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(54) PHARMACEUTICAL COMPOSITIONS

(71) We, SANDOZ LTD., of Lichstrasse 35, 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 a pharmaceutical composition.

The invention provides a pharmaceutical composition comprising a) a reserpine constituent, b) a dihydroergocristine constituent, and c) N - (cis - 2,6 - dimethylpiperidine) - 4 - chloro-3-sulphamoyl benzamide.

Approximate proportions, by weight, of a) : b) : c) may be 1 : 1—20 : 5—1000, 1 : 1.5—15 : 10—500, 1 : 2—10 : 20—500, and preferably 1 : 2—10 : 20—150.

A) Reserpine	0.1 mg
Dihydroergocristine	0.5 mg
Clopamide	5.0 mg

B) Reserpine	0.1 mg
Dihydroergocristine	0.5 mg
Clopamide	10.0 mg

The dihydroergocristine and reserpine constitutents may be in the form of water-soluble, pharmaceutically acceptable salts thereof, e.g. hydrochlorides, hydrobromides, sulphates, methane-, benzene- or toluene sulphonates. The reserpine constituent, however, is preferably used in free base form, and the dihydroergocristine constituent in the form of its methane sulphonate.

It is to be undertsood that the pharmaceutical composition of the invention extends to galenical preparations thereof, suitable for enteral or parenteral administration, e.g. tablets, dragées and injectable solutions. In order to produce such medicinal preparations the mixture of active compounds is worked up with the usual organic or inorganic, physiologically inert adjuvants. Examples of such adjuvants are: lactose, starch, polyvinyl pyrrolidone, stearic acid, sorbic acid, talcum, methyl cellulose, alcohols and glycerin. The preparations may furthermore contain suitable sweetening and colouring substances and flavourings.

Reserpine, having the formula $C_{33}H_{40}N_2O_9$, is a chief alkaloid of *Rauwolfia serpentina* Benth. Dihydroergocristine, having the formula $C_{35}H_{41}N_5O_5$, is a hydrogenation product of ergocristine, an ergot alkaloid of the peptide type. The international name "clopamide" is hereinafter used for N-(cis - 2,6 - dimethylpipieridino)-4-chloro-3-sulphamoyl benzamide, having the formula $C_{14}H_{20}ClN_3O_3S$.

A single dose of the pharmaceutical composition may, for example, comprise the following amounts of individual constituents.

Examples of galenical preparations:

1) Dragees (Composition A)

Reserpine	0.00010	g
Dihydroergocristine methanesulphonate	0.00058	g*)
Clopamide	0.0050	g
Methanesulphonic acid	0.00018	g
Stearic acid	0.0020	g
Polyvinyl pyrrolidone	0.0050	g
Talcum	0.0070	g
Maize starch	0.0080	g
Lactose	0.09214	g
Coating mass	0.020	g
For a dragée of	0.140	g

*) corresponding to 0.5 mg of the free base.

Dihydroergocristine methanesulphonate, clopamide, polyvinyl pyrolidone, talcum, part of the maize starch and lactose are mixed. This mixture is granulated with an aqueous methanesulphonic acid solution and an alcoholic stearic acid solution. Reserpine and the remainder of maize starch are added to the dried and crushed granulate. The mixture is pressed into kernals which are coated in accordance with known processes.

2) Tablets (Composition B)

Reserpine	0.00010	g
Dihydroergocristine methanesulphonate	0.00058	g*)
Clopamide	0.010	g
Yellow orange S	0.00010	g
Stearic acid	0.0020	g
Polyvinyl pyrrolidone	0.0050	g
Talcum	0.0070	g
Maize starch	0.0080	g
Lactose	0.08722	g
For a tablet of	0.120	g

*) corresponding to 0.5 mg of the free base.

Reserpine, dihydroergocristine methansulphonate and clopamide are mixed with polyvinyl pyrrolidone, talcum, maize starch and lactose. The mixture is moistened and mixed with an aqueous solution of yellow orange S until the colour is evenly distributed. An alcoholic stearic acid solution is subsequently added and the mass is kneaded until it can be granulated. The dried and crushed granulate is pressed into tablets.

The combination preparation exhibits valuable pharmacodynamic properties while it is generally well tolerated and its toxicity is low. Thus, it produces a pronounced blood pressure lowering effect of long duration which sets in rapidly, in normotonic and hypertonic test animals. The pressoric effect of the sympathetic transmitters is inhibited, that of adrenalin is inhibited permanently and that of noradrenalin temporarily; furthermore a mild, but lasting salidiuresis is produced.

The blood pressure lowering effect of the new combination preparation may, for example, be ascertained in hypertonic rats which have not been narcotized (Grollman hypertonia).

In a first test series reserpine, dihydroergocristine and clopamide were administered on 4 consecutive days, individually on the one hand and in combination on the other; a control group was treated with a placebo (inert preparation). The results may be seen in Table I; $\bar{\Delta}$ indicates the average values of the changes in blood pressure observed (in mm of Hg), p indicates their statistical signficance (i.e. the probability of error calculated from the deviations from the average values, with the assumption of a significant difference between the treated group and the control group; the difference is considered significant when $p \leqslant 0.05$).

TABLE I

Active compounds	Treatment			
	once		four times	
	$\bar{\Delta}$	p	$\bar{\Delta}$	p
Reserpine 0.01 mg/kg s.c.	+4	0.505	+16	0.416
Dihydroergocristine 0.05 mg/kg s.c.	+8	0.264	−4	0.276
Clopamide 1 mg/kg p.o.	−7	0.422	−5	0.435
Reserpine 0.01 mg/kg s.c. + Dihydroergocristine 0.05 mg/kg s.c. + Clopamide 1 mg/kg p.o.	−11	0.085	−22	0.001

The components, therefore, do not exert a significant influence on the blood pressure when administered individually ($p > 0.05$), i.e. their effects did not differ from those obtained by treatment with a placebo. When, however, the same doses of the three active compounds were administered in combination, a pronounced blood pressure reduction could be observed, which may be considered as highly significant after the fourth treatment ($p = 0.001$, i.e. the probability of error only amounts to 0.1%).

In a second test series the combination of reserpine, dihydroergocristine and clopamide was compared in analogous manner with the three possible combinations of two of the individual components. The results may be seen in Table II.

TABLE II

Active compounds	Treatment			
	once		4 times	
	$\bar{\Delta}$	p	$\bar{\Delta}$	p
Dihydroergocristine 0.05 mg/kg s.c. + Clopamide 1 mg/kg p.o.	−11	0.239	−33	0.965
Reserpine 0.01 mg/kg s.c. + Clopamide 1 mg/kg p.o.	−26	0.001	−50	0.055
Reserpine 0.01 mg/kg s.c. + Dihydroergocristine 0.05 mg/kg s.c.	+1	0.930	−35	0.805
Reserpine 0.01 mg/kg s.c. + Dihydroergocristine 0.05 mg/kg s.c. + Clopamide 1 mg/kg p.o.	−14	0.009	−65	0.006

The two-compound combinations dihydroergocristine/clopamide and reserpine/dihydroergocristine, therefore, showed no significant effect on the blood pressure during the entire test period. The two-compound combination reserpine/clopamide produced a significant lowering of the blood pressure after one administration, as compared with the control group, but during the further course of the test the probability of error increased and after 4 administrations amounted to over 5% (i.e. the lowering of the blood pressure can no longer be considered significant). The three-compound combination reserpine/dihydroergocristine/clopamide, however, had a significant antihypertensive effect after one administration and after 4 administrations, whereby the probability of error decreased during the course of the test from 0.9% (after the first administration) to 0.6% (after the fourth administration).

In the tests described above, it can be seen that the blood pressure lowering effect of the new combination preparation clearly surpasses that of the individual components and that of the two-compound combinations.

The toxicity of the preparation is very low, since the LD 50 of the active compound mixture is between 5000 and 10000 mg/kg p.o. (mice), i.e. a many times higher dose than that required for the lowering of the blood pressure.

The above indicated pharmacodynamic properties make the combination preparation indicated for use in the treatment of various forms of high blood pressure illnesses, particularly the essential and renal hypertonia. A suitable daily dose is one in which an average of 0.05—0.6 mg of reserpine, 0.25—3 mg of dihydroergocristine and 2.5—60 mg of clopamide are administered. It is preferred to administer an average daily dose of 1—2, optionally 3 of the dragées indicated above (composition A) or tablets (composition B), in milder cases 1 dragée or 1 tablet every second day.

In one form, the pharmaceutical composition of the invention contains amounts of con-

stituents such that the proportion, by weight, of reserpine constituent: dihydroergocristine constituent: N-(cis-2,6-dimethylpiperidino)-4-chloro-3-sulphamoyl benzamide, is from 1:2:20 to 1:10:150.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition comprising a) a reserpine constituent, b) a dihydroergocristine constituent, and c) N-(cis-2,6-dimethylpiperidino)-4-chloro-3-sulphamoyl benzamide.

2. A pharmaceutical composition according to Claim 1 comprising a), b) and c), in the following proportions by weight 1:1—20:5—1000.

3. A pharmaceutical composition according to Claim 1 comprising a), b) and c) in the following proportions by weight 1:1.5—15:10—500.

4. A pharmaceutical composition according to Claim 1 comprising a), b) and c) in the following proportions by weight 1:2—10:20—500.

5. A pharmaceutical composition according to Claim 1, in which the proportion, by weight, of reserpine constituent : dihydroergocristine constituent : N-(cis-2,6-dimethylpiperidino)-4-chloro-3-sulphamoyl benzamide, is from 1:2:20 to 1:10:150.

6. A pharmaceutical composition according to Claim 1 in unit dosage form, and comprising 0.1 mg of reserpine constituent, 0.5 mg of dihydroergocristine constituent, and 5.0 mg of N-(cis-2,6-dimethylpiperidino)-4-chloro-3-sulphamoyl benzamide.

7. A pharmaceutical composition according to Claim 1 in unit dosage form, and comprising 0.1 mg of reserpine constituent, 0.5 mg of dihydroergocristine constituent, and 10.0 mg of N-(cis-2,6-dimethylpiperidino)-4-chloro-3-sulphamoyl benzamide.

8. A pharmaceutical composition according to any one of the preceding Claims, in which the dihydroergocristine and reserpine constituents are in the form of water-soluble, pharmaceutically acceptable salts thereof.

9. A pharmaceutical composition according to any one of Claims 1 to 7, in which the reserpine constitutent is in free base form.

10. A pharmaceutial composition according to any one of the preceding Claims, in which the dihydroergocristine constituent is in the form of its methane sulphonate.

11. A pharmaceutical composition comprising reserpine constituent, a dihydroergocristine constituent, and N-(cis-2,6-dimethylpiperidino)-4-chloro-3-sulphamoyl benzamide, substantially as herein described, with reference to Examples 1 and 2.

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