COMPLAINT

Plaintiffs Pfizer Inc. and Pfizer Ireland Pharmaceuticals (collectively, “Pfizer”), by their attorneys, for their Complaint, allege as follows:

1. This is an action for patent infringement under the patent laws of the United States, Title 35, United States Code, that arises out of the submission by defendant Apotex Inc. (collectively with Apotex Corp., “Apotex”) of an Abbreviated New Drug Application ("ANDA") to the U.S. Food and Drug Administration ("FDA") seeking approval to manufacture and sell a generic version of Pfizer’s RELPAX® eletriptan hydrobromide tablets for oral administration ("RELPAX®") prior to the expiration of U.S. Patent No. 6,110,940 ("the ’940 patent").

2. RELPAX® tablets are indicated for the acute treatment of migraine with or without aura in adults. The active ingredient in RELPAX® is eletriptan hydrobromide. Each
RELPA\textsuperscript{X} tablet contains 24.2 mg or 48.5 mg of eletriptan hydrobromide, equivalent to 20 mg or 40 mg of eletriptan, respectively.

3. By letter dated May 28, 2010 (the “Notice Letter”), Apotex notified Pfizer that Apotex had submitted to the FDA an ANDA, No. 201536, for eletriptan hydrobromide tablets 20 mg, 40 mg (“Apotex’s ANDA Product”). Apotex’s ANDA Product is a drug product that is a generic version of RELPA\textsuperscript{X}.

PARTIES

4. Plaintiff Pfizer Inc. is a corporation organized and existing under the laws of the State of Delaware and has a place of business at 235 East 42nd Street, New York, New York 10017. Pfizer Inc. is the assignee of the '940 patent.

5. Plaintiff Pfizer Ireland Pharmaceuticals is a partnership, organized and existing under the laws of the Republic of Ireland, with registered offices at Pottery Road, Dun Laoghaire, Co. Dublin, Ireland. Pfizer Ireland Pharmaceuticals is a wholly owned, indirect subsidiary of Pfizer Inc.

6. Upon information and belief, defendant Apotex Corp. is a corporation organized and existing under the laws of Delaware, having its principal place of business at 2400 North Commerce Parkway, Suite 400, Weston, Florida 33326.

7. Upon information and belief, defendant Apotex Inc. is a corporation organized and existing under the laws of Canada, having its principal place of business at 150 Signet Drive, Toronto, Ontario M9L 1T9, Canada.

8. Upon information and belief, Apotex Inc. is in the business of manufacturing, marketing and selling generic drug products. As a part of this business, upon information and belief, Apotex Inc., directly or through agents (including but not limited to
Apotex Corp.), regularly files ANDAs with the FDA seeking approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of generic versions of drug products that are covered by United States patents. Upon information and belief, as a part of these ANDAs, Apotex Inc., directly or through agents (including but not limited to Apotex Corp.), regularly files certifications of the type described in Section 505(j)(2)(A)(vi)(IV) of the Federal Food, Drug, and Cosmetic Act ("FDCA") to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of generic drug products prior to the expiration of U.S. patents that cover them. Upon information and belief, Apotex Inc.'s ordinary business operations include litigating in the courts of the United States, including the U.S. District Court for the Southern District of New York, the infringement, validity, and/or enforceability of United States patents that cover or are alleged to cover generic drug products that are the subject of ANDAs filed by Apotex.

9. Upon information and belief, Apotex Inc. manufactures drug products for the purpose of sale within the United States, including in New York, by Apotex Corp.

10. Upon information and belief, Apotex Corp. is a wholly-owned subsidiary of Apotex Inc. that serves as Apotex Inc.'s United States sales agent and distributor and sells and offers for sale Apotex Inc.'s drug products throughout the United States, including in New York. Upon information and belief, Apotex Inc. derives substantial revenue from services or things used or consumed in the state of New York. Apotex Inc. has stated on its web site that "Apotex Inc. serves a marketplace of over 115 countries, and is committed to growth on a global basis through affiliates such as Apotex Corp. in the United States of America."

11. Upon information and belief, Apotex Inc. and Apotex Corp. are two arms of the same business group, operate in concert with each other, and enter into agreements with
each other that are nearer than arm’s length. Upon information and belief, employees of Apotex Inc., including Apotex Inc. CEO Dr. Bernard Sherman, frequently speak on behalf of Apotex Corp. Apotex Inc. has also stated on its web site that Apotex is “a vertically integrated company” with a “preference . . . to develop, manufacture and market our own products—from API to finished dosage form to marketing and distribution.”

12. The Notice Letter listed Ellen Gettenberg, the “Director-Marketing” of “Apotex Corp” as the agent in the United States authorized to accept service of process for Apotex.

13. Upon information and belief, the web site of Apotex Corp. is http://www.apotexcorp.com. Upon information and belief, apotexcorp.com is registered to “Apotex” at the Ontario address of Apotex Inc., and the administrative and technical contact listed by the Internet domain registrar for apotexcorp.com is an employee of Apotex Inc. Upon information and belief, visitors to http://www.apotexcorp.com are redirected to a web page on the web site of Apotex Inc., http://www.apotex.com, that is directed towards and is accessible to residents of the United States, including New York, and that makes available a product catalog describing products sold, through Apotex Corp., in the United States, including New York.

14. Upon information and belief, the corporate registration of Apotex Corp. with the New York Department of State, Division of Corporations, lists the Ontario address of Apotex Inc. as Apotex Corp.’s “entity address” and “principal executive office.”

**JURISDICTION AND VENUE**

15. Jurisdiction and venue are proper in this district pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, 1391, and 1400(b).
16. Apotex Corp. is subject to personal jurisdiction in New York because, among other things, upon information and belief, Apotex Corp. is in the business of marketing drug products, which it distributes and sells throughout the United States, including in New York, it derives substantial revenue from services or things used or consumed in the state of New York, it transacts business with companies located and/or headquartered in New York, and, upon receiving FDA approval, it intends to offer to sell and sell Apotex’s ANDA Product in the United States, including in New York. Upon information and belief, Apotex Corp. is registered to do business and has a registered agent in New York.

17. Apotex Inc. is subject to personal jurisdiction in New York because, among other things, upon information and belief, (1) Apotex Inc. is in the business of manufacturing drug products which it manufactures, distributes, and sells or offers to sell, primarily through Apotex Corp., throughout the United States, including in New York, derives substantial revenue from services or things used or consumed in the state of New York, and transacts business with companies located and/or headquartered in New York; (2) as part of its ordinary business practice of engaging in U.S. patent litigation, Apotex Inc. has regularly and routinely litigated ANDA cases in this District, including by asserting counterclaims; (3) Apotex Inc. has, directly or through an agent, filed an ANDA, and/or been actively involved in the preparation and submission of an ANDA, for the purpose of seeking approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Apotex’s ANDA Product in the United States, including in New York; (4) upon receiving FDA approval, Apotex Inc. intends to offer to sell and sell, primarily through Apotex Corp., Apotex’s ANDA Product throughout the United States, including in New York; and (5) Apotex Corp., acting as Apotex Inc.’s agent and/or alter ego, regularly does and solicits business in New York and is engaged in
a persistent, continuous and systematic course of conduct in New York in which it distributes, sells, and offers to sell Apotex Inc.'s drug products in New York and derives substantial revenue from services or things used or consumed in the state of New York on behalf of Apotex Inc.

BACKGROUND

18. The '940 patent has been listed in connection with RELPAX® in the FDA's publication, Approved Drug Products with Therapeutic Equivalence Evaluations, commonly (and hereinafter) known as the "Orange Book."

19. The purpose of Apotex’s submission of ANDA No. 201536 was to obtain approval under the FDCA to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Apotex’s ANDA Product prior to the expiration of the '940 patent.

20. In the Notice Letter, Apotex also notified Pfizer that, as part of its ANDA No. 201536, Apotex had filed certifications of the type described in Section 505(j)(2)(A)(vii)(IV) of the FDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV), with respect to the '940 patent. Upon information and belief, Apotex submitted ANDA No. 201536 to the FDA containing a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) asserting that the '940 patent will not be infringed by the manufacture, use, offer for sale, sale, or importation of Apotex’s ANDA Product.

21. In the Notice Letter, Apotex asserted that the Apotex ANDA Product does not infringe any claim of the '940 patent because it contains an amorphous solid form of eletriptan hydrobromide and does not contain the α-polymorphic form of eletriptan hydrobromide. Apotex also asserted that the IR and PXRD spectra of the Apotex ANDA Product differ from the IR and PXRD spectra required by certain dependent claims of the '940 patent.
22. In the Notice Letter, Apotex included an Offer of Confidential Access to “certain information from its ANDA 201536,” subject to certain specified conditions. Apotex did not specify what information from its ANDA that it was willing to provide, and the conditions were unreasonably more stringent than the conditions customarily included in protective orders in ANDA litigation.

23. On June 22, 2010, Pfizer, through counsel, sent Mr. Shashank Upadhye, Esq., the contact person listed in Apotex’s Offer of Confidential Access, a letter (the “Request for Confidential Access”). The Request for Confidential Access was sent by facsimile and Federal Express, and, upon information and belief, was successfully received by facsimile on June 22, 2010. The Request for Confidential Access proposed certain modifications to the conditions specified in Apotex’s Offer of Confidential Access, including, inter alia, the ability to share samples and data with expert consultants retained on behalf of Pfizer. The Request for Confidential Access also requested particular documents, data, and samples necessary to verify the accuracy of Apotex’s noninfringement claims and to determine whether Apotex’s ANDA Product infringes the ’940 patent. Upon information and belief, Apotex never responded to the Request for Confidential Access.

COUNT I – INFRINGEMENT OF U.S. PATENT NO. 6,110,940

24. Pfizer incorporates each of the preceding paragraphs 1–23 as if fully set forth herein.

25. The ’940 patent, entitled “Salts of an Anti-Migraine Indole Derivative” (Exhibit A hereto), was duly and legally issued on August 29, 2000, to Pfizer Inc., as assignee of Valerie Denise Harding, Ross James Macrae, and Ronald James Ogilvie, and is incorporated herein by reference.
26. Pfizer will be substantially and irreparably damaged by infringement of the '940 patent.

27. Apotex has knowledge of the '940 patent.

28. Apotex’s submission of ANDA No. 201536 for the purpose of obtaining approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Apotex’s ANDA Product prior to the expiration of the '940 patent was an act of infringement of the '940 patent under 35 U.S.C. § 271(e)(2)(A).

29. Upon information and belief, the manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of Apotex’s ANDA Product would infringe one or more claims of the '940 patent.

30. Upon information and belief, Apotex will engage in the manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of Apotex’s ANDA Product with its proposed labeling immediately and imminently upon approval of ANDA No. 201536.

31. Upon information and belief, the use of Apotex’s ANDA Product in accordance with and as directed by Apotex’s proposed labeling for that product would infringe one or more claims of the '940 patent.

32. Upon information and belief, Apotex plans and intends to, and will, actively induce infringement of the '940 patent when ANDA No. 201536 is approved, and plans and intends to, and will, do so immediately and imminently upon approval.

33. Upon information and belief, Apotex knows that Apotex’s ANDA Product and its proposed labeling are especially made or adapted for use in infringing the '940 patent, and that Apotex’s ANDA Product and its proposed labeling are not suitable for substantial noninfringing use. Upon information and belief, Apotex plans and intends to, and will,
contribute to infringement of the '940 patent immediately and imminently upon approval of
ANDA No. 201536.

34. The foregoing actions by Apotex constitute and/or will constitute
infringement of the '940 patent, active inducement of infringement of the '940 patent, and
contribution to the infringement by others of the '940 patent.

35. Upon information and belief, Apotex acted without a reasonable basis for
believing that it would not be liable for infringing the '940 patent, actively inducing infringement
of the '940 patent, and contributing to the infringement by others of the '940 patent.

36. Unless Apotex is enjoined from infringing the '940 patent, actively
inducing infringement of the '940 patent, and contributing to the infringement by others of the
'940 patent, Pfizer will suffer irreparable injury. Pfizer has no adequate remedy at law.

WHEREFORE, Pfizer requests the following relief:

(a) A judgment that Apotex has infringed the '940 patent;

(b) A judgment ordering that the effective date of any FDA approval for
Apotex to make, use, offer for sale, sell, market, distribute, or import Apotex’s ANDA Product,
or any product or compound the making, using, offering for sale, sale, marketing, distributing, or
importation of which infringes the '940 patent, be not earlier than the expiration date of the '940
patent, inclusive of any extension(s) and additional period(s) of exclusivity;

(c) A preliminary and permanent injunction enjoining Apotex, and all persons
acting in concert with Apotex, from making, using, selling, offering for sale, marketing,
distributing, or importing Apotex’s ANDA Product, or any product or compound the making,
using, offering for sale, sale, marketing, distributing, or importation of which infringes the '940
patent, or the inducement of or the contribution to any of the foregoing, prior to the expiration date of the '940 patent, inclusive of any extension(s) and additional period(s) of exclusivity;

(d) A judgment declaring that making, using, selling, offering for sale, marketing, distributing, or importing Apotex's ANDA Product, or any product or compound the making, using, offering for sale, sale, marketing, distributing, or importation of which infringes the '940 patent, prior to the expiration date of the '940 patent, will infringe, actively induce infringement of, and/or contribute to the infringement by others of the '940 patent;

(e) A declaration that this is an exceptional case and an award of attorneys' fees pursuant to 35 U.S.C. § 285;

(f) An award of Pfizer's costs and expenses in this action; and

(g) Such further and other relief as this Court may deem just and proper.

Dated: July 9, 2010

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Attorneys for Plaintiffs,
Pfizer Inc. and Pfizer Ireland Pharmaceuticals
Exhibit A
United States Patent

Harding et al.

[54] SALTS OF AN ANTI-MIGRAINE INDOLE DERIVATIVE

[75] Inventors: Valerie Denise Harding; Ross James Macrae; Ronald James Ogilvie, all of Sandwich, United Kingdom

[73] Assignee: Pfizer Inc., New York, N.Y.

[21] Appl. No.: 08/776,680

[22] PCT Filed: May 17, 1995

[86] PCT No.: PCT/EP95/01914

§ 371 Date: Feb. 2, 1997

§ 102(c) Date: Feb. 2, 1997

[87] PCT Pub. No.: WO96/06842

PCT Pub. Date: Mar. 7, 1996

[30] Foreign Application Priority Data

Aug. 27, 1994 [GB] United Kingdom 9417310

[51] Int. Cl? -------------. A01N 43/40; A61K 31/445;

C07D 401/00; C07D 209/02

[52] U.S. Cl. -------------. 514/323; 546/201; 548/468

[58] Field of Search -------------. 546/201; 548/468;

514/323

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Assistant Examiner—Tamhom N. Truong

Attorney, Agent, or Firm—Peter C. Richardson; Paul H. Ginsburg; Grever F. Fuller, Jr.

[57] ABSTRACT

The present invention relates to hydrobromide salts of 3-(N-methyl-2(R)-pyrrolidinylmethyl)-5-(2-phenylsulphonyl)ethyl)-1H-indole having the formula (I):

![Chemical Structure](image)

14 Claims, 6 Drawing Sheets
SALTS OF AN ANTI-MIGRAINE INDOLE DERIVATIVE

This is a 371 application of PCT/EP 95/01914 filed May 17, 1995.

The present invention relates to hydrobromide salts of 3-(N-methyl-2-(R)-pyrrolidinylmethyl)-5-(2-phenylsulphonylphenethyl)-1H-indole having the formula (I):

In a preferred aspect, the invention relates to a particular polymorphic form, hereinafter referred to as the α-form, of the hydrobromide salt identified above. In addition it relates to an intermediate polymorphic form, hereinafter referred to as the β-form, of the said hydrobromide salt, to processes for the preparation of the α- and β-forms, to pharmaceutical compositions containing the α-form, and to uses of the α-form in medicine.

WO-A-92/06973 relates to a series of 3,5-disubstituted indoles and pharmaceutically acceptable salts thereof useful in the treatment of migraine and other disorders. Examples cited therein of such salts are the hydrochloride, hydrobromide, hydroiodide, nitrate, sulphate or bisulphate, phosphate or acid phosphate, lactate, citrate or acid citrate, tartrate or bitartrate, succinate, maleate, fumarate, glutarate, saccharate, benzoate, methanesulphonate and pamoate. Specifically disclosed therein is 3-(N-methyl-2-(R)-pyrrolidinylmethyl)-5-(2-phenylsulphonylphenethyl)-1H-indole and its hemisuccinate salt, the latter being characterised as a noncrystalline form. Further studies have confirmed that this salt is unsuitable for pharmaceutical formulation, as numerous attempts to obtain it in a form which has the properties required for formulation have been unsuccessful.

Thus the problem addressed by the present invention is the provision of a pharmaceutically acceptable salt of 3-(N-methyl-2-(R)-pyrrolidinylmethyl)-5-(2-phenylsulphonylphenethyl)-1H-indole which can be efficiently processed to provide stable and effective formulations of the drug, in particular solid and compressible dosage forms. Such dosage forms include conventional-release oral tablets, controlled-release (matrix) tablets, fast-dissolving tablets (e.g. freeze-dried), sublingual tablets, buccal tablets, oral powder- and granule-filled capsules, powders for reconstituted suspensions, conventional and controlled-release multiparticulate systems filled into capsules or compressed into tablets, lozenges, drages, suppositories, pessaries, solid implants, lyophilic plugs, nanoparticles and microparticles and powders for suspension and nasal delivery, and dry inhalation systems.

Important criteria to be satisfied are, inter alia, that the selected salt should be crystalline, of suitable melting point, non-hygrosopic, compressible and possess solid-state stability, coupled with acceptable solubility and dissolution behaviour.

This problem has been solved by the surprising finding of a novel α-form of the hydrobromide salt of formula (I) which meets the above requirements; thus it is pre-eminently suitable for providing pharmaceutical formulations in solid dosage form, in particular for oral, buccal and sublingual administration.

The first step in approaching the solution to the problem was the generation of an acid addition salt of the monoacetic base, 3-(N-methyl-2-(R)-pyrrolidinylmethyl)-5-(2-phenylsulphonylphenethyl)-1H-indole, which is both crystalline and of high enough melting point (ca. 130°C) to have the potential to undergo pharmaceutical processing during solid dosage form manufacture and compaction.

Attempts were made to obtain a suitable form of the following salts: hydrochloride, hydrobromide, hemisulphate, bisulphate, nitrate, acid phosphate, phosphate, methanesulphonate, benzencesulphonate, p-toluencesulphonate, (+)-camphorsulphonate, acetate, benzoate, citrate, hemifumarate, fumarate, hemimaleate, maleate, hemisuccinate, succinate, hemi-1-tartrate, L-tartrate, hemi-D-tartrate, D-tartrate, L-lactate, (R)-(+)-mandelate, hippurate, hemiphthalate, phthalate and hemi-terephthalate.

Of these thirty possible salts, only four could be obtained as crystalline solids, namely the hemisulphate, hydrochloride, hydrobromide and benzencesulphonate; the remainder were obtained as non-crystalline, low or non-sharp melting/sticky solids, gums, glasses, froths, resins or oils. Moreover, of the four crystalline salts, the benzencesulphonate proved to have an insufficiently high melting point (m.p.) of 74–75°C. Thus only the hemisulphate, hydrochloride and hydrobromide salts were progressed to more detailed studies.

Hemisulphate Salt

The hemisulphate salt initially isolated (m.p. 145–147°C), designated the β-form, does not show a clean single-melting endotherm when examined by differential scanning calorimetry (DSC) but rather a complex trace indicative of polymorphic transition. Indeed, this β-form is very hygroscopic at relative humidities (RH) higher than 50% and, under certain conditions, water uptake can cause polymorphic conversion to an alternative form, designated the α-form, of m.p. 185°C, or even degradation. Furthermore, the β-form undergoes a colour change on compression and causes punch-filling during tableting and thus, for a variety of reasons, its physicochemical properties render it unsuitable for the development of solid dosage forms.

Whilst the α-form of the hemisulphate salt does not display solid state instability associated with water uptake, it is extremely hygroscopic nevertheless and therefore also unsuitable for development because of consequential difficulties with variable flow properties, and bulk and dosage form instability which precludes, inter alia, accurate assignment of drug activity.

Hydrochloride Salt

Depending on the solvent used as reaction medium and for crystallisation, either of two forms of the hydrochloride salt can be obtained. The first of these to be isolated and characterised, designated the β-form, of m.p. 123–129°C and broad endotherm at 135°C at a scan rate of 20°C/min. by DSC, but no dehydration endotherms apparent, was found to have a water content of 4.42% (1.08 mol) by Karl Fischer titrimetry (KFI). However, although hygroscopicity studies revealed that the β-form does not display solid state instability, it was excluded from further development by its behaviour during compression studies in which melting and sticking of the disk to the punches were observed, thus reinforcing the requirement for a higher melting solid.

The alternative hydrochloride salt, designated the α-form, showed a major, sharp endotherm at 165°C by DSC (scan rate 20°C/min.). Determination of its hygroscopicity profile revealed that after seven days at a temperature (T) of 40°C and RH of 75%, unlike the β-form, a significant amount of
water had been taken up. This water uptake was found to be associated with changes in the DSC trace which demonstrated that, at least under these humidity conditions, the anhydrous α-form converts to the hydrated β-form. Thus, pharmaceutical development of the α-form is also precluded by inadequate physical stability.

Hydrobromide Salt

The hydrobromide salt is also isolable in one of two forms, depending on the preparative conditions employed. The lower melting form, designated the β-form, was found not to be a viable option for the development of a solid dosage form because, when attempts are made to improve its quality, it undergoes polymorphic conversion to a higher melting form, designated the α-form.

However, by contrast, the novel α-form of the hydrobromide salt of formula (I) was found to be unique in unexpectedly possessing the combination of properties required to enable the efficient development of solid dosage forms, namely those of crystallinity, sufficiently high m.p., lack of hygroscopicity, solid-state stability, compressibility and lack of polymorphic conversion, together with satisfactory solubility and dissolution rate profiles.

The present invention therefore provides a crystalline, polymorphic α-form of a hydrobromide salt of formula (I), whose infra-red (IR) spectrum as a melt in nujol shows significant absorption bands at 32371, 3293, 2713, 2524, 1419, 1343, 1307, 1264, 1151, 1086, 1020, 1008, 999, 922, 900, 805, 758, 740, 726, 689, 672, 652, 640, 598, 581, 573, 531, 498, 465, 457, 443, 428, 422, 414 and 399 cm⁻¹.

The α-form is further characterised by its powder X-ray diffraction (PXRD) pattern obtained using copper radiation filtered with a graphite monochromator (λ=0.15405 nm) which shows major peaks at 9.7, 10.7, 15.9, 16.5, 17.8, 18.3, 19.3, 19.8, 20.1, 21.2, 24.4, 25.5, 25.8, 26.7, 27.6 and 29.4 degrees 2θ.

The α-form is yet further characterised by its differential scanning calorimetry (DSC) trace which shows a sharp endotherm at 176.8°C at a scan rate of 20°C/min.

The invention also provides a crystalline, polymorphic β-form of a hydrobromide salt of formula (I), which can be used as an intermediate in the preparation of the α-form. Its IR spectrum as a melt in nujol shows significant absorption bands at ν=3239, 2765, 2656, 2632, 1409, 1366, 1351, 1334, 1303, 1293, 1152, 1138, 1122, 1098, 1086, 791, 771, 746, 688, 634, 577, 528, 484, 476, 469, 463, 455, 432, 424, 413 and 401 cm⁻¹.

The β-form is further characterised by its PXRD pattern obtained using copper radiation filtered with a graphite monochromator (λ=0.15405 nm) which shows major peaks at 11.0, 17.2, 19.2, 20.1, 21.6, 22.6, 23.6 and 24.8 degrees 2θ.

The β-form is yet further characterised by its DSC trace which shows a sharp endotherm at 154.8°C at a scan rate of 20°C/min.

The invention further provides processes for the preparation of the α-form of a compound of formula (I), as illustrated by the following.

(A) Treatment of a solution of 3-[(N-methyl-2-(R)-pyrrolidinylmethyl)-5-(2-phenylsulphonyl)ethyl]-1H-indole in a suitable solvent, preferably acetone, at room temperature, with an aqueous solution of hydrobromide, followed by crystallisation of the isolated crude oil from a suitable solvent, preferably 2-propanol, affords the α-form of the required hydrobromide salt.

(B) Treatment of a solution of 3-[(N-methyl-2-(R)-pyrrolidinylmethyl)-5-(2-phenylsulphonyl)ethyl]-1H-indole in a suitable solvent, preferably acetone or an ether solvent such as tetrahydrofuran or 1,2-dimethoxyethane, more preferably 1,2-dimethoxyethane, at from 0 to 10°C, with an aqueous solution of hydrogen bromide, furnishes the β-form of the required hydrobromide salt.

Crystalisation of the β-form from a suitable solvent, preferably aqueous acetone, followed by slurring of the resulting mixture, gives the desired α-form.

(C) Treatment of a solution of 3-[(N-methyl-2-(R)-pyrrolidinylmethyl)-5-(2-phenylsulphonyl)ethyl]-1H-indole in a suitable solvent, preferably acetone, at from 0 to 5°C, with an aqueous solution of hydrogen bromide and then slurring of the reaction mixture, optionally followed by heating under reflux, cooling and further slurring, provides the required α-form.

As previously mentioned, WO-A-92/06973 discloses 3-[(N-methyl-2-(R)-pyrrolidinylmethyl)-5-(2-phenylsulphonyl)ethyl]-1H-indole and pharmaceutically acceptable salts thereof for the treatment of migraine and other disorders (incorporated herein by reference). Thus the present invention also relates to pharmaceutical compositions containing the α-form of the hydrobromide salt thereof, uses of the α-form as a medicament and for the manufacture of a medicament for the treatment of migraine and said other disorders, and a method of treating a mammal having migraine or any of said other disorders with the α-form.

The in vitro evaluation of the peripheral 5-HT₁ receptor agonist activity of the α-form can be carried out by testing the extent to which it mimics sumatriptan in contracting the isolated dog saphenous vein strip (P. A. Humphrey et al., Brit. J. Pharmacol., 1988, 94, 1123). This effect can be blocked by methiothepin, a known 5-HT₁ antagonist. Sumatriptan is known to be useful in the treatment of migraine and produces a selective increase in carotid vascular resistance in the anaesthetized dog and a consequent decrease in carotid arterial blood flow. It has been suggested (W. Feniuk et al., Brit. J. Pharmacol., 1989, 96, 83) that this is the basis of its efficacy.

The central 5-HT₁ receptor agonist activity of the α-form can be measured in vivo in receptor binding assays as described for the 5-HT₁₄ receptor, using rat cortex as the receptor source and [³H]8-OH-DPAT as the radioligand (D. Hoyer et al., Europ. J. Pharmacol., 1985, 118, 13), and as described for the 5-HT₂ receptor, using bovine caudate as the receptor source and [³H]-5-HT as the radioligand (R. E. Heuring and S. J. Porozuk, J. Neuroscience, 1987, 7, 894).

In therapy, the α-form of the hydrobromide salt of formula (I) can be administered alone, but will generally be administered in admixture with pharmaceutically acceptable excipients, including glidants, disintegrants and lubricants, selected with regard to the intended route of administration and standard pharmaceutical practice. In particular, it may be administered orally in the form of tablets, dragees or lozenges containing excipients such as starch or lactose, or in capsules, ovules or implants, either alone or in admixture with excipients. For buccal or sublingual administration, it may be administered in the form of tablets, dragees or lozenges which can be formulated in a conventional manner.

For oral, buccal or sublingual administration to patients, the daily dosage level of the α-form of the salt of formula (I) will be from 0.01 mg to 20 mg/Kg (in single or divided doses). Thus tablets or capsules will contain from 0.5 mg to 0.5 g of active compound for administration singly, or two or more at a time, as appropriate. The physician in any event will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above doses are
exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Thus the invention provides a pharmaceutical composition comprising the α-form of a compound of formula (I) together with a pharmaceutically acceptable diluent or carrier.

The invention also provides the α-form of a compound of formula (I), or a pharmaceutical composition thereof, for use as a medicament.

The invention further includes the use of the α-form of a compound of formula (I), or a pharmaceutical composition thereof, both for the manufacture of a medicament for the curative or prophylactic treatment of migraine or an associated condition such as cluster headache, chronic paroxysmal hemicrania or headache associated with a vascular disorder, or of depression, anxiety, an eating disorder, obesity, drug abuse, hypertension or emesis, and also for the manufacture of a medicament for the curative or prophylactic treatment of a medical condition for which a selective agonist of 5-HT₃ receptors is indicated.

In a method to treat a human being to cure or prevent migraine or an associated condition such as cluster headache, chronic paroxysmal hemicrania or headache associated with a vascular disorder, or depression, anxiety, an eating disorder, obesity, drug abuse, hypertension or emesis, and also a method of treating a human being to cure or prevent a medical condition for which a selective agonist of 5-HT₃ receptors is indicated, which comprises administering to said human being an effective amount of the α-form of a compound of formula (I), or a pharmaceutical composition thereof.

The preparation of the α-form of the hydrobromide salt of formula (I) and pharmaceutical compositions thereof are illustrated by the following Examples.

Room temperature means 20 to 25°C. and m.p. means melting point.


**EXAMPLE 1**

3-(N-Methyl-2(R)-pyrrolidinylmethyl)-5-(2-phenylsulphonyl)ethyl)-1H-indole hydrobromide, α-form

49% w/w Hydrobromic acid (432 mg, 0.3 ml, 2.6 mmol) was added to a stirred solution of 3-(N-methyl-2(R)-pyrrolidinylmethyl)-5-(2-phenylsulphonyl)ethyl)-1H-indole (1.0 g, 2.6 mmol) in acetone (10 ml) at room temperature. After a further 15 minutes, the reaction mixture was evaporated under reduced pressure to give a yellow liquid; the residual water therein was then azeotropically removed using 2-propanol. The resulting cloudy, yellowish oil (1.55 g) was triturated with ether and then dissolved in hot 2-propanol (25 ml); this solution, on cooling, provided the title compound (1.13 g) as a pale yellow crystalline solid after filtration, washing with 2-propanol and drying in vacuo, m.p. 165-170°C. Found: C, 56.67; H, 5.78; N, 5.82. C₁₃H₁₉NO₃S; HBr requires C, 57.02; H, 5.87; N, 6.04%.

**EXAMPLE 2**

3-(N-Methyl-2(R)-pyrrolidinylmethyl)-5-(2-phenylsulphonyl)ethyl)-1H-indole hydrobromide, α-form

(a) 3-(N-Methyl-2(R)-pyrrolidinylmethyl)-5-(2-phenylsulphonyl)ethyl)-1H-indole hydrobromide, β-form

49% w/w Hydrobromic acid (27.86 ml, 0.25 mol) was added over 1 hour to a stirred solution of 3-(N-methyl-2(R)-pyrrolidinylmethyl)-5-(2-phenylsulphonyl)ethyl)-1H-indole (92.86 g, 0.24 mol) in 1,2-dimethoxyethane (2.08 l) at about 5°C. The cooling bath was removed and the resulting slurry was allowed to granulate by stirring at room temperature for a further 18 hours. Filtration, followed by washing with 1,2-dimethoxyethane and drying in vacuo, afforded the required product (97.9 g) as a solid, m.p. 150-151°C.

Found: C, 56.77; H, 5.87; N, 5.85. C₁₃H₁₉NO₃S; HBr requires C, 57.02; H, 5.87; N, 6.04%.

(b) A stirred mixture of the previous product (20 g), acetone (140 ml) and water (6 ml) was heated under reflux until complete dissolution of the β-form was achieved. The solution was then allowed to cool to room temperature, stirred for 1 hour and then acetone (460 ml) added to the resulting slurry. After a further 1 hour, the slurry was cooled to 0-5°C. and stirring continued for up to 18 hours. The colourless, crystalline solid was collected by filtration, washed with acetone and dried in vacuo to furnish the title compound (13.22 g), which was identical to that of Example 1.

**EXAMPLE 3**

3-(N-Methyl-2(R)-pyrrolidinylmethyl)-5-(2-phenylsulphonyl)ethyl)-1H-indole hydrobromide, α-form

62% w/w Hydrobromic acid (1.706 g, 13.07 mmol) was added over 1 hour to a stirred solution of 3-(N-methyl-2(R)-pyrrolidinylmethyl)-5-(2-phenylsulphonyl)ethyl)-1H-indole (5.0 g, 13.07 mmol) in acetone (112 ml) at 0-5°C. After stirring of the reaction mixture at 0-5°C. for 3 hours, heating under reflux for 2 hours was effected followed by cooling to 0-5°C. and further stirring for 1 hour at this temperature. Filtration, followed by washing with acetone and drying in vacuo, furnished the title compound (5.18 g), which was identical to that of Example 1.

In Examples 4 to 6, “active ingredient” means the α-form of the hydrobromide salt.

**EXAMPLE 4**

Tablets for Oral Administration

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>mg/tablet</th>
<th>for 50 g mix</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>12.12</td>
<td>6.06</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>25.00</td>
<td>12.50</td>
</tr>
<tr>
<td>Ph Eur</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactose Ph Eur</td>
<td>60.88</td>
<td>30.44</td>
</tr>
<tr>
<td>Crosscarmellose sodium NF</td>
<td>1.00</td>
<td>0.50</td>
</tr>
<tr>
<td>Magnesium stearate Ph Eur</td>
<td>1.00</td>
<td>0.50</td>
</tr>
</tbody>
</table>

The active ingredient is sieved and blended with the other components. The resultant mix is compressed into tablets using a rotary tablet press (Manesty Betapress) fitted with 6 mm normal concave punches. The resultant tablets can be film coated with an appropriate film coating material.
The polyvinylpyrrolidone is dissolved in purified water to an appropriate concentration. The active ingredient is sieved and blended with all of the other components except the magnesium stearate. Suitable volumes of the polyvinylpyrrolidone solution are added and the powders are granulated. After drying, the granules are screened and blended with the magnesium stearate. The granules are then compressed into tablets using suitable diameter punches.

Tablets of other strengths may be prepared by altering the ratio of active ingredient to excipients or the compression weight and using punches to suit.

**EXAMPLE 5**

<table>
<thead>
<tr>
<th>Capsules</th>
<th>mg/capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>18.18</td>
</tr>
<tr>
<td>Lactose Ph Eur</td>
<td>268.89</td>
</tr>
<tr>
<td>Maize starch Ph Eur</td>
<td>69.63</td>
</tr>
<tr>
<td>Colloidal anhydrous silica Ph Eur</td>
<td>0.30</td>
</tr>
<tr>
<td>Magnesium Stearate Ph Eur</td>
<td>3.00</td>
</tr>
<tr>
<td>Fill weight</td>
<td>300.00</td>
</tr>
</tbody>
</table>

The active ingredient is sieved and blended with the other components. The mix is filled into size No 2 hard gelatin capsules using suitable machinery. Other doses may be prepared by altering the fill weight and, if necessary, changing the capsule size to suit.

**EXAMPLE 6**

<table>
<thead>
<tr>
<th>Sublingual Tablets</th>
<th>mg/tablet for 50 g mix</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>1.2 0.750 0.500 0.050 g</td>
</tr>
<tr>
<td>Lactose Ph Eur</td>
<td>25.0 15.625 9.188 5.631 g</td>
</tr>
<tr>
<td>Maize starch Ph Eur</td>
<td>25.0 15.625 9.188 5.631 g</td>
</tr>
<tr>
<td>Mannitol Ph Eur</td>
<td>25.0 15.625 9.188 5.631 g</td>
</tr>
<tr>
<td>Croscarmellose sodium NF</td>
<td>3.0 1.875 1.188 0.750 g</td>
</tr>
<tr>
<td>Magnesium Stearate Ph Eur</td>
<td>0.8 0.500 0.312 0.188 g</td>
</tr>
</tbody>
</table>

The active ingredient is sieved through a suitable sieve, blended with the excipients and compressed using suitable punches. Tablets of other strengths may be prepared by altering either the ratio of active ingredients to excipients or the compression weight and using punches to suit.
change was evident. As previously mentioned, the hygroscopicity of the β-form of the hemisulphate salt leads to polymorphic conversion to the α-form and, eventually, to degradation.

No change in DSC profile was apparent for the α-form of the hydrobromide salt in the T=40°C C/RH=90% samples, whilst HPLC analysis confirmed its stability under all the conditions studied.

Table 2 shows hygroscopicity results for the α- and β-forms of the hydrochloride salt, expressed as moisture changes determined by % weight change at T=40°C C/RH=75%.

The β-form was judged to be non-hygroscopic on the basis of both the α-forms displayed in Table 2 and the closely comparable results obtained by KPT analysis at week 4, with no solid state instability being detected. Although only 1 week of incubation was conducted for the α-form in this study, it is clear that it had picked up a significant amount of moisture even by this time-point and that this water uptake was associated with changes in the DSC trace which revealed the transformation of the α-form to the β-form under these conditions.

Compression Studies

Samples (200 mg) were compressed using a bench press (Graseby Specac Model 15.01) at 5 tonnes for 1 minute using a 13 mm punch and die set, then assessed for colour change and evidence of melting. Further analysis (DSC and HPLC) was conducted after grinding of the compact using a mortar and pestle.

For the α-form of the hydrobromide salt, no changes to the thermogram in respect of either melting point or enthalpy of fusion, after either compression or grinding, were observed. In addition, there was no evidence of a change in sample appearance or punch film on compaction.

As previously mentioned, the β-form of the hemisulphate salt undergoes a colour change on compression and also causes punch film on compaction, whilst the β-form of the hydrochloride salt melts and causes sticking of the disk to the punches during compression, which behaviour is unsurprising given the significantly lower m.p. of the latter. The α-form of the hydrochloride salt did not melt on compaction.

Polymorphic Conversion

DSC was used to determine both the polymorphic conversions of the β-forms of the hydrobromide and hemisulphate salts to their respective α-forms, and also the conversion of the α-form of the hydrochloride salt to its β-form which is believed to be an anhydrate-hydrate transition.

No polymorphic transitions of the α-form of the hydrobromide salt were observed under the conditions investigated.

We claim:

1. α-polymorphic form of a compound of formula (I):

![Chemical Structure](image)

2. A crystalline, α-polymorphic form of a compound according to claim 1 further characterised by an infra-red spectrum as a null in nujol which shows significant absorption bands at ν=3371, 3292, 2713, 2524, 1419, 1343, 1307, 1264, 1151, 1086, 1020, 1008, 999, 922, 900, 805, 7581, 740, 728, 689, 672, 652, 640, 598, 581, 573, 531, 498, 465, 457, 443, 428, 422, 414 and 399 cm⁻¹.

3. A compound according to claim 2 which is further characterised by a powder X-ray diffraction pattern obtained using copper radiation filtered with a graphite monochromator (λ=0.15405 nm) which shows main peaks at 9.7, 10.7, 15.9, 16.3, 17.8, 18.3, 19.3, 19.8, 20.1, 21.2, 24.4, 25.5, 25.8, 26.7, 27.6 and 29.4 degrees 2θ.

4. A pharmaceutical composition for the treatment of a medical condition for which a selective agonist of 5-HT1 receptors is indicated, comprising an amount of the compound of claim 1 effective in treating such condition and a pharmaceutically acceptable carrier.

5. A pharmaceutical composition for the treatment of a medical condition selected from the group consisting of migraine, cluster headache, chronic paroxysmal hemicrania or headache associated with a vascular disorder, depression, anxiety, an eating disorder, obesity, drug abuse, hypertension and emesis, comprising an amount of the compound of claim 1 effective in treating such condition and a pharmaceutically acceptable carrier.

6. A method of treatment of a human being for a medical condition for which a selective agonist of 5-HT1 receptors is indicated, comprising administering to said human being an amount of a compound according to claim 1 effective in treating such condition.

7. A method for the treatment of a medical condition selected from the group consisting of migraine, cluster headache, chronic paroxysmal hemicrania or headache associated with a vascular disorder, depression, anxiety, an eating disorder, obesity, drug abuse, hypertension, and emesis, comprising administering to said human being an amount of a compound according to claim 1 effective in treating such condition.

8. A process for the preparation of a crystalline, α-polymorphic form of a compound of formula (I):
b) the suitable solvent is aqueous acetone; and
c) the suitable solvent is acetone, the aqueous solution of hydrogen bromide is 62% w/w and the treatment therewith is conducted at from 0 to 5°C.

10. A process according to claim 8 wherein the α-polymorphic form of a compound of formula (I) is further characterised by a powder X-ray diffraction pattern obtained using copper radiation filtered with a graphite monochromator (λ=0.15405 nm) which shows main peaks at 9.7, 10.7, 15.9, 16.5, 17.8, 18.3, 19.3, 19.8, 20.1, 21.2, 24.4, 25.5, 25.8, 26.7, 27.6 and 29.4 degrees 2θ and the β-polymorphic form of a compound of formula (I) is further characterised by a powder X-ray diffraction pattern obtained using copper radiation filtered with a graphite monochromator (λ=0.15405 nm) which shows main peaks at 11.0, 17.2, 19.2, 20.1, 21.6, 22.6, 23.6 and 24.8 degrees 2θ.

11. A pharmaceutical composition for the treatment of a medical condition for which a selective agonist of 5-HT1 receptors is indicated, comprising an amount of the compound of claim 2 effective in treating such condition and a pharmaceutically acceptable carrier.

12. A pharmaceutical composition for the treatment of a medical condition selected from the group consisting of migraine, cluster headache, chronic paroxysmal hemicrania or headache associated with a vascular disorder, depression, anxiety, an eating disorder, obesity, drug abuse, hypertension and emesis, comprising an amount of the compound of claim 2 effective in treating such condition and a pharmaceutically acceptable carrier.

13. A method of treatment of a human being for a medical condition selected from the group consisting of migraine, cluster headache, chronic paroxysmal hemicrania or headache associated with a vascular disorder, depression, anxiety, an eating disorder, obesity, drug abuse, hypertension and emesis, comprising administering to said human being an amount of a compound according to claim 2 effective in treating such condition.

14. A method for the treatment of medical condition selected from the group consisting of migraine, cluster headache, chronic paroxysmal hemicrania or headache associated with a vascular disorder, depression, anxiety, an eating disorder, obesity, drug abuse, hypertension and emesis, comprising administering to said human being an amount of a compound according to claim 2 effective in treating such condition.

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