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AMENDED SPECIFICATION

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PATENT SPECIFICATION

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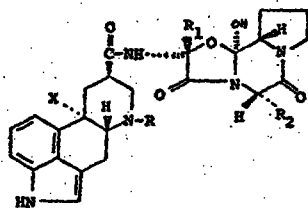
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(54) PHARMACEUTICAL COMPOSITIONS CONTAINING AN
 ERGOT ALKALOID AND HEPARIN

(71) We, SANDOZ LTD., of 35 Lichstrasse, 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:



in which

- R is methyl or isopropyl,
 R₁ is methyl,
 R₂ is isopropyl or benzyl, and
 X is hydrogen, with the proviso that R and R₂ are not both isopropyl and heparin, in association with a pharmacologically acceptable diluent or carrier, the proportion of the compound of formula I (in mg) to heparin (in international units) being 1:500 to 1:70,000.

By the terms "compounds of formula I" and "heparin" 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 acid or base. Examples of such salts are the methanesulfonate, maleate

and tartrate salts of compounds of formula I, and the sodium, potassium and calcium salts of heparin.

Compounds of formula I are dihydroergotamine, in which R is methyl and R₂ is benzyl; 6-nor-6-isopropyl-9,10-dihydro-2'-β-methyl-5'-α-benzylergopeptin in which R is isopropyl and R₂ is benzyl; and dihydroergovaline in which R is methyl and R₂ is isopropyl. Especially preferred is dihydroergotamine.

Pharmacologically acceptable diluents and carriers include polymers for example polyvinyl pyrrolidone and organic esters, particularly esters of C₁₀—C₂₄ fatty acids, including natural plant oils.

The proportions of compound of formula I (in mg) to heparin (in international units, I.U.) is preferably 1:2000 to 1:20,000.

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 heparin together with a pharmaceutically acceptable diluent or carrier.

Preferred processes according to the invention are:

- working up a compound of formula I with a pharmaceutically acceptable polymer, preferably polyvinylpyrrolidone, to obtain a solid material which is then mixed with heparin,
- suspending a compound of formula I together with heparin in a pharmaceutically acceptable organic liquid, preferably an organic ester, or
- freeze drying, separately or together, a solution of a compound of formula I

and a solution of heparin, and, if separately, mixing together the freeze-dried products.

Process a) 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 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 in the total mixture together with the optional additives, is suitably from 0.1 to 5%, preferably from 0.5 to 1.0% 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 heparin, to give a solid product which may be dissolved in sterile distilled water to provide an injectable solution. Preferably this injectable solution will be isotonic and buffered to a physiologically acceptable pH. In order to accomplish this, the solid product is preferably mixed with sodium chloride and/or sodium hydrogen phosphate in quantity sufficient to give an isotonic solution of pH 7—7.5 when dissolved in the volume of water required to give the desired concentration of active ingredients.

Process b) may be carried out by suspending the compound of formula I together with heparin in an organic ester, suitably isopropyl myristate, isopropyl palmitate, ethyl oleate, olive oil, peanut oil, sesame oil and other common plant oils, or mixtures of these.

For a mixture of from 0.1 to 2 mg compound of formula I and 1000 to 7000 I.U. heparin, a quantity of from 0.3 to 10 ml of organic ester may be used. Preferably a mixture of 0.5 mg dihydroergotamine methane-sulfonate and 5000 I.U. sodium heparin is suspended in 1 ml isopropyl myristate. The suspension is preferably prepared by stirring at room temperature (15°—25°C).

In process c) the solvent used in the solutions to be freeze-dried is preferably water and freeze-drying is carried out in conventional manner. The process may be carried out by freeze drying an aqueous solution of a compound of formula I, preferably in the form of an acid addition salt, and mixing the finely dispersed dried product with the product of freeze-drying an aqueous solution of heparin, preferably in alkali metal salt form.

Alternatively and preferably, a common solution containing both heparin and a compound of formula I may be prepared and freeze-dried to give an intimate mixture of the active components. A further preferred procedure is to prepare the two solutions separately, to pass them alternately into the freeze-drying apparatus so that alternate thin layers of compound of formula I and of heparin are built up on the collecting surface. The product is then collected and homogenised.

The solid mixture may then be dissolved in sterile distilled water to provide an injectable solution. As described above under process a), the solid mixture preferably contains salts such as sodium chloride and/or sodium phosphate so that the resulting injectable solution will be isotonic and buffered to a physiological pH value. The mixture may also contain other adjuvants, for example polyvinyl pyrrolidone. Such salts and other adjuvants may be incorporated by mixing with the freeze-dried solid product or, preferably, by dissolving in the solution or solutions prior to freeze drying.

The pharmaceutical compositions according to the invention have surprisingly good anti-thrombotic properties, as shown by the I^{125} -fibrinogen uptake test of K. H. Fey *et al* (Med. Klin. 70 (1975), pp. 1553—1558), in which radiation from I^{125} -fibrinogen, which is selectively concentrated in thrombotic material in leg veins, is measured externally in human patients.

In this test, patients undergoing major surgery, for example total hip replacement, receive 100 μ ci of I^{125} -fibrinogen parenterally the day before surgery and their legs are scanned for I^{125} radiation each day for between 2 and 3 weeks thereafter. The fibrinogen injection is repeated after 8—10 days if the count rate remains low. A Logic 121 counter/ratemeter is used for recording radioactivity, counting being performed according to the technique of Kakkar *et al* (Lancet 1970, 1, 130

540). Deep vein thrombosis (DVT) is diagnosed if the counts at any site differ by 20% or more from those at an adjacent point on the same leg or the same position on the opposite leg, and if this difference persists or increases in the subsequent 24 hours. The incidence of DVT in patients receiving prophylaxis by administration of a compound of formula I in conjunction with heparin is compared with that of control groups receiving heparin prophylaxis or no prophylaxis.

The compositions are therefore indicated for anti-thrombotic use, particularly in prophylaxis of post-operative thrombosis in mammals. A suitable indicated daily dosage is from 0.2 to 4 mg, preferably from 0.5 to 2 mg compound of formula I and from 2000 to 14,000 I.U., preferably from 4000 to 10,000 I.U. heparin. This daily dosage may suitably be administered in divided dosages of from 0.05 to 2 mg, preferably 0.125 to 1 mg compound of formula I and from 500 to 7,000 I.U., preferably from 1000 to 5000 I.U. heparin, two to four times daily. Particularly preferred is a mixture of 0.5 mg dihydroergotamine methanesulfonate and 5000 I.U. sodium heparin, administered thrice 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 mixing so as to obtain a composition according to the invention.

The compositions themselves, or galenic preparations thereof such as sterile injectable solutions, may suitably be packaged in unit dosage forms, for example ampoules of sterile injectable suspensions containing a unit dosage of the active ingredients.

The following Examples illustrate the invention:

EXAMPLE 1.

Dry mixture to make up injectable solution.

Dihydroergotamine methanesulfonate (4.0 g) and 476 g polyvinyl pyrrolidone (average MW 25,000) is added to 1600 ml methanol in a 4 l flask. The flask is connected to a rotary evaporator, and rotated in a bath at 60°C until the flask contents reach approximately 60°C. A clear solution is obtained.

The solvent is then evaporated under reduced pressure (ca. 250 Torr) at a bath temperature of 60°C, until the residue in the flask has a syrupy consistency. The residue is transferred to an evaporating dish and left to stand for two hours at room temperature. The solid residue is dried in a vacuum oven at 30°C, ca. 1 Torr for 12 hours, then milled and redried.

The dried residue (480 g) is then mixed under aseptic conditions with a quantity of sodium heparin corresponding to 40,000,000 I.U., 8 g disodium hydrogen phosphate dihydrate and 72 g sodium chloride, specially purified. The mixture is then made up in bottles of unit dosage sealed with a pierceable septum, each bottle containing 105 mg of the dry mixture, comprising 0.5 mg dihydroergotamine methanesulfonate and 5000 I.U. sodium heparin.

In use, the septum is pierced by the needle of a syringe containing 1 ml of sterile distilled water which is injected into the bottle. When the solid mixture is dissolved, the solution is withdrawn into the syringe and administered parenterally.

EXAMPLE 2.

Suspension.

Dihydroergotamine methanesulfonate (0.5 g) and a quantity of sodium heparin corresponding to 5,000,000 I.U. are dispersed in 1 l of sterile filtered isopropyl myristate by stirring under aseptic conditions. Ampoules of 1 ml capacity are then filled with the suspension.

EXAMPLE 3.

Freeze dried mixture to make up injectable solution.

a) A quantity of sodium heparin corresponding to 5,000,000 I.U., together with disodium hydrogen phosphate (1 g) and sodium chloride (9 g) is dissolved in 500 ml of water suitable for injection.

b) Dihydroergotamine methanesulphonate (0.5 g) and polyvinylpyrrolidone (59.5 g) are dissolved in 500 ml of water suitable for injection.

c) The solutions prepared according to a) and b) are mixed together and sterile filtered.

The filtrate is used to fill ampoules under sterile conditions, each ampoule containing 1 ml of the combined solution. The unsealed ampoules are then subjected to freeze drying until all the water is removed. Finally the ampoules are sealed with a pierceable septum as in Example 1.

EXAMPLES 4, 5, 6.

Examples 1, 2 and 3 are repeated using in place of dihydroergotamine methanesulfonate an equivalent quantity of 6 - nor-6 - isopropyl - 9,10 - dihydro - 2'β - methyl-5 - α - benzylergopeptin methanesulfonate.

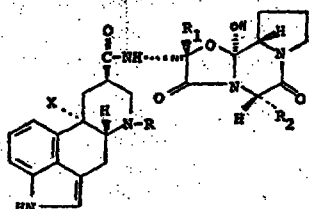
EXAMPLES 7, 8, 9.

Examples 1, 2 and 3 are repeated using instead of dihydroergotamine methane-

sulfonate an equivalent quantity of dihydroergovaline methanesulfonate.

WHAT WE CLAIM IS:—

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



in which

R is methyl or isopropyl,

R₁ is methyl,

R₂ is isopropyl or benzyl, and

X is hydrogen with the proviso that R and R₂ are not both isopropyl and heparin, in association with a pharmaceutically acceptable diluent or carrier, the proportion of compound of formula I (in mg) to heparin (in international units) being from 1:500 to 1:70,000.

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, in which the compound of formula I is 6-nor-6-isopropyl-9,10-dihydro-2'-β-methyl-5'-α-benzylergopeptin.

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

5. A pharmaceutical composition as claimed in any one of the preceding claims in which the said proportion is from 1:2000 to 1:20,000.

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

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

8. A pharmaceutical composition as claimed in Claim 6 or Claim 7 in which the proportion of compound of formula I to polyvinylpyrrolidone is from 0.1% to 5% by weight.

9. A pharmaceutical composition as claimed in Claim 8 in which the said proportion is from 0.5% to 1.0% by weight.

10. A pharmaceutical composition as claimed in any one of Claims 6—9 in the form of a solid mixture containing sodium chloride and/or sodium hydrogen phosphate.

11. A pharmaceutical composition as claimed in any one of Claims 1—5 in which the pharmaceutically acceptable diluent or carrier is an organic ester.

12. A pharmaceutical composition as claimed in Claim 11 in which the organic ester is isopropyl myristate.

13. A pharmaceutical composition as claimed in Claim 11 or Claim 12 which contains from 0.1 to 2 mg of compound of formula I and 1000 to 7000 I.U. of heparin in from 0.3 to 10 ml of organic ester.

14. A pharmaceutical composition as claimed in any one of Claims 11—13 in the form of a sterile injectable suspension.

15. A pharmaceutical composition as claimed in Claim 1, containing a mixture of freeze-dried compound of formula I and freeze-dried heparin.

16. A pharmaceutical composition as claimed in Claim 15, in the form of a solid mixture containing sodium chloride and/or sodium hydrogen phosphate.

17. A pharmaceutical composition as claimed in any one of Claims 1—5 in which the pharmaceutically acceptable diluent or carrier is water.

18. A pharmaceutical composition as claimed in Claim 17 in the form of a sterile injectable solution.

19. An injectable solution as claimed in Claim 18 prepared by dissolving in water a composition as claimed in Claim 10.

20. An injectable solution as claimed in Claim 18 prepared by dissolving in water a composition as claimed in Claim 16.

21. A pharmaceutical composition as claimed in any one of the preceding claims, in unit dosage form, containing from 0.05 to 2 mg of compound of formula I and from 500 to 7,000 I.U. heparin per unit.

22. A pharmaceutical composition in unit dosage form as claimed in Claim 21, containing from 0.125 to 1 mg of compound of formula I and from 1000 to 5000 I.U. heparin per unit.

23. A twin-pack preparation comprising separate containers of compound of formula I and of heparin together with instructions for their mixing so as to give a composition as claimed in Claim 1.

24. A twin-pack preparation as claimed in Claim 23 in which the containers contain unit dosages of compound of formula I and of heparin.

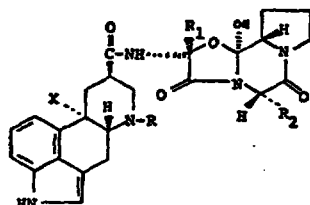
25. A method for the preparation of a pharmaceutical composition as claimed in Claim 6, characterised by working up a compound of formula I with polyvinylpyrrolidone to obtain a solid material which is then mixed with heparin.

26. A method as claimed in Claim 25 in which the compound of formula I, together with polyvinylpyrrolidone, is dissolved in a

sulfonate an equivalent quantity of dihydroergovaline methanesulfonate.

WHAT WE CLAIM IS:—

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



I

in which

- R is methyl or isopropyl,
- R₁ is methyl,
- R₂ is isopropyl or benzyl, and
- X is hydrogen with the proviso that R and R₂ are not both isopropyl and heparin, in association with a pharmaceutically acceptable diluent or carrier, the proportion of compound of formula I (in mg) to heparin (in international units) being from 1:500 to 1:70,000.
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, in which the compound of formula I is 6 - nor - 6 - isopropyl - 9,10-dihydro - 2'β - methyl - 5'α - benzylergopeptin.
4. A pharmaceutical composition as claimed in Claim 1, in which the compound of formula I is dihydroergovaline.
5. A pharmaceutical composition as claimed in any one of the preceding claims in which the said proportion is from 1:2000 to 1:20,000.
6. A pharmaceutical composition as claimed in any one of the preceding claims in which the pharmacologically acceptable diluent or carrier is uncrosslinked poly-N-vinyl-2-pyrrolidone of average molecular weight from 10,000 to 100,000.
7. A pharmaceutical composition as claimed in Claim 6 in which the polyvinylpyrrolidone has an average molecular weight of from 11,500 to 40,000.
8. A pharmaceutical composition as claimed in Claim 6 or Claim 7 in which the proportion of compound of formula I to polyvinylpyrrolidone is from 0.1% to 5% by weight.
9. A pharmaceutical composition as claimed in Claim 8 in which the said proportion is from 0.5% to 1.0% by weight.
10. A pharmaceutical composition as claimed in any one of Claims 6—9 in the form of a solid mixture containing sodium chloride and/or sodium hydrogen phosphate.

11. A pharmaceutical composition as claimed in any one of Claims 1—5 in which the pharmacologically acceptable diluent or carrier is an organic ester.
12. A pharmaceutical composition as claimed in Claim 11 in which the organic ester is isopropyl myristate.
13. A pharmaceutical composition as claimed in Claim 11 or Claim 12 which contains from 0.1 to 2 mg of compound of formula I and 1000 to 7000 I.U. of heparin in from 0.3 to 10 ml of organic ester.
14. A pharmaceutical composition as claimed in any one of Claims 11—13 in the form of a sterile injectable suspension.
15. A pharmaceutical composition as claimed in Claim 1, containing a mixture of freeze-dried compound of formula I and freeze-dried heparin.
16. A pharmaceutical composition as claimed in Claim 15, in the form of a solid mixture containing sodium chloride and/or sodium hydrogen phosphate.
17. A pharmaceutical composition as claimed in any one of Claims 1—5 in which the pharmacologically acceptable diluent or carrier is water.
18. A pharmaceutical composition as claimed in Claim 17 in the form of a sterile injectable solution.
19. An injectable solution as claimed in Claim 18 prepared by dissolving in water a composition as claimed in Claim 10.
20. An injectable solution as claimed in Claim 18 prepared by dissolving in water a composition as claimed in Claim 16.
21. A pharmaceutical composition as claimed in any one of the preceding claims, in unit dosage form, containing from 0.05 to 2 mg of compound of formula I and from 500 to 7,000 I.U. heparin per unit.
22. A pharmaceutical composition in unit dosage form as claimed in Claim 21, containing from 0.125 to 1 mg of compound of formula I and from 1000 to 5000 I.U. heparin per unit.
23. A twin-pack preparation comprising separate containers of compound of formula I and of heparin together with instructions for their mixing so as to give a composition as claimed in Claim 1.
24. A twin-pack preparation as claimed in Claim 23 in which the containers contain unit dosages of compound of formula I and of heparin.
25. A method for the preparation of a pharmaceutical composition as claimed in Claim 6, characterised by working up a compound of formula I with polyvinylpyrrolidone to obtain a solid material which is then mixed with heparin.
26. A method as claimed in Claim 25 in which the compound of formula I, together with polyvinylpyrrolidone, is dissolved in a



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- 5 solvent which is then evaporated, and the dried residue is mixed with heparin.
27. A method as claimed in Claim 26 in which the solvent is methanol.
- 5 28. A method for the preparation of a pharmaceutical composition as claimed in Claim 11, characterised by suspending a compound of formula I together with heparin in an organic ester.
- 10 29. A method for the preparation of a pharmaceutical composition as claimed in Claim 15 comprising the steps of freeze drying an aqueous solution of a compound of formula I, freeze drying separately an aqueous solution of heparin and mixing together the freeze-dried products.
- 15 30. A method for the preparation of a pharmaceutical composition as claimed in Claim 15 comprising the step of freeze drying a common aqueous solution of a compound of formula I and heparin.
- 20 31. A method for the preparation of a pharmaceutical composition as claimed in Claim 15 comprising the steps of freeze drying alternately in the same apparatus an aqueous solution of a compound of formula I and an aqueous solution of heparin, and homogenising the freeze-dried product.
- 25 32. A method for the preparation of a pharmaceutical composition as claimed in Claim 1, substantially as herein described with reference to any one of the Examples.
- 30 33. A pharmaceutical composition as claimed in Claim 1 whenever prepared by a method as claimed in any one of Claims 25—32.
- 35

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