1 565 447

PATENT SPECIFICATION (11) 1 565 447

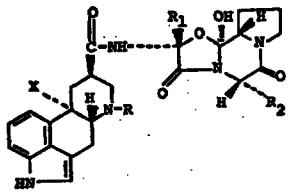
(21) Application No. 20210/77 (22) Filed 13 May 1977
(31) Convention Application No. 2621906
(32) Filed 17 May 1976 in
(33) Federal Republic of Germany (DE)
(44) Complete Specification published 23 April 1980
(51) INT CL³ A61K 31/495 (A61K 31/495 31/135)
(52) Index at acceptance
A5B 180 382 38Y 422 42Y 431 43Y 482 48Y 502 503 50Y 510 51Y 551 552 554 55Y 575 576 57Y 586 58Y 606 60Y 651 65Y 676 67Y J

(72) Inventors HANS BÜHLMANN and DIETER WELZEL

(54) PHARMACEUTICAL PREPARATIONS FOR VENOTONIC USE

(71) We, SANDOZ LTD., of 35 Lichtstrasse, 4002 Basle, Switzerland, a Swiss Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new pharmaceutical compositions containing compounds of formula I:



I

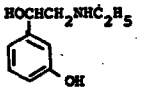
in which

R is hydrogen or alkyl having from 1 to 4 carbon atoms, other than *t*-butyl,
R_1 is methyl, ethyl or isopropyl,
R_2 is isopropyl, *sec.*-butyl, isobutyl or benzyl, and
X is hydrogen or methoxy.

The invention provides a pharmaceutical composition comprising a mixture of a compound of formula I and etilefrin in association with a pharmacologically acceptable diluent or carrier.

By the terms "compounds of formula I" and "etilefrin" are included pharmacologically acceptable salts of these compounds. A pharmacologically acceptable salt is one which does not have substantially higher toxicity than the corresponding free base. Examples of such salts are the methanesulphonate, maleate and tartrate of compounds of formula I, and the hydrochloride and sulphate of etilefrin.

The preferred compound of formula I is dihydroergotamine (DHE), in which R= methyl, R_1=methyl, R_2=benzyl and X= hydrogen. Etilefrin is the generic name for the compound α - [(ethylamino)methyl] - 3 - hydroxybenzenemethanol, of formula II



II

Pharmacologically acceptable diluents and carriers include binding agents for example polyvinylpyrrolidone and gelatine; tablet lubricants, for example stearic acid, magnesium stearate and talc; fillers, for example lactose and calcium carbonate; disintegrants, for example starches and alginic acid; flavourings and colourings.

The proportion of compound of formula I to etilefrin is suitably from 1:5 to 1:15 by weight, preferably 1:10 by weight.

The invention also provides a process for the preparation of a pharmaceutical composition according to the invention, characterised by mixing a compound of formula I and etilefrin together with a pharmacologically acceptable diluent or carrier.

One preferred process according to the invention comprises working up a compound of formula I with a pharmacologically acceptable polymer, preferably polyvinylpyrrolidone, to obtain a solid material which is then mixed with etilefrin. Preferably the etilefrin is in the form of a granulate containing one or more pharmacologically acceptable adjuvants, for example lactose, starch and gelatine.

A further preferred process according to the invention comprises forming a granulate of one of the active components together with one or more pharmacologically acceptable adjuvants, and mixing this granulate with the other component.

The first process is preferably carried out by mixing the compound of formula I together with polyvinylpyrrolidone in the form of an uncrosslinked poly(N - vinyl - 2 - pyrrolidone) of average molecular weight from 10,000 to 100,000, preferably from 11,500 to

SPECIFICATION DRAWINGS ATTACHED

40,000, particularly 25,000, optionally together with pharmacologically acceptable additives. Such additives may include surfactants, for example polyethylene glycol fatty acid esters, particularly polyethylene glycol stearate, as well as stabilizing additives for example acids, particularly methanesulphonic acid, maleic acid and tartaric acid, to maintain a pH of less than 7, preferably 4—5. The proportion of compound of formula I to polyvinylpyrrolidone is suitably from 1 to 30%, preferably from 5 to 15% by weight.

The mixture is then worked up so as to obtain a dry homogeneous material, for example by dissolving in a suitable solvent, and evaporating the solution. Suitable solvents include alcohols having from 1 to 4 carbon atoms, for example methanol and ethanol. The mixture may suitably be dissolved at an elevated temperature, preferably from 30° to 80°C, more preferably from 40° to 70°C. After complete solution, the solvent may be evaporated under the above conditions of temperature; preferably initially under atmospheric pressure and finally under vacuum. Optionally, only a part of the polyvinylpyrrolidone and/or the further additives may be added to the compound of formula I before the solution is prepared, and the addition of the remainder may take place during the evaporation stage. The solid residue obtained by complete removal of the solvent and cooling to room temperature (15°—25°C) may be ground to a fine powder in conventional manner and dried for example *in vacuo* for 12 hours at 30°C.

The dried product is then mixed with the corresponding quantity of etilefrin, preferably in the form of a granulate with conventional pharmacologically acceptable adjuvants.

The second process is preferably carried out by forming a granulate of one component in conventional manner, and mixing this with the other component optionally together with other pharmacologically acceptable adjuvants, so as to give a solid mixture suitable for filling capsules or for pressing into tablets. If desired, both components may be converted to granulates before being mixed.

The pharmaceutical compositions according to the invention give a surprisingly high increase in venous tone as indicated by the measurement of the volume elasticity coefficient E'_{15} in human subjects as described by M. Echt and L. Lange in "Das Orthostatesyndrom" (5th Rothenburg Conference, page 109, F. K. Schattauer Verlag, Stuttgart-New York, 1973). For these measurements, the left hand of the subject was isolated from the circulation in the left lower arm by a wrist cuff inflated to a high pressure (200 mm Hg), and a cuff around the upper arm was slowly inflated at a rate of 0.25 mm Hg/second. The venous pressure in the lower arm was measured by means of a catheter running from the back of the left hand to the distal third of the lower arm, and the change in the circumference of the left lower arm was measured by means of mercury-filled strip of silicone rubber tubing. These two measurements were recorded continuously on an x—y plotter during inflation of the upper arm cuff, and the slope of the curve at a venous pressure of 15 mm Hg was measured. This slope corresponds to the volume elasticity coefficient of the veins in the corresponding part of the body, E'_{15}, which may be expressed in units of

$$\frac{\text{mm Hg}}{\text{ml} \cdot 100 \text{ g tissue}}$$

and which is a measure of venous tone. An increase in venous tone is shown directly by an increase in the E'_{15} value. In this way venous tone may be measured independently of the blood flow.

It is found that administration of etilefrin alone (0.5 mg/min. for 20 min. by intravenous infusion) gives an increase of E'_{15} to 145% of the initial level before medication. Administration of DHE alone (0.5 mg intravenously) raises the E'_{15} level to 256% of the initial level. However, it has been found that administration of DHE (0.5 mg intravenously) followed by etilefrin (0.5 mg/min. for 20 min. by intravenous infusion) caused the E'_{15} level to rise to a peak of 562% of the initial value. This increase is considerably greater than could be accounted for by a purely additive effect of the two agents, and is attributed to a synergistic effect.

The compositions according to the invention are therefore indicated for venotonic use, particularly in the treatment of orthostatic and hypotonic circulatory disorders in mammals. A suitable indicated daily dosage is from 0.5 to 5 mg of compound of formula I and from 5 to 50 mg etilefrin. This daily dosage may suitably be administered in divided dosages of from 0.125 to 2.5 mg of compound of formula I and from 1.25 to 25 mg etilefrin 2 to 4 times daily, or in retard form. Particularly preferred is a mixture of 2 mg dihydroergotamine methanesulphonate and 20 mg etilefrin hydrochloride, for administration twice daily.

The active ingredients may also be administered separately, and may be supplied for this purpose in separate containers in the same package (twin-pack) with instructions for concomitant administration.

The compositions may be made up into galenic forms such as capsules, tablets, or solutions for oral administration by conventional methods. The compositions themselves, or galenic preparations thereof, may suitably be packaged in unit dosage forms, for example capsules, tablets or ampoules of

solution each containing a unit dosage of the active ingredients.

The following Examples illustrate the invention:

EXAMPLE 1

a) Preparation of solid solution of dihydroergotamine in polyvinyl pyrrolidone

To a 4 l round bottomed flask were added 34.6 g dihydroergotamine methanesulphonate, 195.4 g polyvinyl pyrrolidone (average M.W. 25,000) and 500 ml methanol. The flask was connected to a rotary evaporator and rotated in a water bath maintained at 60°C until a clear solution was obtained.

The solution was then evaporated at reduced pressure (~250 Torr) at a bath temperature of 60°C until the residue had a syrupy consistency. This liquid was transferred to an evaporating basin and left approximately 2 hours at room temperature to solidify. The resulting solid was dried in a vacuum oven for 12 hours at 30°C, approximately 1 Torr, then ground to a powder and dried further.

b) Preparation of etilefrin granulate

Etilefrin hydrochloride (346.0 g) was mixed with 650.8 g lactose and 110.4 g corn starch in a planetary mixer. The mixture was evenly dampened with a solution of 17.3 g gelatin in 70 g water, granulated through a sieve of mesh size 1.3 mm, and dried in a drying cupboard at 50°C for 12 hours. The dried granulate was then separated from fines by means of a sieve of mesh size 1.0 mm.

c) Mixing and Tabletting

230 g of the solid solution prepared as in a) and 1124.5 g of the granulate prepared according to b) were mixed homogeneously in a free fall mixer together with 895.0 g lactose, 86.5 g corn starch, 467.0 g cellulose powder, 294.0 g talc and 17.0 g silicic acid. The mixture was then worked into tablets of 180 mg nominal weight in a conventional tabletting press.

The tablets consisted of the following ingredients:

Etilefrin hydrochloride	20.0 mg
Dihydroergotamine methanesulphonate	2.0 mg
silicic acid	1.0 mg
gelatine	1.0 mg
corn starch	11.3 mg
polyvinylpyrrolidone	11.3 mg
talc	17.0 mg
cellulose powder	27.0 mg
lactose	89.4 mg
	180.0 mg

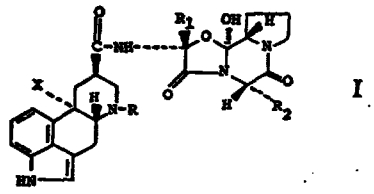
EXAMPLE 2

1124.5 g of the granulate prepared as in Example 1 b) was mixed to a homogenous state with 34.6 g dihydroergotamine methanesulphate, 895.0 g lactose, 86.5 g corn starch, 662.4 g cellulose powder, 294.0 g talc and 17.0 g silicic acid. The mixture so prepared was worked into tablets of 180 mg nominal weight on a conventional tabletting press, to give tablets of the following composition;

Etilefrin hydrochloride	20.0 mg
Dihydroergotamine methanesulphonate	2.0 mg
silicic acid	1.0 mg
gelatine	1.0 mg
corn starch	11.3 mg
talc	17.0 mg
cellulose powder	38.8 mg
lactose	89.4 mg
	180.0 mg

WHAT WE CLAIM IS:—

1. A pharmaceutical composition comprising a mixture of a compound of formula I



I

in which

R is hydrogen or alkyl having from 1 to 4 carbon atoms, other than *t*-butyl,

R_1 is methyl, ethyl or isopropyl,

R_2 is isopropyl, *sec.*-butyl, isobutyl or benzyl, and

X is hydrogen or methoxy,

and etilefrin, in association with a pharmaceutically acceptable diluent or carrier.

2. A pharmaceutical composition as claimed in Claim 1, in which the compound of formula I is dihydroergotamine.

3. A pharmaceutical composition as claimed in Claim 1 or Claim 2 in which the proportion of compound of formula I to etilefrin is from 1:5 to 1:15 by weight.

4. A pharmaceutical composition as claimed in Claim 3 in which the proportion of compound of formula I to etilefrin is 1:10 by weight.

5. A pharmaceutical composition as claimed in any one of the preceding claims in which the pharmacologically acceptable diluent or carrier comprises uncrosslinked poly - N - vinyl - 2 - pyrrolidone of average molecular weight from 10,000 to 100,000.

6. A pharmaceutical composition as claimed in Claim 5 in which the polyvinylpyrrolidone has an average molecular weight of from 11,500 to 40,000.

7. A pharmaceutical composition as claimed

solution each containing a unit dosage of the active ingredients.

The following Examples illustrate the invention:

EXAMPLE 1

a) Preparation of solid solution of dihydroergotamine in polyvinyl pyrrolidone

To a 4 l round bottomed flask were added 34.6 g dihydroergotamine methanesulphonate, 195.4 g polyvinyl pyrrolidone (average M.W. 25,000) and 500 ml methanol. The flask was connected to a rotary evaporator and rotated in a water bath maintained at 60°C until a clear solution was obtained.

The solution was then evaporated at reduced pressure (~250 Torr) at a bath temperature of 60°C until the residue had a syrupy consistency. This liquid was transferred to an evaporating basin and left approximately 2 hours at room temperature to solidify. The resulting solid was dried in a vacuum oven for 12 hours at 30°C, approximately 1 Torr, then ground to a powder and dried further.

b) Preparation of etilefrin granulate

Etilefrin hydrochloride (346.0 g) was mixed with 650.8 g lactose and 110.4 g corn starch in a planetary mixer. The mixture was evenly dampened with a solution of 17.3 g gelatin in 70 g water, granulated through a sieve of mesh size 1.3 mm, and dried in a drying cupboard at 50°C for 12 hours. The dried granulate was then separated from fines by means of a sieve of mesh size 1.0 mm.

c) Mixing and Tabletting

230 g of the solid solution prepared as in a) and 1124.5 g of the granulate prepared according to b) were mixed homogeneously in a free fall mixer together with 895.0 g lactose, 86.5 g corn starch, 467.0 g cellulose powder, 294.0 g talc and 17.0 g silicic acid. The mixture was then worked into tablets of 180 mg nominal weight in a conventional tabletting press.

The tablets consisted of the following ingredients:

Etilefrin hydrochloride	20.0 mg
Dihydroergotamine methanesulphonate	2.0 mg
silicic acid	1.0 mg
gelatine	1.0 mg
corn starch	11.3 mg
polyvinylpyrrolidone	11.3 mg
talc	17.0 mg
cellulose powder	27.0 mg
lactose	89.4 mg
	180.0 mg

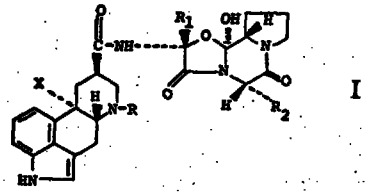
EXAMPLE 2

1124.5 g of the granulate prepared as in Example 1 b) was mixed to a homogenous state with 34.6 g dihydroergotamine methanesulphate, 895.0 g lactose, 86.5 g corn starch, 662.4 g cellulose powder, 294.0 g talc and 17.0 g silicic acid. The mixture so prepared was worked into tablets of 180 mg nominal weight on a conventional tabletting press, to give tablets of the following composition;

Etilefrin hydrochloride	20.0 mg
Dihydroergotamine methanesulphonate	2.0 mg
silicic acid	1.0 mg
gelatine	1.0 mg
corn starch	11.3 mg
talc	17.0 mg
cellulose powder	38.8 mg
lactose	89.4 mg
	180.0 mg

WHAT WE CLAIM IS:—

1. A pharmaceutical composition comprising a mixture of a compound of formula I



I

in which

R is hydrogen or alkyl having from 1 to 4 carbon atoms, other than *t*-butyl,

R_1 is methyl, ethyl or isopropyl,

R_2 is isopropyl, *sec.*-butyl, isobutyl or benzyl, and

X is hydrogen or methoxy,

and etilefrin, in association with a pharmaceutically acceptable diluent or carrier.

2. A pharmaceutical composition as claimed in Claim 1, in which the compound of formula I is dihydroergotamine.

3. A pharmaceutical composition as claimed in Claim 1 or Claim 2 in which the proportion of compound of formula I to etilefrin is from 1:5 to 1:15 by weight.

4. A pharmaceutical composition as claimed in Claim 3 in which the proportion of compound of formula I to etilefrin is 1:10 by weight.

5. A pharmaceutical composition as claimed in any one of the preceding claims in which the pharmacologically acceptable diluent or carrier comprises uncrosslinked poly - N - vinyl - 2 - pyrrolidone of average molecular weight from 10,000 to 100,000.

6. A pharmaceutical composition as claimed in Claim 5 in which the polyvinylpyrrolidone has an average molecular weight of from 11,500 to 40,000.

7. A pharmaceutical composition as claimed

in Claim 5 or Claim 6 in which the proportion of compound of formula I to polyvinylpyrrolidone is from 1% to 30% by weight.

8. A pharmaceutical composition as claimed in Claim 7 in which the said proportion is from 5% to 15% by weight.

9. A pharmaceutical composition as claimed in any one of the preceding claims, in which the compound of formula I is dihydroergotamine in the methanesulphonate salt form.

10. A pharmaceutical composition as claimed in any one of the preceding claims, in which the etilefrin is in the hydrochloride salt form.

11. A pharmaceutical composition as claimed in any one of the preceding claims, in unit dosage form, containing from 0.125 to 2.5 mg of the compound of formula I and 1.25 to 25 mg etilefrin per unit dosage.

12. A pharmaceutical composition as claimed in Claim 11 containing 2 mg dihydroergotamine methanesulphonate and 20 mg etilefrin hydrochloride per unit dosage.

13. A pharmaceutical composition as claimed in Claim 11 or Claim 12, in capsule form.

14. A pharmaceutical composition as claimed in Claim 11 or Claim 12, in capsule form.

15. A twin-pack preparation comprising separate containers of compound of formula I and of etilefrin together with instructions for their concomitant administration.

16. A twin-pack preparation as claimed in Claim 15 in which the containers contain unit dosages of dihydroergotamine and of etilefrin.

17. A method for the preparation of a pharmaceutical composition as claimed in Claim 5, characterised by working up a compound of formula I with polyvinylpyrrolidone to obtain a solid material which is then mixed with etilefrin.

18. A method as claimed in Claim 17 in which the compound of formula I, together with polyvinylpyrrolidone, is dissolved in a solvent which is then evaporated, and the dried residue is mixed with etilefrin.

19. A method as claimed in Claim 18 in which the solvent is methanol.

20. A method as claimed in any one of Claims 17—19 in which the etilefrin is in the form of a granulate containing one or more pharmacologically acceptable adjuvants.

21. A method for the preparation of a pharmaceutical composition as claimed in Claim 1 characterised by forming a granulate of one of the active components together with one or more pharmacologically acceptable adjuvants, and mixing the granulate with the other component.

22. A method as claimed in any one of Claims 17—21, in which the compound of formula I is dihydroergotamine.

23. A method for the preparation of a pharmaceutical composition as claimed in Claim 1, substantially as herein described with reference to Example 1 or Example 2.

24. A pharmaceutical composition as claimed in Claim 1 whenever prepared by a method as claimed in any one of Claims 17—23.

B. A. YORKE & CO.
Chartered Patent Agents
98, The Centre,
Feltham,
Middlesex TW13 4EP
Agents for the Applicants

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1980
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

(11)

ERRATA

SPECIFICATION No. 1,565,447

Page 2, line 56, *for* statesyndrom *read* stase-syndrom

Page 4, line 25, *after* in *delete* capsule *insert* tablet

THE PATENT OFFICE
27th October, 1980