

UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

PFIZER INC. and PFIZER IRELAND
PHARMACEUTICALS,

Plaintiffs,

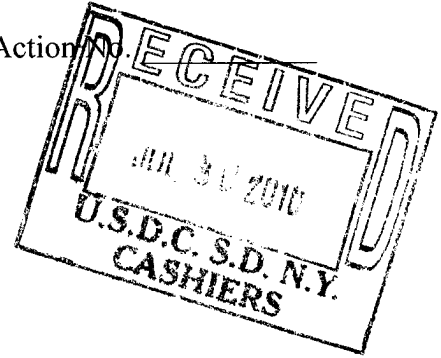
v.

TEVA PHARMACEUTICALS USA INC.,

Defendants.

10 CIV 5794

Civil Action No.



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 Teva Pharmaceuticals USA Inc. (“Teva”) 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”) attached hereto as Exhibit 1.

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 RELPAX[®] 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 June 17, 2010 (the “Notice Letter”), Teva notified Pfizer that Teva had submitted to the FDA an ANDA, No. 202040, for eletriptan hydrobromide tablets 20 mg, 40 mg (“Teva’s ANDA Product”). Teva’s ANDA Product is a drug product that is a generic version of RELPAX[®].

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 Teva is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 1090 Horsham Road, North Wales, Pennsylvania 19454.

JURISDICTION AND VENUE

7. Jurisdiction and venue are proper in this district pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, 1391, and 1400(b).

8. Teva is subject to personal jurisdiction in New York because, among other things: Upon information and belief, Teva is in the business of manufacturing, distributing, and selling drug products 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 Teva's ANDA Product in the United States, including in New York, which will cause injury to Pfizer Inc., a corporation headquartered in New York. As a part of its business, upon information and belief, Teva 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, Teva regularly files certifications of the type described in Section 505(j)(2)(A)(vii)(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, Teva'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 Teva. Upon information and belief, Teva is registered with the New York Department of State, Division of Corporations, to conduct business in the State of New York, and has a registered agent in the State of New York. Upon information and belief, Teva has a physical presence in the State of New York, including a place of business in Pomona, New York.

BACKGROUND

9. 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."

10. The purpose of Teva's submission of ANDA No. 202040 was to obtain approval under the FDCA to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Teva's ANDA Product prior to the expiration of the '940 patent.

11. In the Notice Letter, Teva also notified Pfizer that, as part of its ANDA No. 202040, Teva 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, Teva submitted ANDA No. 202040 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 Teva's ANDA Product.

12. In the Notice Letter, Teva asserted that Teva's ANDA Product does not infringe any claim of the '940 patent because "[t]here is no evidence of the α -polymorphic form of eletriptan hydrobromide in the eletriptan hydrobromide used to make the [Teva's ANDA Product] or in [Teva's ANDA Product] [it]self." Accordingly, Teva asserted, Teva's ANDA Product does not contain eletriptan hydrobromide in the α -polymorphic form.

13. In the Notice Letter, Teva included an Offer of Confidential Access to "relevant portions" of its ANDA, subject to certain specified conditions.

14. On June 29, 2010, Pfizer, through counsel, sent Mr. Philip Erickson, the contact person listed in Teva's Offer of Confidential Access, a letter requesting, in addition to the offered portions of Teva's ANDA, particular documents, data, and samples necessary to verify Teva's noninfringement claims and to determine whether Teva's ANDA Product infringes the '940 patent. Upon information and belief, through counsel, Teva responded that it was unwilling to share all of the documents Pfizer requested, and was also unwilling to share any samples.

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

15. Pfizer incorporates each of the preceding paragraphs 1–14 as if fully set forth herein.

16. 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.

17. Pfizer will be substantially and irreparably damaged by infringement of the '940 patent.

18. Teva has knowledge of the '940 patent.

19. Teva's submission of ANDA No. 202040 for the purpose of obtaining approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Teva'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).

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

21. Upon information and belief, Teva will engage in the manufacture, use, offer for sale, sale, marketing, distribution, and/or importation of Teva's ANDA Product with its proposed labeling immediately and imminently upon approval of ANDA No. 202040.

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

23. Upon information and belief, Teva plans and intends to, and will, actively induce infringement of the '940 patent when ANDA No. 202040 is approved, and plans and intends to, and will, do so immediately and imminently upon approval.

24. Upon information and belief, Teva knows that Teva's ANDA Product and its proposed labeling are especially made or adapted for use in infringing the '940 patent, and that Teva's ANDA Product and its proposed labeling are not suitable for substantial noninfringing use. Upon information and belief, Teva plans and intends to, and will, contribute to infringement of the '940 patent immediately and imminently upon approval of ANDA No. 202040.

25. The foregoing actions by Teva 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.

26. Upon information and belief, Teva 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.

27. Unless Teva 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 Teva has infringed the '940 patent;
- (b) A judgment ordering that the effective date of any FDA approval for Teva to make, use, offer for sale, sell, market, distribute, or import Teva'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 Teva, and all persons acting in concert with Teva, from making, using, selling, offering for sale, marketing, distributing, or importing Teva'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 Teva'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;

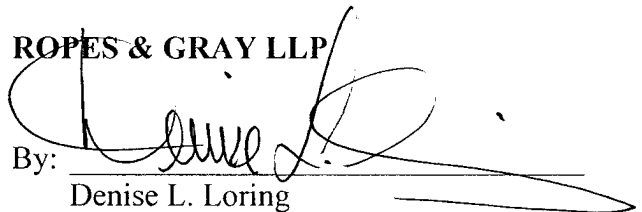
(e) A declaration that this is an exceptional case and an award of attorneys' fees pursuant to 35 U.S.C. § 285;

(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.

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Exhibit A



US006110940A

United States Patent [19]**Harding et al.**[11] **Patent Number:** **6,110,940**[45] **Date of Patent:** **Aug. 29, 2000**[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.⁷** 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[56] **References Cited****U.S. PATENT DOCUMENTS**

2,773,875	12/1956	Finkelstein	548/466
3,037,031	5/1962	Lewis et al.	548/466
4,092,315	5/1978	Bianco	544/291
4,252,803	2/1981	Webb	424/248.5
4,803,218	2/1989	Stanley et al.	548/466
4,855,314	8/1989	Oxford et al.	514/415
5,208,248	5/1993	Baker et al.	514/364
5,348,968	9/1994	Lavielle	548/468 X
5,409,941	4/1995	Nowakowski	514/33
5,498,626	3/1996	Macor	514/414
5,545,644	8/1996	Macor et al.	514/323
5,559,129	9/1996	Macor et al.	514/323
5,559,246	9/1996	Macor et al.	514/468
5,578,612	11/1996	Macor et al.	514/323
5,594,014	1/1997	Macor et al.	514/364

FOREIGN PATENT DOCUMENTS

465398	1/1992	European Pat. Off.
497512	8/1992	European Pat. Off.
74527	4/1954	Netherlands
74786	5/1954	Netherlands
851780	10/1960	United Kingdom
886684	1/1962	United Kingdom
893707	4/1962	United Kingdom

966562	8/1964	United Kingdom
2081717	2/1982	United Kingdom
9206973	4/1992	WIPO
9311106	6/1993	WIPO
9314087	7/1993	WIPO
9318032	9/1993	WIPO
9320073	10/1993	WIPO
9321177	10/1993	WIPO
9321178	10/1993	WIPO
9321180	10/1993	WIPO
9323396	11/1993	WIPO
9424127	10/1994	WIPO
9425023	11/1994	WIPO
9506636	3/1995	WIPO

OTHER PUBLICATIONS

Bader et al., *J. Am. Chem. Soc.*, 79, 5686–5689 (1957).
 Gray, *J. Org. Chem.*, 23, 1453–1454 (1958).
 Moore, et al., *J. Org. Chem.*, 29, 2860–2864 (1964).
 Cain, et al., *J. Am. Chem. Soc.* 105 908, 911, 912, (1983).
 Markowitz, et al. *J. Neurosci.* 7 (12) 4736 (1987).
 Lee, et al., *Brain Res.*, 626, 303–305 (1993).
 P.P.A. Humphrey, et al., *Br. J. Pharmacol.*, 94, 1128 (1988).
 W. Feniuk, et al., *Br. J. Pharmacol.*, 96, 83 (1989).
 Reagent for Org. Syn, 1, 112 (1967).
 Mohr, et al., *Tetrahedron*, 38(1), 147–152 (1982).
 Friderichs, et al., *Chem. Ab.*, 83, 28056 (1975).
 Kiyooka, et al., *J. Org. Chem.*, 5409 (1989).
 Hamada, et al., *Chem. Pharm. Bull.*, 1921 (1982).
 Lee, et al., *Soc. Neurosci Nov. 1993 Meeting* 19 (Part 2), #565.6.
 Moskowitz, *7th World Congress on Pain Aug. 1993*, #667.
 Leonard, et al., *Neuropharm.*, 11, 373–384 (1972).

Primary Examiner—Mukund J. Shah**Assistant Examiner**—Tamthom N. Truong**Attorney, Agent, or Firm**—Peter C. Richardson; Paul H. Ginsburg; Grover 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):

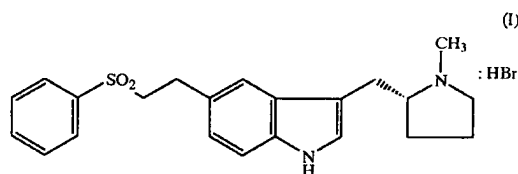
**14 Claims, 6 Drawing Sheets**

FIG. 1A

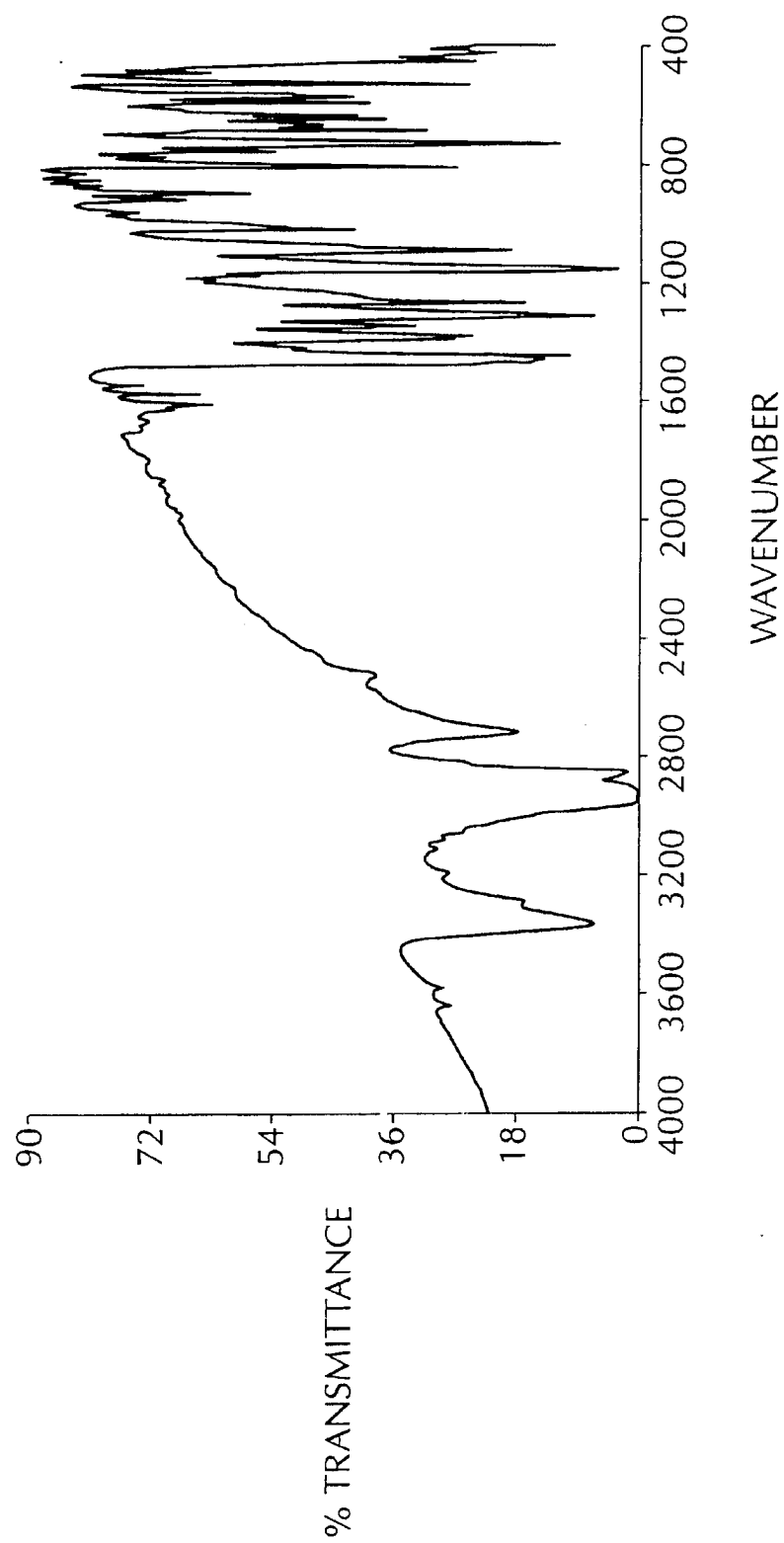


FIG. 1B

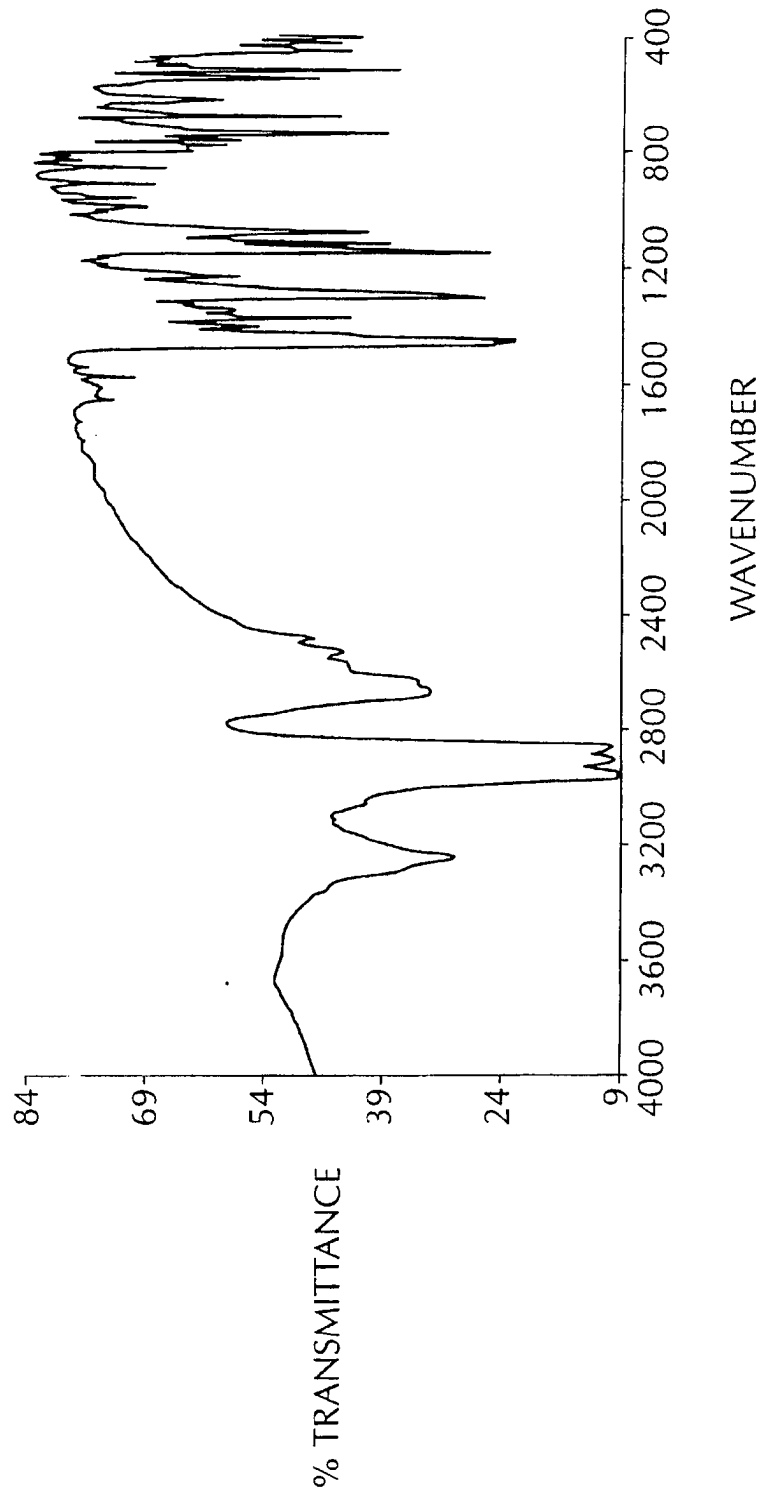


FIG. 2A

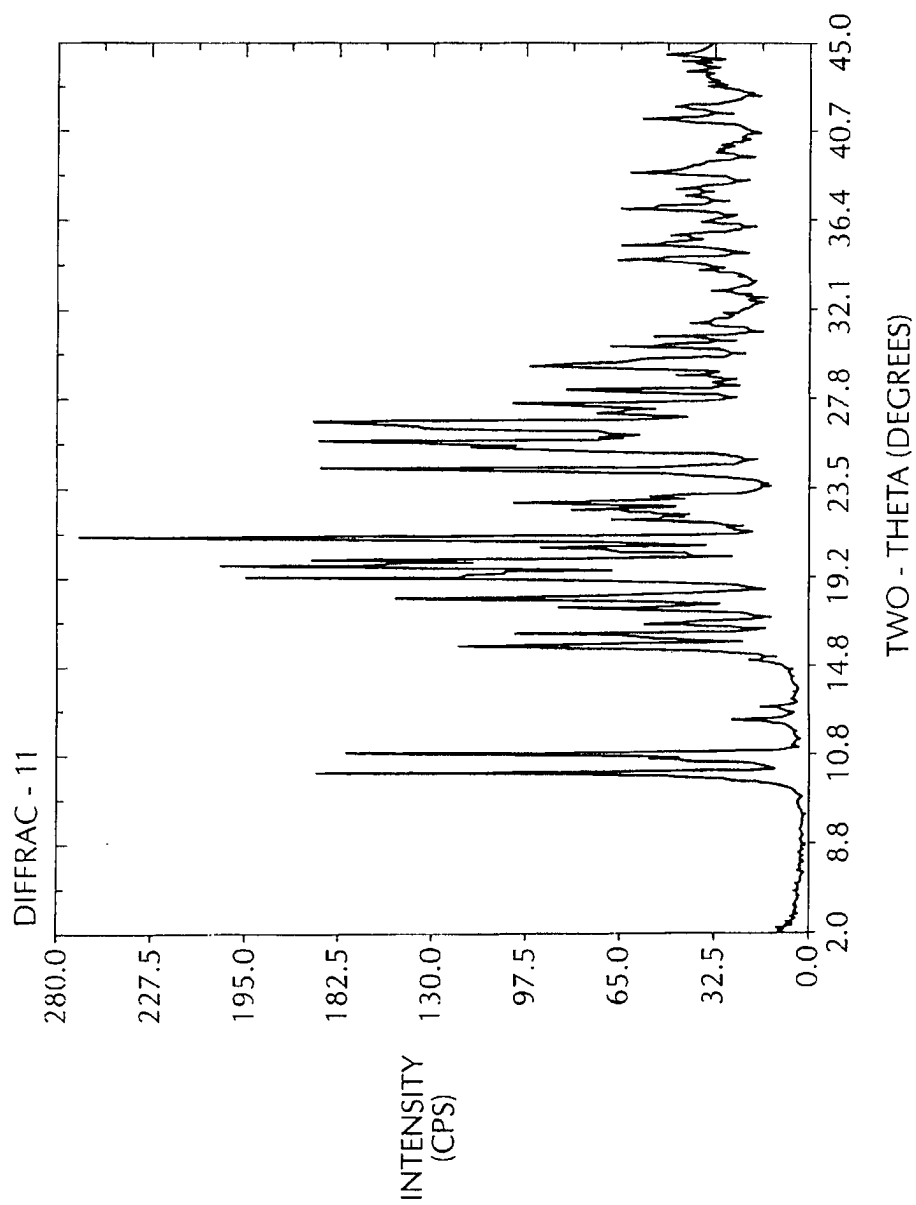


FIG. 2B

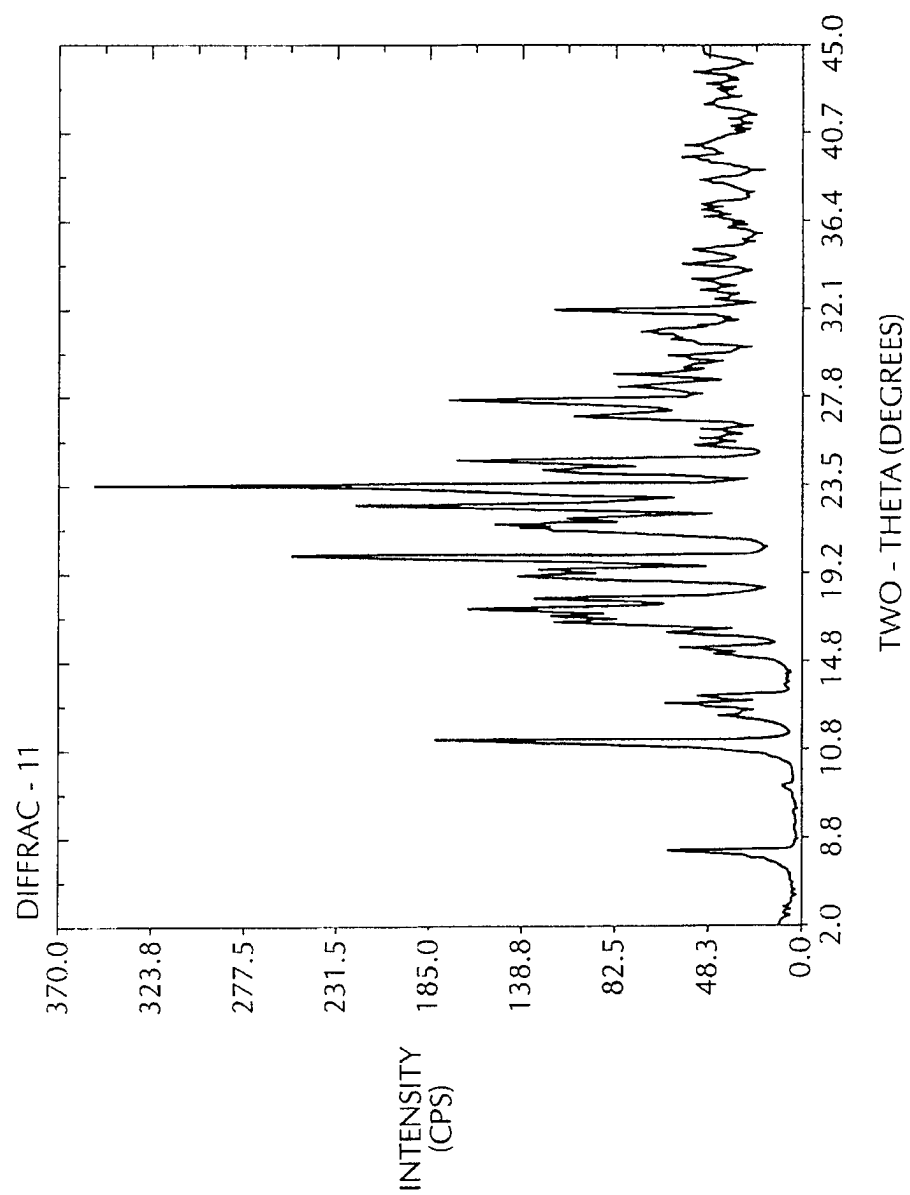


FIG. 3A

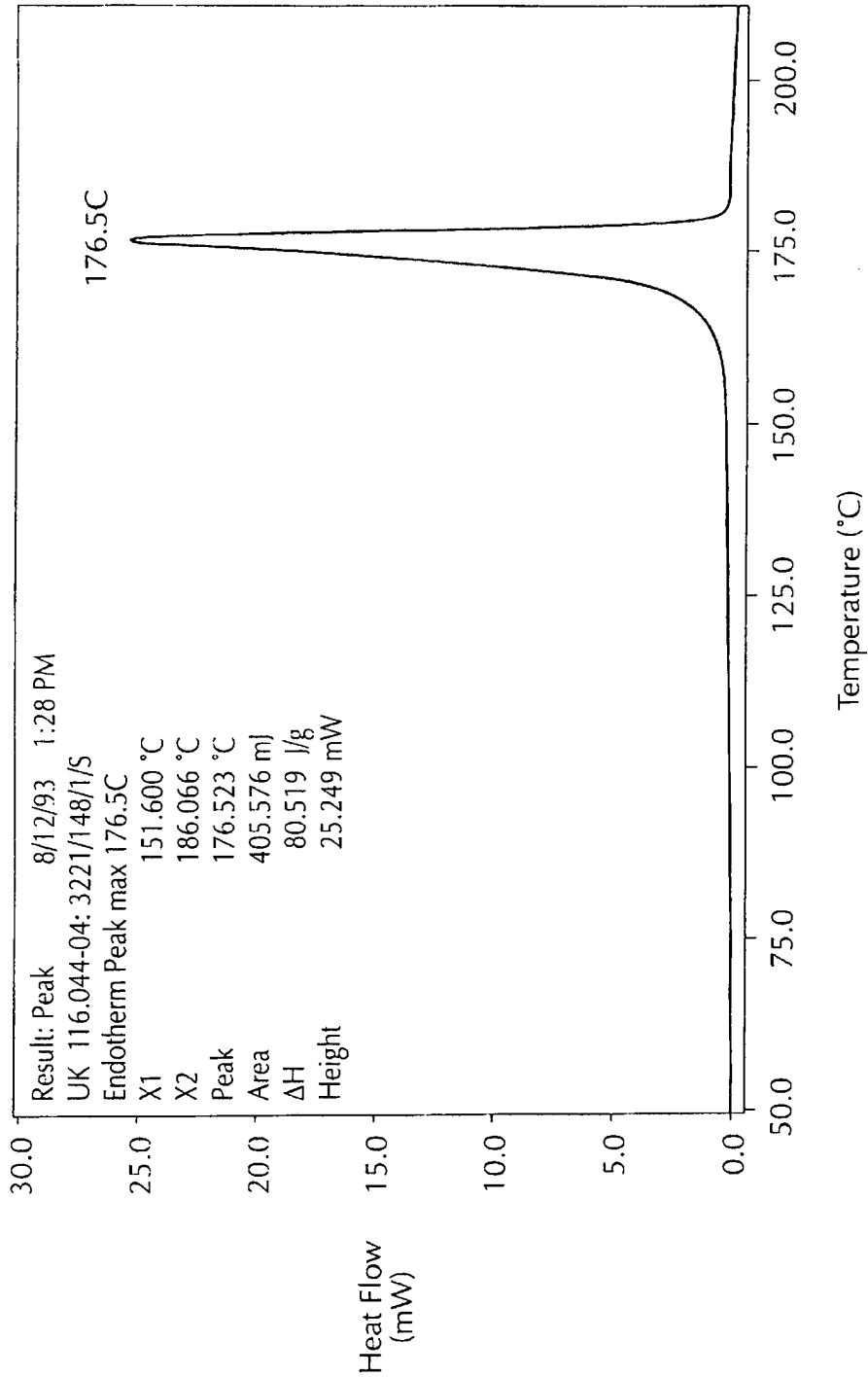
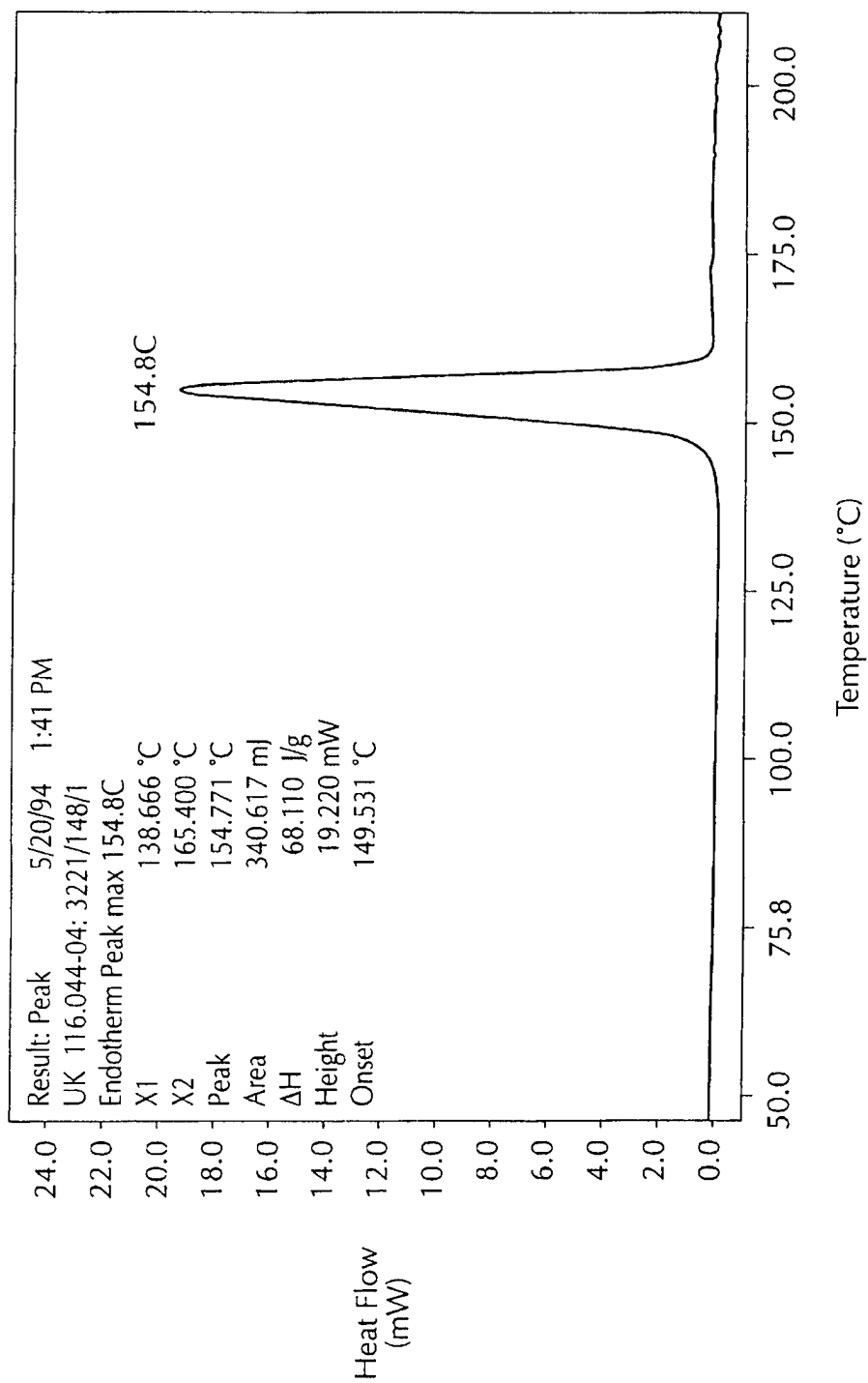


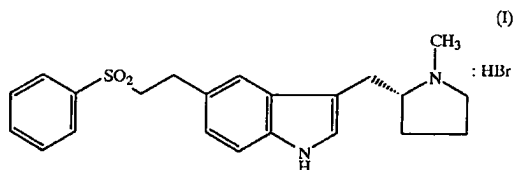
FIG. 3B



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-phenylsulphonylethyl)-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-92106973 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, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulphonate and pamoate. Specifically disclosed therein is 3-(N-methyl-2(R)-pyrrolidinylmethyl)-5-(2-phenylsulphonylethyl)-1H-indole and its hemisuccinate salt, the latter being characterised as a noncrystalline foam. 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-phenylsulphonylethyl)-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, dragees, suppositories, pessaries, solid implants, lyophile plugs, nanoparticles and microparticles and powder 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-hygroscopic, 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 monoacidic base, 3-(N-methyl-2(R)-pyrrolidinylmethyl)-5-(2-phenylsulphonylethyl)-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, benzenesulphonate, p-toluenesulphonate, (+)-camphorsulphonate, acetate, benzoate, citrate, hemifumarate, fumarate, hemimalate, maleate, hemisuccinate, succinate, hemi-L-tartrate, L-tartrate, hemi-D-tartrate, D-tartrate, L-lactate, (R)-(-)-mandelate, hippurate, hemiphthalate, phthalate and hemiterephthalate.

Of these thirty possible salts, only four could be obtained as crystalline solids, namely the hemisulphate, hydrochloride, hydrobromide and benzenesulphonate; 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 benzenesulphonate 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-filming 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. 125–129° C. (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 (KFT). 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 mull in nujol shows significant absorption bands at $\nu=3371, 3293, 2713, 2524, 1419, 1343, 1307, 1264, 1151, 1086, 1020, 1008, 999, 922, 900, 805, 758, 740, 728, 689, 672, 652, 640, 598, 581, 573, 531, 498, 465, 457, 443, 428, 422, 414$ 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 ($\lambda=0.15405\text{ nm}$) 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 .

The α -form is yet further characterised by its differential scanning calorimetry (DSC) trace which shows a sharp endotherm at 176.5°C . at a scan rate of $20^\circ\text{C}/\text{min}$.

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 mull in nujol shows significant absorption bands at $\nu=3239, 2672, 2656, 2632, 1409, 1366, 1351, 1334, 1303, 1293, 1152, 1138, 1122, 1098, 1086, 791, 771, 746, 688, 634, 557, 528, 484, 476, 469, 463, 455, 432, 424, 413$ and 401 cm^{-1} .

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

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 $20^\circ\text{C}/\text{min}$.

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 hydrogen bromide, 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.

Crystallisation 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. 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 agonist activity of the α -form can be measured in in vitro receptor binding assays as described for the 5-HT_{1A} 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-HT_{1D} receptor, using bovine caudate as the receptor source and [³H]5-HT as the radioligand (R. E. Heuring and S. J. Peroutka, 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 dosages 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-HT₁ receptors is indicated.

In a further aspect, the invention provides both a method of treating 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-HT₁ 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.

IR means infra red, PXRD means powder X-ray diffraction, DSC means differential scanning calorimetry, T means temperature, RH means relative humidity, HPLC means high performance liquid chromatography, KFT means Karl Fischer titrimetry.

EXAMPLE 1

3-(N-Methyl-2(R)-pyrrolidinylmethyl)-5-(2-phenylsulphonylethyl)-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-phenylsulphonylethyl)-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. C₂₂H₂₆N₂O₂S; HBr requires C, 57.02; H, 5.87; N, 6.04%.

EXAMPLE 2

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

(a) 3-(N-Methyl-2(R)-pyrrolidinylmethyl)-5-(2-phenylsulphonylethyl)-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-phenylsulphonylethyl)-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. C₂₂H₂₆N₂O₂S; 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-phenylsulphonylethyl)-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-phenylsulphonylethyl)-1H-indole (5.0 g, 13.07 mmol) in acetone (112 ml) at 0–5° C. After slurring 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 slurring 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

A. Direct Compression		
	mg/tablet	for 50 g mix
Active ingredient	12.12	6.06 g
Microcrystalline cellulose Ph Eur	25.00	12.50 g
Lactose Ph Eur	60.88	30.44 g
Croscarmellose sodium NF	1.00	0.50 g
Magnesium stearate Ph Eur	1.00	0.50 g

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.

B. Wet Granulation		
	mg/tablet	for 50 g mix
Active ingredient	1.21	0.76 g
Lactose Ph Eur	56.03	35.02 g
Maize starch Ph Eur	18.68	11.67 g
Polyvinylpyrrolidone (2% w/v soln)	1.60	1.00 g
Colloidal anhydrous silica Ph Eur	0.08	0.05 g
Croscarmellose sodium NF	1.60	1.00 g
Magnesium stearate Ph Eur	0.80	0.50 g

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

Capsules	
	mg/capsule
Active ingredient	18.18
Lactose Ph Eur	208.89
Maize starch Ph Eur	69.63
Colloidal anhydrous silica Ph Eur	0.30
Magnesium stearate Ph Eur	3.00
Fill weight	300.00

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

Sublingual Tablets		
	mg/tablet	for 50 g mix
Active ingredient	1.2	0.750 g
Lactose Ph Eur	25.0	15.625 g
Maize starch Ph Eur	25.0	15.625 g
Mannitol Ph Eur	25.0	15.625 g
Croscarmellose sodium NF	3.0	1.875 g
Magnesium stearate Ph Eur	0.8	0.500 g

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.

Characterisation of the Hydrobromide Salt α - and β -forms by IR, PXRD and DSC Analysis

BRIEF DESCRIPTION OF DRAWINGS

(a) IR Spectroscopy

The IR spectra were determined over the wave number (ν) range 4000 to 400^{-1} as nujol mulls using a Nicolet 800 FT-IR spectrometer and are represented by FIGS. 1A and 1B. For identification of the ν of significant absorption bands, vide supra.

(b) PXRD

The PXRD patterns were obtained using a Siemens D500 diffractometer which was operated at 40 kV/30 mA and using copper radiation filtered with a graphite monochromator ($\lambda=0.15405\text{nm}$) and a scintillation counter detector. For each form, beam intensity as a function of the angle 2θ was recorded over the range 2° to $45^\circ 2\theta$ using a step scan mode counting for six seconds at step intervals of $0.03^\circ 2\theta$. For identification of the main peaks (degree 2θ) seen in each pattern, represented by FIGS. 2A and 2B, vide supra.

(c) DSC

Samples (ca 5 mg) of each form were analysed using a Perkin-Elmer 7 Series thermal analyser at a scanning rate of $20^\circ \text{C. per minute}$. For identification of the respective endotherms, shown in the representative DSC thermograms of FIGS. 3A and 3B, vide supra.

Hygroscopicity/Solid State Stability Studies

Samples (ca 10 mg) were sieved ($250 \mu\text{m}$) and then stored at each of the following conditions of temperature (T) and relative humidity (RH) for up to 4 weeks:

30°C. at 11, 75 and 90% RH

and

40°C. at 11, 75 and 90% RH,

the required humidities being achieved using the appropriate saturated salt solution in a dessicator. Measurements of water content changes were conducted by weight analysis using a microbalance and by Karl Fischer titrimetry (KFT), and chemical and physical stability evaluation by high performance liquid chromatography (HPLC) and DSC.

HPLC analyses were performed on a LDC isocratic system under the following conditions:

column—Novapak C_{18} , $5 \mu\text{m}$, 15 cm; mobile phase—pH 6.0, 60:40 v/v 0.02M KH_2PO_4 (0.5% triethylamine): methanol; detection—UV (254 nm); flow rate—1.0 ml/min; injection volume— $20 \mu\text{l}$; sample 0.1 mg/ml in mobile phase.

KFT was performed using a Mitsubishi moisturemeter and ca 10 mg of each sample.

Table 1 shows hygroscopicity results for the α -form of the hydrobromide salt and the α - and β -forms of the hemisulphate salt, expressed as moisture changes determined by % weight change under various conditions of T($^\circ\text{C.}$) and RH(%).

It can be seen from Table 1 that the α -form of the hydrobromide salt showed relatively stable weights throughout the course of the study, with slight loss of moisture at low (11%) RH being observed at both 30°C. and 40°C. , and these results were corroborated by those obtained by KFT analysis. Particularly noteworthy is that little change in its moisture content was noted at a RH of 75%, by comparison with the significant uptake seen at 40°C. for both the β -form and, especially, the α -form of the hemisulphate salt. Moreover, water uptake by the β -form of the hemisulphate salt was accompanied by a change in colour of the sample from cream to yellow; although the α -form of the hemisulphate salt absorbed water even more rapidly than the β -form, no concomitant colour

TABLE 1

SALT FORM	T/RH	Week 1	Week 2	Week 3	Week 4
α -HBr	30/11	-0.45	-0.51	+0.20	+0.09
	30/75	+0.08	+0.01	+0.17	+0.25
	30/90	+0.53	+0.46	+0.50	+0.49
	40/11	-0.48	+0.58	-0.51	-0.49
	40/75	+0.06	+0.23	0.00	+0.11
β - $\frac{1}{2}$ H ₂ SO ₄	40/90	+0.87	+1.27	+1.16	+1.23
	40/75	+1.33	+3.79	+3.38	+1.69
α - $\frac{1}{2}$ H ₂ SO ₄	40/75	+6.0	+4.85	+5.46	+4.04

TABLE 2

(T/RH 40/75)					
SALT FORM	Day 5	Week 1	Week 2	Week 3	Week 4
β -HCl	ND	0	+0.27	+0.23	+0.19
α -HCl	+0.56	+0.79	ND	ND	ND

ND = not determined

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./RH=90% samples, whilst HPLC analysis confirmed its stability under all of 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./RH=75%.

The β -form was judged to be non-hygroscopic on the basis of both the results displayed in Table 2 and the closely comparable results obtained by KFT 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 IR press (Graseby Specac Model 15.011) 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 filming on compaction.

As previously mentioned, the β -form of the hemisulphate salt undergoes a colour change on compression and also causes punch filming 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

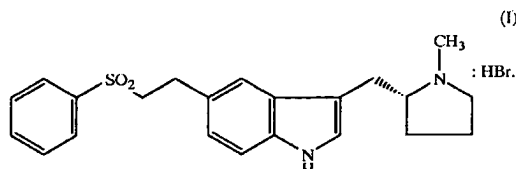
DSC was used to determine both the polymorphic conversions of the β -forms of the hydrobromide and hemisul-

phate 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):



2. A crystalline, α -polymorphic form of a compound according to claim 1 further characterised by an infra-red spectrum as a mull in nujol which shows significant absorption bands at ν =3371, 3293, 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, 16.5, 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 2 θ .

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.

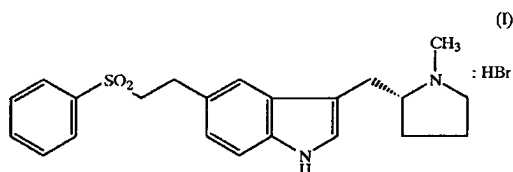
5. A pharmaceutical composition for the treatment of a medical condition selected from the group consisting of migraine, cluster headache, chronic paroxysmal hemicrania or headache associated with a vascular disorder, depression, anxiety, an eating disorder, obesity, drug abuse, hypertension and emesis, 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.

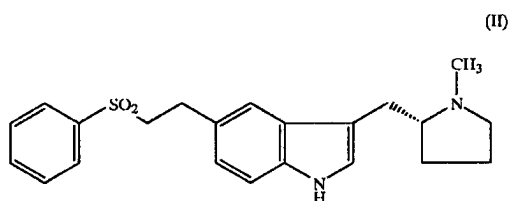
8. A process for the preparation of a crystalline, α -polymorphic form of a compound of formula (I):

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characterised by an infra-red spectrum as a mull in nujol which shows significant absorption bands at $\nu=3371, 3293, 2713, 2524, 1419, 1343, 1307, 1264, 1151, 1086, 1020, 1008, 999, 922, 900, 805, 758, 740, 728, 689, 672, 652, 640, 598, 581, 573, 531, 498, 465, 457, 443, 428, 422, 414$ and 399 cm^{-1} , which comprises

a) treatment of a solution of a compound of formula (II):



in a first suitable solvent with an aqueous solution of hydrogen bromide, followed by crystallisation of the isolated crude oil from a second suitable solvent;

b) crystallisation of a β -polymorphic form of a compound of formula (I), characterised by an infra-red spectrum as a mull in nujol which shows significant absorption bands at $\nu=3239, 2672, 2656, 2632, 1409, 1366, 1351, 1334, 1303, 1293, 1152, 1138, 1122, 1098, 1086, 791, 771, 746, 688, 634, 557, 528, 484, 476, 469, 463, 455, 432, 424, 413$ and 401 cm^{-1} , from a suitable solvent, followed by slurring of the resulting mixture; or

c) treatment of a solution of a compound of formula (II) in a suitable solvent with an aqueous solution of hydrogen bromide and then slurring of the reaction mixture, optionally followed by heating under reflux, cooling and further slurring.

9. A process according to claim 8 wherein in

a) the first suitable solvent is acetone, the second suitable solvent is 2-propanol, the aqueous solution of hydrogen bromide is 49% w/w and the treatment therewith is conducted at from $20-25^\circ \text{C}$;

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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 ($\lambda=0.15405 \text{ nm}$) 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 ($\lambda=0.15405 \text{ nm}$) 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-HT_1 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 for which a selective agonist of 5-HT_1 receptors is indicated, 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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