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PATENT SPECIFICATION (11) 1 592 563

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(21) Application No. 47437/77 (22) Filed 15 Nov. 1977
(31) Convention Application No. 14575/76
(32) Filed 19 Nov. 1976
(31) Convention Application No. 6989/77
(32) Filed 7 June 1977 in
(33) Switzerland (CH)
(44) Complete Specification published 8 July 1981
(51) INT CL³ A61K 31/48
(52) Index at acceptance
A5B 821 822 823 825 829 832 X



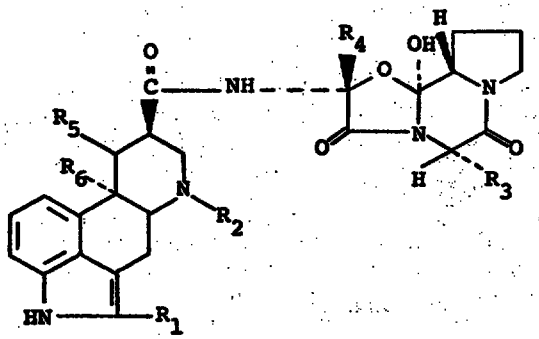
(72) Inventors MOISE AZRIA and
THOMAS CAVANAK

(54) NASAL PHARMACEUTICAL COMPOSITIONS

(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 ergot peptide alkaloids.

The present invention provides a nasal pharmaceutical composition in finished form for nasal administration comprising as active agent a compound of formula I.



I

wherein

R_1 is hydrogen or halogen,

R_2 is hydrogen or alkyl of 1 to 4 carbon atoms,

either (i)

R_3 is isopropyl, sec-butyl, or isobutyl,

R_4 methyl, ethyl or isopropyl and

R_5 is hydrogen and R_6 is hydrogen or methoxy or R_5 and R_6 are together a single bond,

or (ii)

R_3 is benzyl, R_4 is methyl, R_5 is hydrogen and R_6 is hydrogen or methoxy,

in free base form or in pharmaceutically acceptable acid addition salt form, the composition either being in liquid form containing from 0.25 to 12.5% by weight of the active agent or being in powder form. Conveniently the composition contains more than 0.5% of active agent and more conveniently more than 1% of active agent.

Satisfactory formulations may be formed in conventional manner, e.g. to be compatible with the nasal passage surface, e.g. to be isotonic and to have an acceptable pH. The exact formulation will naturally depend on *inter alia* the active agent used, the carrier or diluent used and mode of administration. Nasal compositions may comprise an aqueous solution, conveniently containing a viscosity-increasing agent such as methyl cellulose. Such liquid compositions may be in nasal dropper or pipette, or is a nasal spray applicator such as an atomiser. The compounds may be in solid powder form. The carrier or diluent may be

lactose, which may comprise 87.5 to 97.5% of the total weight, in a hard capsule, e.g. for administration via an insufflator, e.g. for nasal administration.

The composition may be in the presence of a pharmaceutically acceptable propellant such as a halogenated hydrocarbon and may be in a closed container under pressure. The container may be adapted to deliver a discrete dosage, e.g. from 0.1 to 5 mg of the compound. The container may be an aerosol. The viscosity of the composition may be conveniently from 5 to 40 centipoise at room temperature, e.g. 20°C.

The present invention also provides a nasal applicator containing as active agent a compound of formula I.

The applicator may be any conventional applicator for administering an active agent to the nose. Generally, a dry or liquid spray is produced by such an applicator. The particle size of the spray should be naturally chosen so that most of the particles do not flow right through the nasal region into e.g. the lungs.

The applicator may be adapted to provide a unit dosage of the active agent.

Various forms of applicators and compositions therefor will now be discussed.

1) Any aerosol device which produces a spray may be used, e.g. a neubulizer. For example, spraying by means of propellant gas pressure bottles is preferred. In this instance, the active agents are conveniently present in the form of solutions or suspensions.

The solutions may be obtained by dissolving the active agent in a mixture of ethanol and water and conveniently adding to the resulting solution isotonizing additives, such as sodium chloride, and buffer substances, such as acetate buffer. The amount of active agent ranges conveniently from 0.25 mg to 5 mg/ml. The water/ethanol mixture used as solvent contains conveniently water and ethanol at a ratio of from 98:2 and 80:20, preferably 90:10, (by volume) respectively. Other additives used in order to obtain isotonia and buffering substances should be present at an amount totalling 1% or less by weight relative to the total solution. Furthermore, it is possible to add stabilizers, such as sodium pyrosulfite, and ascorbic acid.

If the active agent is to be sprayed by means of propellant gas pressure bottles, the above solutions may be added to compressed propellant gases, for example, fluorinated and/or chlorinated hydrocarbons, e.g. trichlorofluoromethane (Frigen® 11), dichlorodifluoromethane (Frigen® 12), trichlorotrifluoroethane (Frigen® 113) or dichlorotetrafluoroethane (Frigen® 114).

In place of the solutions in propellant gas pressure bottles, suspensions of the micronized active agent in the compressed propellant may be used. In this case, it is convenient to add a tenside, for example, Tween® 80, or polyethyleneglycol esters of fatty acids, especially sorbitan monooleate. The amount of active agent may be 1 to 10% by weight and the amount of tenside 0.1 to 1% by weight related to the total amount of the suspension, including the propellant.

2) To produce a nasal spray or nasal drops, the composition may comprise the active agent in water, buffering substances, e.g. acetate buffer, isotonizing additives, e.g. sodium chloride, preservatives, e.g. Nipakombin, solution aids, e.g. polyethylene glycol 400, viscosity-increasing agents, e.g. methyl cellulose. The solutions may be in an atomiser, a spray appliance, or a nasal pipette. The amount of weight of the active agent in these solutions should be 1 to 10% by weight, and of the other additives, approximately 0.1 to 1% by weight related to the total amount of the solution. Instead of a solution, emulsions of the active agents in mono- and/or polyvalent alcohols, for example triethylene glycol/ethanol, polyethylene glycol 300—400/ethanol, propylene glycol/ethanol, but also in a mixture of water and mono- and/or polyvalent alcohols, e.g. water/ethanol, water/polyethylene glycol 300—400 may be used. The preferred amounts of the individual components in the solvent mixture are described in Example 3. In the latter, the active agent should be present at an amount of 0.5 to 5% by weight related to the total amount. Furthermore, oils such as sesame oil, paraffin oil, in order to obtain the organic phase as well as tensides (emulsifying agents) e.g. sorbitan monooleate, totalling up to 1% by weight, may be present during the production of emulsions.

The emulsion is conveniently administered by means of atomisers, plastic bottles each equipped with a nozzle or, after adding propellant gas, in pressure packs, the active agent in solution forming an emulsion with the liquified propellant gas upon the addition of the liquified gas.

In the following Examples, all percentages, unless otherwise indicated, refer to parts by weight.

3) For a nasal powder spray, the active agent may be present in micronised form, e.g. of particle diameter about 20 microns to 32 microns, mixed together with micronised and non-micronised lactose. The weight ratio of the active agent to the lactose may be 0.25:12.5% to 99.75:87.5%. The mixture may be filled into hard gelatine capsules (fill weight 20—40 mg per capsule) and sprayed in conventional manner, for example by means of a suitable insufflator.

In formula I, if R_2 signifies an alkyl group, this may especially be methyl or isopropyl. If R_1 signifies halogen, this signifies fluorine, chlorine, bromine or iodine, especially bromine.

Preferred representatives of the compounds of formula I are dihydroergocristine, α- or β-dihydroergocryptine, dihydroergocornine, which are preferably used in the form of a mixture known as dihydroergotoxin, bromocriptine, and dihydroergotamine. The compounds of formula I may be used in the free base form or in acid addition salt forms, for example the methanesulphonate, maleate or tartrate.

The above compounds of formula I are known for oral and parenteral administration, and are typically taken by subjects over a long period of time orally.

It has now been found that the nasal compositions when administered nasally in phencyclidineanaesthetised rhesus monkeys, lead to a notable peak blood concentration of the compounds and/or a short onset time of peak blood concentration of the compounds on administration of, for example, 1 to 10 mg of the compound when compared to oral administration. The concentration of the compound in the blood may be measured by conventional radioimmunoassay, e.g. according to the principles of J. Rosenthaler and H. Munzer, Experientia *32*, 234 (1976).

The above test indicates that a suitable dosage to be administered is from 0.1 to 10 mg of the compound of formula I, which may be administered 1 to 5 times a day, as required.

Tween and Frigen as used herein are Registered Trade Marks.

Nipakombin means a 67:33 mixture by weight of *p*-hydroxybenzoyl methyl ester and *p*-hydroxybenzoyl propyl ester.

Tween® 80 is polyethylene (20) sorbitan monooleate (I.C.I., England).

Frigen® 113 is trichlorotrifluoroethane.

Frigen® 11/12/114 is a 25:50:25 (by volume) mixture of trichlorofluoromethane, dichlorodifluoromethane and dichlorotetrafluoroethane.

EXAMPLE 1
Dihydroergotamine Solution Aerosol

Basic Composition

Dihydroergotamine methanesulphonate	25 mg
Ethanol (94%)	520 mg
Water (distilled)	120 mg
Frigen® 11/12/114	1000 mg

Production

The dihydroergotamine, ethanol and water are mixed to give a solution. The solution is filled into an aerosol bottle. A valve outlet is fitted and crimped to seal the bottle. The required amount of propellant is added through the valve.

EXAMPLE 2
Dihydroergotamine Suspension Aerosol

Basic Composition

Dihydroergotamine methanesulphonate micronised particles	200 mg
Tenside:	
Sorbitan monooleate or Soya bean lecithin	20 mg
Frigen® 113 / Frigen® 11/12/114	to 1 ml

Production

The dihydroergotamine is triturated with the tenside in the presence of a little Frigen® 113 in a cooled mortar. Further Frigen® 113 is added to give a homogenous mixture, if necessary using a polytron. The mixture is filled into aerosol bottles while stirring and cooling continuously. A valve outlet is fitted and

crimped to seal the bottle. The required amount of propellant gas is then added through the valve.

EXAMPLE 3

Dihydroergotamine 2-Phase Aerosol Emulsion

Basic Composition	
Dihydroergotamine methanesulphonate	50 mg
Sorbitan monooleate	5 mg
Ethanol (absolute)	100 mg
Glycol such as Triethylene glycol, propylene glycol, Polyethylene glycol (MW 300—400)	1 ml
Frigen® 11/12/114	q.s.

If desired, the glycol may be replaced by 200—300 mg water.

Production

Analogous to Example 1.

EXAMPLE 4

Dihydroergotamine Nasal Liquid Spray Applicator

Basic Composition	4A	4B	4C	4D
Dihydroergotamine methanesulphonate	1.85%	1.85%	1.85%	1.85%
Nipakombin	0.08%	0.08%	0.08%	—
Sodium acetate trihydrate	0.168%	0.168%	0.168%	0.168%
Glacial acetic acid	0.42%	0.42%	0.42%	0.42%
Methyl cellulose	—	0.5%	0.5%	1.0%
Polyethylene glycol 400	—	—	10%	10%
Tween® 80	—	—	—	0.1%
Chlorohexidine diacetate	—	—	—	0.01%
Ethanol (94%)	15%	15%	15%	15%
Water	to 100%	to 100%	to 100%	to 100%

Production

The ingredients without the dihydroergotamine and with some of the water are mixed together. The dihydroergotamine is then added, and the mixture completed by addition of water. The resulting solution may be made isotonic, if desired, by the addition of sodium chloride, mannitol or sorbitol, and is filled into a nasal spray applicator, e.g. an atomiser.

EXAMPLE 5

Dihydroergotamine Powder Spray Applicator

A mixture of micronised dihydroergotamine methanesulphonate with lactose is filled into a gelatine capsule.

The contents are administered by spraying into the nostril by means of a rubber bulb or other atomiser.

EXAMPLE 6

Bromocriptine Nasal Liquid Spray

Basic Composition	A	B	C
	mg	mg	mg
Bromocriptine methanesulphonate	8.63	8.63	2.87
Ascorbic acid	0.50	0.5	—
Glacial acetic acid	to pH 2.9	to pH 2.9	1.55
Sodium acetate	—	—	1.02
Mannitol	50	50	45
Methyl cellulose	—	10	—
Ethanol (94%)	120	120	—
Water	to 1.00 ml	to 1.00 ml	to 1.00 ml

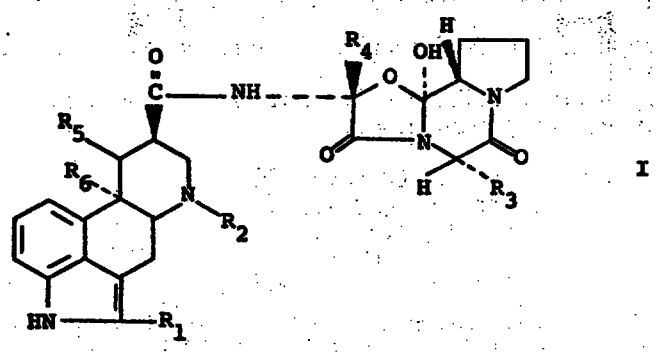
Production

A 14 ml bottle fitted with a piston spray device is filled with the above composition in a CO_2 atmosphere.

Compositions may be made using dihydroergonine (9,10-dihydro-2'β-ethyl-5'α-isopropyl ergopeptine) or dihydroergotoxin in appropriate amounts instead of dihydroergotamine in Examples 1 to 5 or bromocriptine in Example 6.

WHAT WE CLAIM IS:—

1. A nasal pharmaceutical composition in finished form for nasal administration comprising an active agent at least one compound of formula I



I

wherein

R_1 is hydrogen or halogen,

R_2 is hydrogen or alkyl of 1 to 4 carbon atoms,

either (i)

R_3 is isopropyl, sec-butyl, or isobutyl,

R_4 methyl, ethyl or isopropyl and

R_5 is hydrogen and R_6 is hydrogen or methoxy

or

R_5 and R_6 are together a single bond,

or (ii)

R_3 is benzyl, R_4 is methyl, R_5 is hydrogen and R_6 is hydrogen or methoxy,

in free base form or in pharmaceutically acceptable acid addition salt form, the composition either being in liquid form and containing from 0.25 to 12.5% by weight of the active agent or being in powder form.

2. A composition according to Claim 1 in the form of a liquid containing from 0.25 to 10% by weight of the active agent.

3. A composition according to Claim 2 in the form of an aqueous solution.

4. A composition according to Claim 2 in the form of an aqueous emulsion.

5. A composition according to Claim 2, 3 or 4 containing a viscosity increasing agent.

6. A composition according to Claim 5 wherein the viscosity increasing agent is methyl cellulose.

7. A composition according to Claim 2, 3 or 4 having a viscosity of from 5 to 40 cps at room temperature.

8. A composition according to any one of Claims 2 to 7 in a nasal dropper or pipette.

9. A composition according to any one of Claims 2 to 7 in the presence of a compressed propellant gas.

10. A composition according to Claim 9 wherein the propellant is a halogenated hydrocarbon.

11. A composition according to Claim 8 in a nasal spray applicator.

12. A composition according to Claim 1 in the form of a powder.

13. A composition according to Claim 12 in the presence of a compressed propellant gas.

14. A composition according to Claim 12 or 13 containing a tenside.

15. A composition according to Claim 12, 13 or 14 in a nasal spray applicator.

16. A composition according to Claim 12 containing powdered lactose as a carrier or diluent.

17. A composition according to Claim 16 containing by weight from 87.5 to 97.5% lactose.

18. A composition according to Claim 12, 15, 16 or 17 in a hard capsule for use in a nasal insufflator.

19. A composition according to Claim 12, 15, 16, 17 or 18 in a nasal insufflator.

20. A composition according to any one of Claims 1 to 19 wherein the active agent is bromocriptine.

21. A composition according to any one of Claims 1 to 19 wherein the active agent is dihydroergotamine.

22. A composition according to any one of Claims 1 to 19 wherein the active agent is dihydroergotoxin.

23. A nasal pharmaceutical composition comprising a compound of formula I, stated in Claim 1, substantially as hereinbefore described with reference to any one of the Examples.

24. A nasal applicator containing a pharmaceutical composition as claimed in any one of Claims 1 to 23.

25. A nasal applicator containing a pharmaceutical composition as claimed in Claim 1 and a compressed propellant gas.

B. A. YORKE & CO.,
Chartered Patent Agents,
98, The Centre,
Feltham,
Middlesex, TW 13 4 EP.

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Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.