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(71) Applicant *(for all designated States except US)*: BEECHAM GROUP PLC [GB/GB]; SB House, Great West Road, Brentford, Middlesex TW8 9BD (GB).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)* : JOHNSON, Edward, Stewart [GB/GB]; Willow Vale, Castle End Road, Ruscombe, Berkshire RG10 9XG (GB).

(74) Agent: JONES, Pauline; SmithKline Beecham, Corporate Patents, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB).

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(54) Title: PHARMACEUTICAL PREPARATIONS

(57) Abstract

A pharmaceutical product comprising two or three active ingredients as a combined preparation for simultaneous, separate or sequential use in therapy of depression and/or migraine.

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PHARMACEUTICAL PREPARATIONS

The present invention relates to pharmaceutical preparations having antidepressant and/or antimigraine activity.

It has now been found that a combination of two or three active agents having different mechanism of action with respect to 5-HT (5-hydroxytryptamine) has good antidepressant and/or antimigraine activity. The effectiveness of the combination is potentially greater than could be predicted from a consideration of the activities of the individual components and it appears that a synergistic effect is being produced.

Accordingly, the present invention provides a pharmaceutical product comprising two or three active ingredients selected from a 5-HT_3 receptor antagonist, a 5-HT re-uptake inhibitor and a 5-HT_1 receptor agonist, as a combined preparation for simultaneous, separate or sequential use in therapy of depression and/or migraine.

Suitable combinations are as follows:

5-HT_3 antagonist + 5-HT re-uptake inhibitor;
5-HT_3 antagonist + 5-HT_1 agonist;
5-HT_1 agonist + 5-HT re-uptake inhibitor; and
5-HT_3 antagonist + 5-HT re-uptake inhibitor + 5-HT_1 agonist.

Suitable examples of 5-HT_3 receptor antagonists are as described in WO 89/04660 and WO 90/01996 (Beecham Group p.l.c.), in particular BRL 43694A (granisetron) BRL 46470A (Example 5 in EP-A-247266); ondansetron or LY 277359.

Other examples of 5-HT_3 receptor antagonists are described in EP-A-410509 (Duphar International Research B.V.), EP-A-

420086 (Fujisawa Pharmaceutical Co., Ltd.), EP-A-403261 (Glaxo Group Limited), EP-A-405784 (Ono Pharmaceutical Co., Ltd.), EP-A-419397 (A/S Ferrosan), EP-A-417746 (G.O. Searle & Co.) and EP-A-407137 (Yoshitomi Pharmaceutical Industries Ltd.).

Suitable examples of 5-HT re-uptake inhibitors include the antidepressants, paroxetine and femoxetine (U.S. Patent No. 4007196), citalopram, sertraline, fluoxetine, clomipramine, fluvoxamine, cianopramine, ifoxetine, cericlamine, SL 810385 (Synthelabo) and seproxetine.

Suitable examples of 5-HT_1 receptor agonists include those compounds described in GB 2035310A; GB 2124210A; EP-A-145459; GB 2150932; EP-A-147107; GB 2185020A; EP-A-303506; EP-A-303507; EP-A-354777; EP-A-254433; and GB 2162522A (Glaxo Group Limited) in particular the compound GR 43175 (sumatriptan) or GR 85548; and EP-A-313397 (The Wellcome Foundation Limited).

Information with respect to structure and activity of the specific compounds listed hereinbefore may be obtained from well known pharmaceutical industry references, such as "Pharmaprojects", PJB publications Limited, Richmond, Surrey, U.K.

In a preferred aspect, the active components of the product are administered simultaneously although they may be administered separately e.g. the 5-HT_3 antagonist administered first.

The present invention further provides a pharmaceutical composition comprising two or three active ingredients selected from a 5-HT_3 receptor antagonist, a 5-HT re-uptake inhibitor and a 5-HT_1 receptor agonist in combination with a

pharmaceutically acceptable carrier.

The invention yet further provides the use of two or three active ingredients selected from a 5-HT_3 receptor antagonist, a 5-HT re-uptake inhibitor and a 5-HT_1 receptor agonist in the manufacture of a pharmaceutical preparation for simultaneous, separate or sequential use in depression and/or migraine therapy.

The product of the invention may be administered by the oral route to humans and may be compounded in the form of syrup, tablets or capsule for either separate, sequential or simultaneous administration.

However, they may be adapted for other modes of administration, for example parenteral administration. Other alternative modes of administration include sublingual or transdermal administration.

Generally, compositions containing from about 2.5 to 15 mg of granisetron or 0.01 to 10 mg of BRL 46470A, 10-50 mg of paroxetine and 10-50 mg sumatriptan in a ratio of around 1:4:4 are effective, but this will depend on the activity of the 5-HT_3 receptor antagonist, 5-HT re-uptake inhibitor and/or 5-HT_1 agonist.

In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit-dose. Suitable unit dose forms include tablets, capsules and powders in sachets or vials. Such unit dose forms may contain a total of from 0.01 to 100 mg of a 5-HT_3 receptor antagonist and more usually from 0.5 to 50 mg, for example 0.5 to 25 mg such as 0.5, 1, 2, 3, 5, 10, 15 or 20 mg. The unit dose form will normally contain from about 5 to 100 mg of the 5-HT re-uptake inhibitor and/or 5 to 100 mg of the 5-HT_1 agonist, more usually 10 to 50 mg, for example

10, 15, 20, 25, 30 mg. Such compositions may be administered from 1 to 6 times a day, more usually from 2 to 4 times a day, in a manner such that the daily dose of 5-HT_3 receptor antagonist is from 0.5 to 200 mg for a 70 kg human adult and more particularly from 0.5 to 25 mg, and the daily dose of the 5-HT re-uptake inhibitor and/or 5-HT_1 agonist, is from 10 to 500 mg for a 70 kg human adult and more particularly from 10 to 100 mg.

With the above indicated dosage range, no adverse toxicological effects are indicated with the composition of the invention.

The compositions of the invention may be formulated with conventional excipients, such as a filler, a disintegrating agent, a binder, a lubricant, a flavouring agent. They are formulated in conventional manner, for example in a manner similar to that used for anti-hypertensive agents.

It is greatly preferred that the 5-HT_3 receptor antagonist, 5-HT re-uptake inhibitor and/or 5-HT_1 receptor agonist, are administered in the form of a unit-dose composition, such as a unit dose oral or parenteral composition.

Such compositions are prepared by admixture and are suitably adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions or suppositories. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional

excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

These solid oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral formulations also include conventional sustained release formulations, such as tablets or granules having an enteric coating.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

It will be appreciated that each component of the product of the invention may be administered by a different route.

The present invention yet further provides a method of treating depression and/or migraine in mammals including man, which comprises administering to the suffering mammal an effective amount of a pharmaceutical composition

comprising two or three active ingredients selected from a 5-HT_3 receptor antagonist, a 5-HT re-uptake inhibitor and a 5-HT_1 receptor agonist, in combination with a pharmaceutically acceptable carrier.

Standard methods for assessing 5-HT_3 receptor antagonist activity, 5-HT_1 receptor agonist activity and 5-HT re-uptake inhibition activity are known in the art, and are, for example, described or referenced in the aforementioned patent publication references.

Antidepressant and/or antimigraine activity is assessed in appropriate animal models for determining such activities and in appropriate clinical trial methods.

Claims

1. A pharmaceutical product comprising two or three active ingredients selected from a 5-HT_3 receptor antagonist, a 5-HT re-uptake inhibitor and a 5-HT_1 receptor agonist, as a combined preparation for simultaneous, separate or sequential use in therapy of depression and/or migraine.

2. A pharmaceutical product according to claim 1 comprising two active ingredients which are a 5-HT_3 receptor antagonist and a 5-HT re-uptake inhibitor.

3. A pharmaceutical product according to claim 1 comprising two active ingredients which are a 5-HT_3 receptor antagonist and a 5-HT_1 receptor agonist.

4. A pharmaceutical product according to claim 1 comprising two active ingredients which are a 5-HT_1 receptor agonist and a 5-HT re-uptake inhibitor.

5. A pharmaceutical product according to claim 1 comprising three active ingredients which are a 5-HT_3 receptor antagonist, a 5-HT re-uptake inhibitor and a 5-HT_1 receptor agonist.

6. A pharmaceutical product according to claim 1 wherein a 5-HT_3 receptor antagonist is selected from those described in WO 89/04660 and WO 90/01996.

7. A pharmaceutical product according to claim 1 wherein a 5-HT re-uptake inhibitor is selected from paroxetine, femoxetine, citalopram, sertraline, fluoxetine, clomipramine, fluvoxamine, cianopramine, ifoxetine, cericlamine, SL 810385 and seproxetine.

8. A pharmaceutical product according to claim 1 wherein the 5-HT_1 receptor agonist is sumatriptan.

9. A pharmaceutical composition comprising two or three active ingredients selected from a 5-HT_3 receptor antagonist, a 5-HT re-uptake inhibitor and a 5-HT_1 receptor agonist in combination with a pharmaceutically acceptable carrier.

10. The use of two or three active ingredients selected from a 5-HT_3 receptor antagonist, a 5-HT re-uptake inhibitor and a 5-HT_1 receptor agonist in the manufacture of a pharmaceutical preparation for simultaneous, separate or sequential use in depression and/or migraine therapy.

INTERNATIONAL SEARCH REPORT

International Applicat .No PCT/GB 91/00992

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 45/06 A 61 K 31/445 A 61 K 31/415 //
(A 61 K 31/445 A 61 K 31:415 A 61 K 31:40)

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	WO,A,8904660 (BEECHAM GROUP PLC) 1 June 1989, see the whole document (cited in the application) ---	1-10
A	Chemical Abstracts, vol. 113, no. 7, 13 August 1990, (Columbus, Ohio, US), A.J. Sleight et al.: "In vivo effects of sumatriptan (GR 43175) on extracellular levels of 5-HT in the guinea pig", see page 52, abstract 52433q, & Neuropharmacology 1990, 29(6), 511-13 ---	1-10
A	Chemical Abstracts, vol. 107, no. 23, 7 December 1987, (Columbus, Ohio, US), D.R. Thomas et al.: "Biochemical effects of the antidepressant paroxetine, a specific 5-hydroxytryptamine uptake inhibitor", see pages 43,44, abstract 211787c, & Psychopharmacology (Berlin) 1987, 93(2), 193-200 -----	1-10

° Special categories of cited documents : [10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
20-09-1991	17. 10. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Mme. M. van der Drift

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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9100992 SA 48758

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 02/10/91
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A- 8904660	01-06-89	AU-A- 2626488	14-06-89
		EP-A- 0340270	08-11-89
		JP-T- 2502185	19-07-90