AUSTRALIA

PATENTS ACT 1990

NOTICE OF ENTITLEMENT

We, **Glaxo Group Limited**, the applicant/Nominated Person in respect of Application No. 11652/92 state the following:-

The Nominated Person is entitled to the grant of the patent because the Nominated Person derives title to the invention by assignment from a person who would, on the grant of a patent for the invention to the inventors, be entitled to have the patent assigned to it.

The Nominated Person is entitled to claim priority from the application listed in the declaration under Article 8 of the PCT because the Nominated Person made the application listed in the declaration under Article 8 of the PCT, and because that application was the first application made in a Convention country in respect of the invention.

DATED this TWENTY SECOND day of JULY 1993

.....

a member of the firm of
DAVIES COLLISON
CAVE for and on behalf
of the applicant(s)

(DCC ref: 1601170)

AU9211652

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(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 653986

(54) Title
COMPOSITIONS

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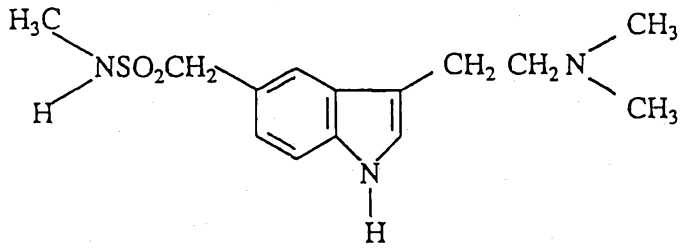
(56) Prior Art Documents
US 5037845
EP 358234
GB 2133691

(57)

3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide, which may be represented by the formula (I)



(I)

and its physiologically acceptable salts and solvates are disclosed in UK Patent Specification No. 2162522. The compound of formula (I) exhibits selective vasoconstrictor activity and is useful in the treatment of migraine.

CLAIM

1. A pharmaceutical composition in a form adapted for intranasal administration which comprises a suspension of 3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide or a suitable physiologically acceptable salt or solvate thereof as active ingredient, wherein the pH is in the range of 8 to 12.

.../2

10. A method of treating a mammal, including man, suffering from or susceptible to cephalic pain, in particular migraine, which comprises intranasal administration of a pharmaceutical composition comprising a suspension of 3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide or a suitable physiologically acceptable salt or solvate thereof as active ingredient, wherein the pH is in the range of 8 to 12.

OPI DATE 27/08/92 APPLN. ID 11652 / 92
AOJP DATE 01/10/92 PCT NUMBER PCT/EP92/00094

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A1

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(81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC (European patent), MG, ML (OAPI patent), MN, MR (OAPI patent), MW, NL, NL (European patent), NO, PL, RO, RU, SD, SE, SE (European patent), SN (OAPI patent), TD (OAPI patent), TG (OAPI patent), US.

Published
With international search report.

(54) Title: COMPOSITIONS

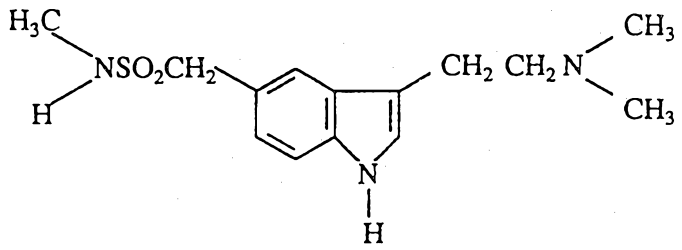
(57) Abstract

A pharmaceutical composition in a form adapted for intranasal administration which comprises a suspension of 3-2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide or a suitable physiologically acceptable salt or solvate thereof as active ingredient, wherein the pH is in the range of 8 to 12. The intranasal compositions are of use in the treatment of conditions associated with cephalic pain, in particular migraine.

COMPOSITIONS

The present invention relates to a pharmaceutical composition containing as active ingredient 3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide, in particular a composition for intranasal administration.

3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide, which may be represented by the formula (I)



(I)

and its physiologically acceptable salts and solvates are disclosed in UK Patent Specification No. 2162522. The compound of formula (I) exhibits selective vasoconstrictor activity and is useful in the treatment of migraine.

Oral compositions have certain disadvantages for the administration of anti-migraine agents. Thus, for example, one of the symptoms associated with migraine is nausea, and the presence of nausea may make it difficult for a patient to take an oral composition. Also, it is desirable that the anti-migraine drug should be rapidly absorbed into the bloodstream. Such rapid absorption can be achieved using intranasal or parenteral administration, but some patients dislike parenteral administration, particularly if the drug is to be self-administered. Intranasal administration therefore represents a preferred route for administration of the compound of formula (I).

We have now found a particularly advantageous formulation for the intranasal administration of the compound of formula (I) comprising an alkaline suspension of the compound of formula (I) or a physiologically acceptable salt or solvate thereof.

There is thus provided according to the invention a pharmaceutical composition in a form adapted for intranasal administration comprising a suspension of 3-[2-dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide or a suitable physiologically acceptable salt or solvate thereof as active ingredient wherein the pH is in the range of 8 to 12.

Suitable physiologically acceptable salts and solvates of 3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide for use in the present invention are those which have relatively low aqueous solubility, e.g. the succinate and hydrochloride salts. Preferably the pharmaceutical compositions according to the invention contain 3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide in the form of the free base.

For satisfactory intranasal administration, an active ingredient must be presented in a form which is readily absorbed through the nasal mucosa but which is unassociated with any adverse effects such as irritancy. Satisfactory intranasal formulations must also be sufficiently stable, chemically and physically, to be consistently dispensed in accurate metered doses, even after prolonged storage with potential temperature fluctuations of between 0 and 40^0C. Accordingly, the active ingredient must be compatible with the excipients used in the formulation and should not aggregate in a manner which would result in a loss of accurate dose delivery.

Surprisingly, we have found that suspensions of 3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide and suitable physiologically acceptable salts and solvates thereof having a pH in the range of 8 to 12 have excellent dispersion properties. In contrast, neutral and acidic formulations containing such active ingredients do not form readily dispersible suspensions and are unsuitable for use as suspensions for intranasal administration.

Preferably the pH of suspensions according to the invention will be in the range of 9 to 11; most preferably the pH of the suspensions according to the invention will be about 10.

Suspensions will generally be aqueous, for example prepared from water alone (for example sterile or pyrogen-free water) or water and a physiologically

acceptable non-aqueous vehicle (for example ethanol, propylene glycol, polyethylene glycols such as PEG 400).

Such suspensions may additionally contain other excipients, for example preservatives (such as benzalkonium chloride and phenylethylalcohol), wetting agents/surfactants such as polysorbates (e.g. Tween 80) and sorbitan esters (e.g. Span 80), buffering agents, isotonicity-adjusting agents (e.g. sodium chloride), suspending agents, absorption enhancers, flavouring agents and sweetening agents (e.g. saccharin)..

Preferably suspensions according to the invention will be sterile and free from preservatives. Sterile formulations may be prepared by methods known in the art, for example by aseptic manufacture or sterilisation of the bulk products.

Preferably suspensions according to the invention will be thickened by addition of a viscosity enhancer such as acacia, bentonite, carboxymethylcellulose sodium, gelatin, guar gum, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylcellulose, or tragacanth. The viscosity enhancer may be present in an amount of about 0.1 to about 5% w/w, preferably 0.5 to 2% w/w. Most preferably the viscosity enhancer used will be microcrystalline cellulose with sodium carboxymethylcellulose, e.g. Avicel RC 591.

Most preferably suspensions according to the invention will be thixotropic. Thixotropic suspensions can be obtained by the use of a suitable viscosity enhancer e.g. Avicel RC 591.

In a particularly preferred aspect the invention provides a suspension of 3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide or a suitable physiologically acceptable salt or solvate thereof and microcrystalline cellulose with sodium carboxymethylcellulose adapted for intranasal administration wherein the pH is in the range of 8 to 12.

Suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multidose form. In the latter case a means of dose metering is provided. In the case of a dropper or pipette this may be achieved by the patient administering an

appropriate, predetermined volume of the suspension. In the case of a spray this may be achieved for example by means of a metering atomising spray pump.

Intranasal administration may also be achieved by means of an aerosol formulation in which the compound is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane or dichlorotetrafluoroethane, a hydrofluorocarbon (HFC) for example 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane, carbon dioxide or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

Preferably a pharmaceutical composition according to the invention will be in the form of an aqueous suspension.

Suspensions according to the invention may be prepared from solutions or suspensions of 3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide or suitable physiologically acceptable salts or solvates thereof, by addition of an appropriate amount of a base, such as an inorganic base, preferably an alkali metal hydroxide, most preferably sodium hydroxide.

Preferably the suspensions of the invention will be prepared by suspending 3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide, or a suitable physiologically acceptable salt or solvate thereof, of small particle size in an aqueous vehicle at high pH.

As used herein small particle size means particle size of the order of 10 microns or less, preferably 2 to 5 microns. Such a particle size may be obtained by means known in the art, for example, micronisation.

Suspensions according to the invention will preferably contain 3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide in a concentration of 20mgml^{-1} to 500mgml^{-1}.

A further aspect of the invention provides a method of treating a mammal, including man, suffering from or susceptible to conditions associated with cephalic pain such as cluster headache, chronic paroxysmal hemicrania, headache associated with vascular disorders, headache associated with substances or their withdrawal (for

example drug withdrawal), tension headache and in particular migraine which comprises intranasal administration of a pharmaceutical composition comprising a suspension of 3-[2-dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide or a suitable physiologically acceptable salt or solvate thereof as active ingredient wherein the pH is in the range of 8 to 12. It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms.

It will be appreciated that the precise therapeutic dose of the active ingredient will depend on the age and condition of the patient and the nature of the condition to be treated and will be at the ultimate discretion of the attendant physician.

However, in general effective doses for the treatment of conditions associated with cephalic pain, for example acute treatment of migraine, will lie in the range of 0.5 to 100mg, preferably 1 to 60mg, most preferably 2 to 40mg of the active ingredient per unit dose which could be administered in single or divided doses, for example, 1 to 4 times per day.

Pharmaceutical compositions according to the invention may conveniently be presented in unit dose form. A convenient unit dose formulation for intranasal administration contains 3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide in an amount of from 0.5mg to 100mg, preferably 1mg to 60mg, most preferably 2mg to 40mg, which may be administered to either one or both nostrils.

A preferred unit dose formulation may be provided as a single dose in a sealed unit, for example a vial of glass or plastics material which may be filled and sealed using conventional manufacturing techniques. Alternatively, a sealed vial of plastics material may be produced by form-fill-seal technology. Preferably the vial and the components of the pharmaceutical formulation filled therein are heat stable. The sealed vial may be sterilised, for example by autoclaving at 121^0C for not less than 15 minutes, to provide a sterile device prior to use. Preferably the unit dose volume is 50 to 200μl, for example 100μl.

The following non-limiting examples further illustrate the invention.

Examples 1 and 2

	Example 1	Example 2
Compound of formula (I)	20mg	400mg
Microcrystalline Cellulose and Carboxymethylcellulose sodium NF (Avicel RC591)	10mg	10mg
Phenylethyl Alcohol USP	4mg	4mg
Benzalkonium Chloride	0.2mg	0.2mg
Polysorbate 80 BP	0.5mg	0.5mg
Purified Water BP	to 1ml	to 1ml

Microcrystalline cellulose and carboxymethylcellulose sodium (Avicel RC591) is dispersed in water and allowed to hydrate. Compound of formula (I) is mixed with a solution of polysorbate 80 and the resultant slurry added to the Avicel RC591 suspension, phenylethyl alcohol and benzalkonium chloride are added and the suspension made to volume with water.

Example 3

Compound of formula (I)	50mg
0.1M $Na_2CO_3/NaHCO_3$ buffer, pH 10.55	to 1.0g

The buffer was added to the compound of formula (I) and mixed thoroughly to give a stable suspension, pH 10.5.

Examples 4 and 5

	Example 4	Example 5
Compound of formula (I)	25mg	50mg

Microcrystalline cellulose and carboxymethylcellulose USNF (Avicel RC591)	15mg	15mg
Water for Injections B.P.	to 1g	to 1g

Microcrystalline cellulose and carboxymethylcellulose USNF (Avicel RC591) was dispersed in water and allowed to hydrate. The compound of formula (I) was added, dispersed thoroughly and the mixture made up to weight with water to give a stable suspension with a pH of 10.3.

Lowering the pH of the suspension of Example 4 to pH 7.6 by the addition of 22.5% H_2SO_4 with stirring resulted in immediate separation of the suspension.

Example 6

Compound of formula (I)	176.5mg
Microcrystalline cellulose and carboxymethylcellulose USNF (Avicel RC 591)	8.8mg
Phenylethyl alcohol	4.0mg
Benzalkonium chloride	0.2mg
Water for Injections BP	to 1g

Microcrystalline cellulose and carboxymethyl cellulose USNF (Avicel RC 591) was dispersed in water and allowed to hydrate. The compound of formula (I) was added and dispersed thoroughly. Phenylethyl alcohol and benzalkonium chloride were added and the suspension was made up to weight with water to give a stable uniform suspension with a pH of 10.3.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

Claims

1. A pharmaceutical composition in a form adapted for intranasal administration which comprises a suspension of 3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide or a suitable physiologically acceptable salt or solvate thereof as active ingredient, wherein the pH is in the range of 8 to 12.

2. A pharmaceutical composition as claimed in Claim 1 wherein the active ingredient is in the form of the free base.

3. A pharmaceutical composition as claimed in Claim 1 or Claim 2 wherein the pH is in the range of 9 to 11.

4. A pharmaceutical composition as claimed in any one of Claims 1 to 3 in the form of an aqueous suspension.

5. A pharmaceutical composition as claimed in any one of Claims 1 to 4 which further comprises a viscosity enhancer.

6. A pharmaceutical composition as claimed in Claim 5 which contains viscosity enhancer in an amount of about 0.1 to about 5% w/w.

7. A pharmaceutical composition as claimed in Claim 5 or Claim 6 wherein the viscosity enhancer is microcrystalline cellulose with sodium carboxymethylcellulose.

8. A pharmaceutical composition as claimed in any one of Claims 1 to 7 which contains the active ingredient in a concentration of 20 to 500mgml^{-1}.

9. A pharmaceutical composition as claimed in any one of Claims 1 to 8 which is presented in unit dosage form comprising 0.5 to 100mg of active ingredient.

10. A method of treating a mammal, including man, suffering from or susceptible to cephalic pain, in particular migraine, which comprises intranasal administration of a pharmaceutical composition comprising a suspension of 3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide or a suitable physiologically acceptable salt or solvate thereof as active ingredient, wherein the pH is in the range of 8 to 12.

11. Pharmaceutical compositions or methods of treatment involving them, substantially as hereinbefore described with reference to the Examples.

DATED this 17th day of August, 1994
Glaxo Group Limited
By Its Patent Attorneys
DAVIES COLLISON CAVE

INTERNATIONAL SEARCH REPORT

International Applica. No PCT/EP 92/00094

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 31/40 A 61 K 9/08

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	FR,A,2568571 (GLAXO GROUP LTD) 7 February 1986, see page 3, line 24 - page 4, line 13; page 6, lines 18-28; page 9, line 19 - page 19, line 11; page 37, line 19 - page 39, line 21; & GB,A,2162522 (cited in the application)	1-10
A	EP,A,0358234 (RORER INTERNATIONAL) 14 March 1990, see page 11, line 40 - page 12, line 20	5-6
A	EP,A,0187433 (TEIJIN LTD) 16 July 1986, see pages 19-20, example 17	7
A	GB,A,2133691 (AKTIEBOLAGET LEO) 1 August 1984, see page 7, example 14	5-7

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
05-03-1992	24. 04. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Danielle van der Haas

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CON. .UED FROM THE SECOND SHEET

V. [X] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claim numbers because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 10 is directed to a method of treatment of the human body (rule 39.1(iv)) the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this International application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9200094 SA 55089

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 17/04/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR-A- 2568571	07-02-86	AT-B- 386196	11-07-88
		AU-B- 573878	23-06-88
		AU-A- 4568985	06-02-86
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		CA-A- 1241004	23-08-88
		CH-A- 666026	30-06-88
		DE-A- 3527648	13-02-86
		GB-A,B 2162522	05-02-86
		JP-A- 61047464	07-03-86
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