

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

PFIZER INC,

Plaintiff,

v.

TORPHARM, INC.,

Defendant.

Civil Act

03C 5289

JUDGE JOAN H. LEFKOW

MAGISTRATE JUDGE MASON

DOCKETED

AUG 01 2003

COMPLAINT

Pfizer Inc ("Pfizer"), by its attorneys, for its complaint against TorPharm, Inc. ("TorPharm") alleges as follows:

1. This is an action by Pfizer against TorPharm for infringement of United States Patent No. 4,879,303 (the "303 patent").

PARTIES, JURISDICTION AND VENUE

2. Pfizer is a corporation organized and existing under the laws of the State of Delaware and having a principal place of business at 235 East 42nd Street, New York, New York. Pfizer invests extensively in designing, developing, and testing and evaluating new and innovative pharmaceutical products and it sells pharmaceutical products to the public throughout the United States.

3. Upon information and belief, TorPharm is a corporation organized and existing under the laws of Canada and has its principal place of business at 50 Steinway Blvd., Etobicoke, Ontario.

1-1

4. TorPharm has designated A. Sidney Katz, Esq. of Welsh & Katz, Ltd. at 120 South Riverside Plaza, Suite 2200, Chicago, Illinois as its agent authorized to accept service of process in the United States.

5. Upon information and belief, TorPharm is in the business of making and selling generic and branded pharmaceutical products.

6. This action arises under the patent laws of the United States, Title 35, United States Code. This Court has subject matter jurisdiction over this action pursuant to the provisions of 28 U.S.C. §§ 1331, 1338, 2201 and 2202.

7. Defendant is subject to personal jurisdiction in this judicial district.

8. Venue is proper in this judicial district pursuant to the provisions of 28 U.S.C. §§ 1391 and 1400(b).

CLAIM FOR RELIEF: INFRINGEMENT OF THE '303 PATENT

9. Pfizer realleges paragraphs 1 through 8 above as if fully set forth herein.

10. On November 7, 1989, the PTO issued to Pfizer the '303 patent, entitled "Pharmaceutically Acceptable Salts," based on the application filed by Edward Davis and James I. Wells, which had been assigned to Pfizer. Pfizer currently holds, and it continuously has held title to the '303 patent since it was issued. A copy of the '303 patent is attached hereto as Exhibit A.

11. Pursuant to 21 U.S.C. § 355(b)(1) and the regulations the FDA promulgated pursuant thereto, the '303 patent is listed in the Orange Book with respect to the Norvasc[®] drug product.

12. Norvasc[®] is entitled to six months of “pediatric exclusivity” pursuant to the provisions of 21 U.S.C. § 355a. Consequently, the Orange Book lists the ’303 patent’s expiration date as September 25, 2007.

13. By letter dated June 23, 2003 (“Notice Letter”), TorPharm gave notice to Pfizer that it had filed with the United States Food and Drug Administration (the “FDA”), pursuant to 21 U.S.C. § 355(j)(2), Abbreviated New Drug Application No. 76-719 (“ANDA No. 76-719”), addressed to a proposed drug product identified as amlodipine besylate tablets (2.5 mg, 5 mg and 10 mg strengths) (“TorPharm Amlodipine Tablets”).

14. The June 23, 2003 Notice Letter states that TorPharm’s ANDA No. 76-719, filed with the FDA, seeks approval to market and sell its TorPharm Amlodipine Tablets before the ’303 patent’s expiration date of September 25, 2007, as listed in the Orange Book, pursuant to 21 C.F.R. § 314.94(a)(12)(i)(A)(4) (“paragraph IV certification”).

15. TorPharm has infringed the ’303 patent under 35 U.S.C. § 271(e)(2)(A) by submitting to the FDA ANDA No. 76-719, which includes the paragraph IV certification as to the ’303 patent and which seeks approval from the FDA to engage in the commercial manufacture, use, or sale of its TorPharm Amlodipine Tablets prior to the expiration of the ’303 patent.

16. Upon information and belief, TorPharm is committed to selling and intends to market its TorPharm Amlodipine Tablets promptly following FDA approval of ANDA No. 76-719.

17. Upon information and belief, TorPharm has knowingly and willfully infringed the '303 patent.

18. Pfizer will be irreparably harmed if TorPharm is not enjoined from infringing the '303 patent.

WHEREFORE, Pfizer requests the following relief:

1. A judgment providing that the effective date of any FDA approval for TorPharm to make, use, sell, offer for sale, or import the TorPharm Amlodipine Tablets described in ANDA No. 76-719 be no earlier than the date on which the '303 patent term, as extended by the pediatric exclusivity period, expires;

2. An order preliminarily enjoining and a judgment permanently enjoining TorPharm from making, using, selling, offering to sell, or importing into the United States the TorPharm Amlodipine Tablets described in ANDA No. 76-719 until after expiration of the '303 patent term, as extended by the pediatric exclusivity period, and a judgment declaring that TorPharm's making, using, selling, offering to sell, or importing into the United States the TorPharm Amlodipine Tablets described in ANDA No. 76-719 will infringe the '303 patent;

3. Attorneys' fees, costs and expenses incurred in pursuing this action as enhanced pursuant to 35 U.S.C. § 285.

4. Such further and other relief as this Court may determine to be just and proper.

Dated: July 30, 2003

Respectfully submitted,



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-and-

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Attorneys for plaintiff

United States Patent [19]

Davison et al.

[11] Patent Number: 4,879,303

[43] Date of Patent: Nov. 7, 1989

- [54] PHARMACEUTICALLY ACCEPTABLE SALTS
- [75] Inventors: Edward Davison, Margate; James I. Wells, Canterbury, both of England
- [73] Assignee: Pfizer Inc., New York, N.Y.
- [21] Appl. No.: 256,938
- [22] Filed: Oct. 13, 1988

Related U.S. Application Data

- [63] Continuation of Ser. No. 30,638, Mar. 25, 1987, abandoned.
- [30] Foreign Application Priority Data
Apr. 4, 1986 [GB] United Kingdom 8608335
- [51] Int. Cl.⁴ C07D 211/86; A61K 31/455
- [52] U.S. Cl. 514/356; 546/321
- [58] Field of Search 514/356; 546/321

[56] References Cited

U.S. PATENT DOCUMENTS

3,816,612 6/1974 Schmidt et al. 425/45
4,032,637 6/1977 Spiegel et al. 514/224

OTHER PUBLICATIONS

Berge et al., *Jour. of Pharmaceutical Science*, Jan. 1977, vol. 66, No. 1.

Primary Examiner—Jane T. Fan
Attorney, Agent, or Firm—Peter C. Richardson, J.
Trevor Lumb; James M. McManus

[57] ABSTRACT

Improved pharmaceutical salts of amlodipine, particularly the besylate salt, and pharmaceutical compositions thereof. These salts find utility as anti-ischaemic and anti-hypertensive agents.

11 Claims, No Drawings

PHARMACEUTICALLY ACCEPTABLE SALTS

This application is a continuation application of co-pending application Ser. No. 07/030,658, filed Mar. 25, 1987, now abandoned.

BACKGROUND OF THE INVENTION

The present invention relates to improved pharmaceutical salts of amlodipine and pharmaceutical compositions thereof.

The compound amlodipine (3-ethyl 5-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methylpyridine-3,5-dicarboxylate) is a potent and long acting calcium channel blocker having utility as an anti-ischæmic and anti-hypertensive agent.

European Patent Application Publication No. 89167 and U.S. Pat. No. 4,372,909 disclose several different pharmaceutically acceptable salt forms of amlodipine. In particular, the pharmaceutically acceptable acid addition salts are said to be those formed from acids which form non-toxic acid anions such as the hydrochloride, hydrobromide, sulphate, phosphate or acid phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate and gluconate salts. Of these salts the maleate is disclosed as being particularly preferred.

SUMMARY OF THE INVENTION

It has now unexpectedly been found that the benzene sulphate salt (hereinafter referred to as the besylate salt) has a number of advantages over the known salts of amlodipine and, additionally, has unexpectedly been found to have a unique combination of good formulation properties which make it particularly suitable for the preparation of pharmaceutical formulations of amlodipine.

Thus according to the present invention there is provided the besylate salt of amlodipine.

In a further aspect the invention provides a pharmaceutical composition of the besylate salt of amlodipine together with a pharmaceutically acceptable diluent or carrier.

The invention further provides a tablet formulation comprising the besylate salt of amlodipine in admixture with excipients. A preferred formulation includes the besylate salt, a compression aid such as microcrystalline cellulose, an additive to provide sheen to the table such as anhydrous dibasic calcium phosphate, a disintegrant such as sodium starch glycolate and a lubricant such as magnesium stearate.

In addition the invention provides a capsule formulation comprising the besylate salt of amlodipine in admixture with excipients. A preferred formulation includes the besylate salt, an inert diluent, a dried disintegrant and a lubricant as described above.

The invention further provides the besylate salt of amlodipine in sterile aqueous solution for parenteral administration. Preferably such solution contains from 10 to 40% by volume of propylene glycol and preferably also sufficient sodium chloride to avoid haemolysis, e.g. about 1% w/v.

The invention also provides the besylate salt of amlodipine for use in treating ischaemic heart disease, especially angina, or hypertension, in a human being.

The invention also provides a process for preparing the besylate salt of amlodipine by reacting amlodipine base with a solution of benzenesulphonic acid in an inert solvent and recovering the besylate salt of amlodipine.

The preferred inert solvent is industrial methylated spirit.

DETAILED DESCRIPTION OF THE INVENTION

Although amlodipine is effective as the free base, in practice it is best administered in the form of a salt of a pharmaceutically acceptable acid. In order to be suitable for this purpose the pharmaceutically acceptable salt must satisfy the following four physicochemical criteria: (1) good solubility; (2) good stability; (3) non-hydroscopicity; (4) processability for tablet formulation, etc.

It has been found that whilst many of the salts outlined above satisfy some of these criteria, none satisfy them all and even the preferred maleate, whilst exhibiting excellent solubility tends to break-down in solution after a few weeks. Consequently a range of pharmaceutically acceptable salts of amlodipine has been made and evaluated using these criteria:

1. Generally, it is known in the art that a good aqueous solubility is necessary for good bioavailability. Usually a solubility of greater than 1 mg ml⁻¹ at pH 1-7.5 is sought although higher solubilities are required to formulate injections. In addition, salts which provide solutions having a pH close to that of blood (7.4) are preferred because they are readily biocompatible and can easily be buffered to the required pH range without altering their solubility.

As can be seen from the following comparative data the besylate salt of amlodipine exhibits good solubility characteristics, compared with other salts.

TABLE I

Salt	solubility mg ml ⁻¹	pH at saturation
Benzene sulphate (besylate)	4.6	6.6
Toluene sulphate (tosylate)	0.9	5.9
Methane sulphate (mesylate)	25	3.1
Succinate	4.4	4.9
Salicylate	1.0	7.0
Maleate	4.3	4.8
Acetate	50	6.6
Hydrochloride	50	3.5

2. Good stability in the solid state is very important for tablets and capsules, whilst good stability in solution is required for an aqueous injection.

In order to screen for chemical stability, each of the salts was blended in a powder vehicle and formed into tablets or capsules. In the case of tablets the vehicle comprised microcrystalline cellulose in 50:50 combination with anhydrous dibasic calcium phosphate. In the case of capsules the vehicles comprised mannitol in 4:1 combination with dried maize starch. These were then stored in sealed vials at 50° and 75° C. for up to three weeks. The drug and any breakdown products were extracted with methanol:chloroform (50:50) and separated on silica tlc plates using a variety of solvent systems.

The results were compared and the salts ranked according to the number and amount of breakdown product produced.

By comparing the results the following rank order emerges with besylate being the most stable salt and hydrochloride the least stable.

TABLE 3

TABLET COMPOSITIONS				
Besylate salt (mg)	Microcrystalline cellulose (mg)	Anhydrous		Magnesium stearate (mg)
		dibasic calcium phosphate (mg)	Sodium starch glycollate (mg)	
1.736	63.514	31.750	2.00	1.00
3.472	62.028	31.500	2.00	1.00
6.944	124.056	63.000	4.00	2.00
13.889	248.111	126.000	8.00	4.00

This method was used to make tablets containing different concentrations of the amlodipine besylate salt as shown in table 3.

EXAMPLE 3

Formulation of Capsules Containing Besylate Salt of Amlodipine

Microcrystalline cellulose and dried maize starch were preblended. The besylate salt of amlodipine was then mixed with some of this preblend and then sieved. The remainder of the preblend was then added and mixed for 10 minutes. This was then sieved again and mixed for a further 5 minutes.

This method was used to make mixtures containing different concentrations of the amlodipine besylate salt as shown in Table 4 and the mixtures were then filled into capsules of appropriate size.

TABLE 4

CAPSULE COMPOSITIONS				
Besylate salt (mg)	Microcrystalline cellulose (mg)	Dried Maize starch (mg)	Magnesium stearate (mg)	Total Capsule weight (mg)
1.736	38.014	10.00	0.250	50
3.472	76.028	20.00	0.500	100
6.944	72.556	20.00	0.500	100
13.889	145.111	40.00	1.00	200

EXAMPLE 4

Formulation of Sterile Aqueous Solution of Besylate Salt of Amlodipine

Sodium chloride was dissolved in water for injection and propylene glycol was mixed with this solution. The besylate salt of amlodipine was added and, when it has dissolved, further water for injection was added to adjust the volume to give the desired concentration of amlodipine (1 mg/ml). The solution was then filtered through a sterilising filter and filled into suitable sterile containers, e.g. ampoules, for use in parenteral, e.g. intravenous, administration.

This methods was used to prepare the formulations shown in Table 5.

TABLE 5

STERILE AQUEOUS SOLUTIONS		
	(1)	(2)
Besylate salt of amlodipine	1.389 g	1.389 g
Sodium chloride	9.000 g	9.000 g

TABLE 5-continued

STERILE AQUEOUS SOLUTIONS		
	(1)	(2)
Propylene glycol	200.000 g	400.000 g
Water for injection	to 1 liter	to 1 liter

EXAMPLE 5

Alternative preparation of Besylate salt of Amlodipine

Ammonium benzenesulphonate (0.943 g) was added to a slurry of amlodipine base (2 g) in industrial methylated spirit (10ml) and the resulting solution was heated at reflux for 10 minutes. The reaction mixture was cooled and granulated at 5° C. for 1 hour. The amlodipine benzenesulphonate was filtered, washed with industrial methylated spirit (2x2 ml) and dried in vacuum.

Yield 1.9 g (70% of theory).

Mpt.: 201.0° C.

Mpt.: 201.0° C.

Analysis %

Found	C, 54.98; H, 5.46; N, 4.90;
Calculated for	C, 55.07; H, 5.51; N, 4.95.

We claim:

1. The besylate salt of amlodipine.
2. A pharmaceutical composition comprising an anti-hypertensive, antiischaemic or angina - alleviating effective amount of the besylate salt of amlodipine as claimed in claim 1 together with a pharmaceutically acceptable diluent or carrier.
3. A tablet formulation comprising an anti-hypertensive, antiischaemic or angina - alleviating effective amount of the besylate salt of amlodipine as claimed in claim 1 in admixture with excipients.
4. A tablet formulation as claimed in claim 3 wherein the excipients comprise a compression and, an additive to provide sheen to the tablet, a disintegrant and a lubricant.
5. A tablet formulation as claimed in claim 4 wherein the excipients comprise microcrystalline cellulose, anhydrous dibasic calcium phosphate, sodium starch glycollate and magnesium stearate.
6. A capsule formulation comprising an antihypertensive, antiischaemic or angina - alleviating effective amount of the besylate salt of amlodipine as claimed in claim 1 in admixture with excipients.
7. A capsule formulation as claimed in claim 6 wherein the excipients comprise an inert diluent, a dried disintegrant and a lubricant.
8. A capsule formulation as claimed in claim 7 wherein the excipients comprise microcrystalline cellulose, dried maize starch and magnesium stearate.
9. A sterile aqueous solution comprising an antihypertensive, antiischaemic or angina - alleviating effective amount of the besylate salt of amlodipine for parenteral administration.
10. A sterile aqueous solution as claimed in claim 9 comprising from 10 to 40% w/v of propylene glycol.
11. A sterile aqueous solution as claimed in claim 9 or claim 10 comprising about 1% w/v sodium chloride.

* * * * *

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UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF ILLINOIS

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Civil Cover Sheet

U.S. DISTRICT COURT

This automated JS-44 conforms generally to the manual JS-44 approved by the Judicial Conference of the United States in September 1974. The data is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. The information contained herein neither replaces nor supplements the filing and service of pleadings or other papers as required by law. This form is authorized for use only in the Northern District of Illinois.

Plaintiff(s): PFIZER INC

Defendant(s): TORPHARM, INC.

DOCKETED

County of Residence:

County of Residence:

AUG 01 2003

Plaintiff's Atty: Michael B. Solow
Kaye Scholer LLC
70 West Madison, Suite 4100,
Chicago, IL 60602
312-583-2300

Defendant's Atty: A. Sidney Katz
Welsh & Katz
120 South Riverside Plaza, Suite
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II. Basis of Jurisdiction:

~~1~~ **FEDERAL QUESTION 03C 5289**

III. Citizenship of Principal Parties
(Diversity Cases Only)

Plaintiff: - N/A
Defendant: - N/A

JUDGE JOAN H. LEFKOW

IV. Origin :

1. Original Proceeding

MAGISTRATE JUDGE MASON

V. Nature of Suit:

830 Patent

VI. Cause of Action:

This action arises under the patent laws of the United States, Title 35, United States Code

VII. Requested in Complaint

Class Action:
Dollar Demand:
Jury Demand: No

VIII. This case IS NOT a refiling of a previously dismissed case.

Signature:

Date:

7/30/03

1-2
7/30/2003

**UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF ILLINOIS**

In the Matter of

Pfizer Inc

v.

Torpharm, Inc.

11:24:00 AM '03

Case Number

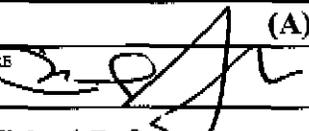
030 5289

APPEARANCES ARE HEREBY FILED BY THE UNDERSIGNED AS ATTORNEY(S) FOR:

PFIZER INC

JUDGE JOAN H. LEFKOW

MAGISTRATE JUDGE MASO

(A)		(B)	
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E-MAIL ADDRESS msolow@kayescholer.com		E-MAIL ADDRESS	
IDENTIFICATION NUMBER (SEE ITEM 4 ON REVERSE) 6188259		IDENTIFICATION NUMBER (SEE ITEM 4 ON REVERSE)	
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STREET ADDRESS		STREET ADDRESS	
CITY/STATE/ZIP		CITY/STATE/ZIP	
TELEPHONE NUMBER	FAX NUMBER	TELEPHONE NUMBER	FAX NUMBER
E-MAIL ADDRESS		E-MAIL ADDRESS	
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