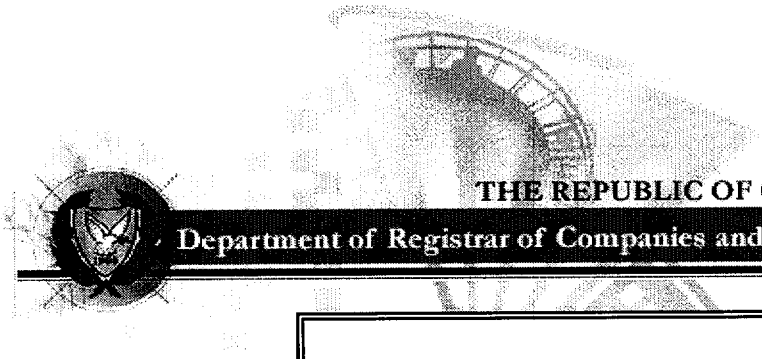


**ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ**

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**PUBLICATION NUMBER**

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ΗΝΩΜΕΝΟΥ ΒΑΣΙΛΕΙΟΥ
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Το έγγραφο που παρουσιάζεται πιο κάτω καταχωρήθηκε στο «Γραφείο Διπλωμάτων Ευρεσιτεχνίας» στην Αγγλία σύμφωνα με το Νόμο Κεφ. 266 πριν την 1η Απριλίου 1998. Δημοσίευση έγινε μετέπειτα από το Γραφείο Διπλωμάτων Ευρεσιτεχνίας του Ηνωμένου Βασιλείου μόνο στην Αγγλική γλώσσα.

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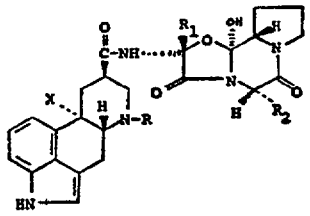
# (54) Pharmaceutical compositions containing ergot alkaloids and heparin

(57) A pharmaceutical composition comprises a mixture of a hydrogenated ergot alkaloid of formula (I):–



I

wherein R is hydrogen or a $C_{1-4}$ alkyl group other than *t*-butyl; $R_1$ is methyl, ethyl or *iso*propyl; $R_2$ is *iso*propyl, *sec*-butyl, *iso*butyl or benzyl; and X is hydrogen or methoxy; together with heparin, the proportion of compound (I) in mgs. to heparin in International Units being 1:5000. The composition may be in unit dosage form containing 0.5 mgs. of the alkaloid and 2,500 I.U. of heparin, together with a pharmaceutical carrier or diluent for injection (eg. poly - N - vinyl - 2 - pyrrolidone).

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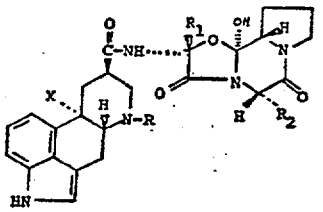
SPECIFICATION

**Improvements in or relating to organic compounds**

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.

Belgian Patent 849010, the contents of which are incorporated herein by reference, discloses pharmaceutical compositions comprising a mixture of a compound of formula I and heparin, the proportions of compound of formula I (in mg) to heparin (in international units, I.U.) being from 1:500 to 1:70,000. The only mixtures which are specifically exemplified, however, have a ratio of compound of formula I to heparin of 1:10,000; and are given as a unit dosage of 0.5 mg compound of formula I and 5000 I.U. heparin. The compositions are useful in the prophylaxis of thrombosis, particularly post-operative thrombosis, in mammals.

It has now been surprisingly found that a particularly useful combination is that having a ratio of compound of formula I to heparin of 1:5000, and a unit dosage of 0.5 mg compound of formula I and 2500 I.U. heparin.

By the use of this novel dosage, the advantageous antithrombotic effect is retained whereas side-effects associated with the use of heparin are reduced.

Accordingly, the invention provides a pharmaceutical composition comprising a mixture of a compound of formula I and heparin, in association with a pharmacologically acceptable diluent or carrier, the proportion of compound of formula I (in mg) to heparin (in I.U.) being 1:5000.

Preferably the compound of formula I is dihydroergotamine.

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.

A preferred diluent or carrier is uncrosslinked poly - N - vinyl - 2 - pyrrolidone of average molecular weight from 2000 to 100,000, preferably from 2000 to 40,000.

The compositions may be prepared, tested and administered as disclosed in the above Belgian Patent.

A suitable indicated daily dosage is from 1 to 2 mg of compound of formula I and from 5000 to 10,000 I.U. heparin, preferably in the form of divided dosages of 0.5 mg compound of formula I and 2500 I.U. heparin 2 to 4 times daily.

All ratios given above are calculated on the basis that the compound of formula I is in free base form.

The following Examples illustrate the invention.

*EXAMPLE 1: Dry mixture to make up injectable solution*

Dihydroergotamine methanesulfonate (4.6 g, corresponding to 4.0 g free base) and 476 g polyvinyl pyrrolidone (average MW 2000) 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 20,000,000 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 90 mg of the dry mixture, comprising 0.5 mg dihydroergotamine (as methanesulfonate) and 2500 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 has dissolved, the solution is withdrawn into the syringe and administered parenterally.

*EXAMPLE 2: Suspension*

Dihydroergotamine methanesulfonate (0.57 mg, corresponding to 0.5 mg free base) and a quantity of sodium heparin corresponding to 2,500,000 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 2,500,000 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 methanesulfonate (0.57 g, corresponding to 0.5 g free base) 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 septim as in Example 1.

*EXAMPLES 4, 5, 6:*

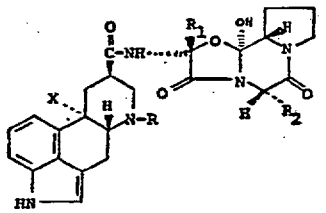
Examples 1, 2 and 3 are repeated using in place of dihydroergotamine methanesulfonate an equivalent quantity of 6 - nor - 6 - isopropyl - 9, 10 - dihydro - 2' $\beta$ - methyl - 5 - $\alpha$ - benzylergopeptin methanesulfonate.

*EXAMPLES 7, 8, 9:*

Examples 1, 2 and 3 are repeated using instead of dihydroergotamine methanesulfonate an equivalent quantity of dihydroergovaline methanesulfonate.

CLAIMS

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 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 1:5000.

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 pharmacologically acceptable diluent or carrier is uncrosslinked poly - N - vinyl - 2 - pyrrolidone of average molecular weight from 2000 to 100,000.

4. A pharmaceutical composition as claimed in Claim 3 in which the polyvinylpyrrolidone has an average molecular weight of from 2000 to 40,000.

5. A pharmaceutical composition as claimed in any one of the preceding claims, in unit dosage form, containing 0.5 mg of compound of formula I and 2500 I.U. heparin per unit.

6. A pharmaceutical composition as claimed in Claim 1, substantially as herein described with reference to any one of the Examples.

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