar, NF 88.529
Confectioners Sugar, NF 89.000
Crospovidone, NF 14.000
Magnesium Stearate, NF 3.000
Total Capsule Fill Weight 200.000

1N.
Terazosin HCl Anhydrous 5.471
Manitol, NF 167.529
Crospovidone, NF 14.000
Magnesium Stearate, NF 3.000
Total Capsule Fill Weight 190.000

1O.
Terazosin HCl Anhydrous 5.471
Dextrose, USP 174.529
Microcrystalline Cellulose, NF 28.000
Sodium Starch Glycolate, NF 14.000
Magnesium Stearate, NF 3.000
Total Capsule Fill Weight 225.000

1P.
Terazosin HCl Anhydrous 5.471
Lactose Monohydrate, NF 174.529
Microcrystalline Cellulose, NF 28.000
Croscarmellose Calcium, NF 14.000
Magnesium Stearate, NF 3.000
Total Capsule Fill Weight 225.000

1Q.
Terazosin HCl Anhydrous 5.471
Lactose Monohydrate, NF 168.529
Microcrystalline Cellulose, NF 30.000
Polacrallin Potassium 14.000
Magnesium Stearate, NF 3.000
Total Capsule Fill Weight 225.000

1R.
Terazosin HCl Anhydrous 5.471
Confectioners Sugar, NF 174.529
Microcrystalline Cellulose, NF 28.000
Crospovidone, NF 14.000
Magnesium Stearate, NF 3.000
Total Capsule Fill Weight 225.000

1S.
Terazosin HCl Anhydrous 5.471
Manitol, USP 172.529
Microcrystalline Cellulose, NF 28.000
Crospovidone, NF 14.000
Sodium Stearyl Fumarate, NF 5.000
Total Capsule Fill Weight 225.000

1T.
Terazosin HCl Anhydrous 5.471

Manitol, NF	199.529
Microcrystaliine Cellulose, NF	28.000
Crospovidone, NF	14.000
Magnesium Stearate, NF	3.000
Total Capsule Fill Weight	250.000

1U.

Terazosin HCl Anhydrous	5.471
Sorbitol, USP	194.529
Hydroxypropyl Methylcellulose	8.000
Crospovidone, NF	14.000
Magnesium Stearate, NF	3.000
Total Capsule Fill Weight	225.000

1V.

Terazosin HCl Anhydrous	5.471
Sorbitol, USP	197.529
Povidone USP	5.000
Crospovidone, NF	14.000
Magnesium Stearate, NF	3.000
Total Capsule Fill Weight	225.000

1W.

Terazosin HCl Anhydrous	5.471
Lactose Monohydrate, NF	170.529
Microcrystalline Cellulose, NF	28.000
Sodium Alginate	16.000
Hydrogenated Castor Oil	5.000
Total Capsule Fill Weight	225.000

An accelerated stability study supports an expiration period of at least two years for each of the formulations. After a single dose to a healthy human subject, each of the above formulations produces a plasma concentration of terazosin in the subject having both C.sub.max and an AUC within the range from -20% to +25% of that produced by a reference liquid-filled terazosin capsule.

* * * * *

EX. B

AO 450 (Rev. 5/85) Judgment in a Civil Case

FILED
JUN 7 2000
U.S. DISTRICT COURT
KINS WV 26241

United States District Court

NORTHERN DISTRICT OF WEST VIRGINIA

Mylan Pharmaceuticals, Inc.

V.

Geneva Pharmaceuticals, Inc. and
Novartis Corporation

JUDGMENT IN A CIVIL CASE

CASE NUMBER: 1:00cv08

☐ **Jury Verdict.** This action came before the Court for a trial by jury. The issues have been tried and the jury has rendered its verdict.

☒ **Decision by Court.** This action came to trial or hearing before the Court. The issues have been tried or heard and a decision has been rendered.

IT IS ORDERED AND ADJUDGED

that the Court upon full consideration of all matters offered has determined that because of the filing of the Covenant Not to Sue by Defendant, there is no longer a controversy extant upon which jurisdiction may be conferred unto this Court. Accordingly, the Court

ORDERED that the Defendants' Motion to Reconsider is GRANTED and that the Order entered by this Court on 4/13/00 is VACATED. It was further, ORDERED that Defendants' Motion to Dismiss is hereby GRANTED.

Thereupon, this civil action being dismissed, the case shall be removed from the active docket of this Court.

June 7, 2000
Date

Wally Edgell, Ph.D.
Clerk

Judy Sutton
(By) Deputy Clerk

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA

MYLAN PHARMACEUTICALS INC.,

Plaintiff,

v. CIVIL ACTION NO. 1:00CV08

GENEVA PHARMACEUTICALS, INC.
and NOVARTIS CORPORATION,

Defendants.

O R D E R

On the 31st day of May, 2000, came the Plaintiff Mylan Pharmaceuticals, Inc. by counsel, Steven Lieberman, Elizabeth A. Leff, and Thomas H. Newbraugh, and also came the Defendants, Geneva Pharmaceuticals, Inc. and Novartis Corporation, by their counsel, Douglass C. Hochstetler, Janine M. Girzadas and Stephen G. Jory, for a hearing upon Defendants' Motion for Reconsideration of the Order entered by this Court on April 13, 2000.

The Court, upon full consideration of all matters offered and presented, including the written memoranda and oral argument of counsel, and for the reasons expressed upon the record, determined that because of the filing of the Covenant Not to Sue by Defendant, there is no longer a case or controversy extant upon which jurisdiction may be conferred unto this Court. Accordingly, the Court

ORDERED that the Defendants' Motion to Reconsider is GRANTED and that the Order entered by this Court on April 13, 2000 is VACATED. It was further

ORDERED that Defendants' Motion to Dismiss is hereby GRANTED.

Thereupon, this civil action being dismissed, the same shall be removed from the active docket of this Court.

ENTER: This the 7th day of June, 2000.

UNITED STATES DISTRICT JUDGE

Order prepared by:

STEPHEN G. JORY
Counsel for Defendants

I hereby certify that the annexed instrument is a true and correct copy of the original filed in my office.
ATTEST: Dr Wally Edgell
Clerk, U.S. District Court
Northern District of West Virginia
By: Deputy Clerk

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA

MYLAN PHARMACEUTICALS, INC.

Plaintiffs

v. CIVIL ACTION 1:00CV8

GENEVA PHARMACEUTICALS, INC. &
NOVARTIS CORPORATION,

Defendants

****

BEFORE: The Honorable Robert E. Maxwell, Senior Judge.

APPEARANCES:

For the Plaintiff: Steven Lieberman, Esq.
Elizabeth A. Leff, Esq.
Washington, D. C.
Thomas H. Newbraugh, Esq.
Morgantown, WV

For the Defendants: Douglass C. Hochstetler, Esq.
Janine M. Girzadas, Esq.
Chicago, IL
Stephen G. Jory, Esq.
Elkins, WV

****

Whereupon, on the 31st day of May, 2000, in the United States District Court, Northern District of West Virginia, sitting at Elkins, the above-styled matter came on for a hearing on pending motions, and the following matters were had, to-wit:

controversy exists at every point in litigation.

At this stage, your Honor, as in GAF, the litigation is occurring, but there is no controversy between the parties, because there is no risk of patent infringement. Today, Mylan cannot infringe any patent and for that reason there is no case or controversy under the Federal Circuit's decisions.

With respect to Lubrizol. Lubrizol was a situation where they made an allegation that the patent had issued and it turned out they were wrong as to that. There, the Court wasn't facing the issue of whether or not a case or controversy existed. And it is totally distinguishable from this one for there is no allegation here that the patent has issued, it hasn't issued and there is no dispute about that.

With respect to Novartis' claims. We have had, as your Honor has pointed out, a restriction requirement on the claims and filed what is known as a "continuation application", your Honor. Which is simply a reprosecution of the claims. And those claims are the ones we expect to issue shortly.

Unless your Honor has any further questions, that's all I have.

THE COURT: No, sir. Thank you very much.

MR. HOCHSTETLER: Thank you very much, your Honor.

THE COURT: This civil action has been filed

pursuant to Title 28, United States Code, Section 2201, which we refer to as the Declaratory Judgment Act, wherein, Mylan Pharmaceuticals, Inc., is the Plaintiff.

Under the Declaratory Judgment Act, a district court has jurisdiction over a declaratory judgment action only when there is an actual case or controversy.

The United States Court of Appeals for the Federal Circuit clarified what is necessary to establish the presence of an actual case or controversy in an action involving the declarations of patent rights and relationships in the case of BP Chemical Limited v. Union Carbide Corporation. The Court set forth a two part test:

> "As applied to declarations of patent rights and relationships for an actual controversy, more is required than the existence of an adversarial held patent. Thus in patent litigation there has evolved a pragmatic two part test for determining declaratory justiciability. There must be both (1) an explicit threat or other action by the patentee, which creates a reasonable apprehension on the part of the declaratory plaintiff that it will face an infringement suit, and (2) present an activity which could constitute infringement or concrete steps taken with the intent to conduct such activity." 4 F.3d 975 at 978 (Fed. Cir. 1993).

The determination of whether an actual controversy exists upon particular facts is, according to the United States Court of Appeals for the Federal Circuit, a question of law that is subject to plenary appellate review. That's from BP Chemicals Limited, 4 F.3d 975 at 978 (1993).

Here, there's no dispute between the parties to this action that both of the required two elements were met at the time the Plaintiff's Complaint was filed. Rather, the issue raised first by the Defendants' Motion To Dismiss The Complaint Due To Absence Of Case Or Controversy and later by the Defendants' Motion For Reconsideration, is whether the "actual controversy" and accordingly, the Court's subject matter jurisdiction over this declaratory judgment action was eliminated by the Defendants filing the Covenant Not To Sue.

The Defendant's Motion To Dismiss The Complaint Due to Absence of Case Or Controversy and the Memorandum In Support, asserts that the filing of the Defendants' Covenant Not To Sue eliminated the actual controversy necessary for this Court's subject matter jurisdiction over the Plaintiff's declaratory judgment action.

Now, in support of this position the Defendants argue that an actual controversy must be present at all stages of review and not merely at the time of the filing of the Complaint. They rely on the opinion of the United States Court of Appeals for the Federal Circuit in the case

of Amana Refrigeration v. Quadlux, Inc., where the Federal Circuit held that a covenant not to sue for any infringing acts involving products made, sold, or used, on or before the filing date is sufficient to divest a trial court of jurisdiction over a declaratory judgment action. 172 F.3d 852 at 855, that's a 1999 decision.

After a careful review of all of the facts and the entire record of this civil action, including the very impressive arguments of counsel presented today and those arguments raised in the very full and very thorough memoranda of law previously filed in this case on behalf of both parties, the Court believes that the position taken by the Defendants in there Motion For Reconsideration and their accompanying Reply Brief In Support Of Defendants' Motion To Dismiss For Lack Of Case Or Controversy is well taken and that the Court's April 13, 2000, Order denying Defendant's Motion To Dismiss The Complaint Due to Absence Of Case Or Controversy, should be vacated.

We are dealing in a very unique area of law that is much different than if counsel were arguing about your clients' cars -- which car was on the wrong side of the road when the impact occurred.

And as urged by the Defendants, the United States Court of Appeals for the Federal Circuit did in the Amana Refrigeration v. Quadlux, Inc., expressly hold that,

"An actual controversy must be extant--" their word, e-x-t-a-n-t -- "at all stages of review, not merely at the time the complaint is filed."

That decision is 172 F.3d 852 at 855 (Fed. Cir. 1999).

The Federal Circuit has noted that, that the burden is on the party bringing a declaratory judgment action to establish that jurisdiction over its declaratory judgment action existed at, and has continued since, the time the complaint was filed. Spectronics Corporation v. H. G. Fuller Company, 940 F.2d 631 at 635 out of the Federal Circuit in 1991. And in that, they cite International Medical at 787 F.2d at 575.

The Court believes that the Defendants are correct in their assertion that the United States Court of Appeals for the Federal Circuit did expressly hold in the Amana case that an actual controversy which exists at the time the complaint is filed may be extinguished by a defendant filing a covenant not to sue. The Federal Circuit Court stated the following in this regard.

"We have held that a covenant not to sue for any infringing acts involving made, sold or used, on or before the filing date is sufficient to divest a trial court of jurisdiction over a declaratory judgment action."

And again, they cite the Amana case at 172 F.3d 852 at 855, a 1999 case.

Now, the Court is also mindful of the opinion of the United States Court of Appeals for the Federal Circuit in the case of the Sacks -- Super Sack Manufacturing Corporation v. Chase Packaging Corporation.

In that case the Federal Circuit held that:

"A patentee defending against an action for a declaratory judgment of invalidity can divest the trial court of jurisdiction over the case by filing a covenant not to assert the patent at issue against the punitive infringer with respect to any of its past, present, or future acts, even when a reissue application covering the same claimed subject matter is then pending."

57 F.3d 1054 at 1058, a 1995 decision and they cite Spectronics as a part of the justification for their decision.

Based on a very thorough and careful review of all issues raised and suggested by the Defendants' Motion To Reconsider and the Defendants' Reply Brief In Support Of Defendant's Motion To Dismiss For Lack Of Case Or Controversy, this Court believes that the Defendant is correct in asserting that the Plaintiff has failed to meet the burden of establishing that there remains, after the

filing of the Defendant's Covenant Not To Sue, an actual controversy sufficient to provide this Court with subject matter jurisdiction over the declaratory judgment action. Which was a substantial cause of action at the time of its filing and has been modified by the decisions and the filing of the Defendant's Covenant Not To Sue.

Accordingly, the Court must order that the Defendants' Motion To Reconsider shall be, and the same is hereby, granted. The Court also orders that the Court's April 13, 2000, Order denying the Defendants' Motion To Dismiss For Lack Of Case Or Controversy shall be, and the same is hereby, vacated. Also, the Court will order that the Defendants' Motion To Dismiss For Lack Of Case Or Controversy shall be, and the same is hereby, granted. Finally, it is ordered that this civil action shall be dismissed and stricken from the active docket of this Court due to an absence of case or controversy for the reasons expressed by the Court at today's hearing.

The Court would, again, want to express its appreciation to counsel on both sides of this case for the very through, able, capable, representation you have given to each of your clients in this matter.

Prevailing counsel, being counsel for the defense, shall prepare an appropriate order in keeping with the Court's findings and rulings.

Is there anything further that anyone has to bring up in this matter at this time?

MR. LIEBERMAN: No, your Honor.

MR. HOCHSTETLER: No, your Honor.

THE COURT: All right. We will stand in recess until our next scheduled matter.

(WHEREUPON, THIS CONCLUDED THIS MATTER AT THIS TIME.)

CERTIFICATE

I, John G. Bell, Official Court Reporter for the United States District Court, Northern District of West Virginia, sitting at Elkins, do hereby certify that the foregoing transcript of matters had in CIVIL ACTION NO. 1:00CV8, had on May 31, 2000, is a full and complete transcript of the above-styled action, and is true and correct to the best of my knowledge and belief.

John G. Bell
Registered Professional Reporter