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PATENT SPECIFICATION

1,175,430



NO DRAWINGS

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COMPLETE SPECIFICATION

Pharmaceutical Compositions containing Ergot Alkaloids

We, SANDOZ LTD., of Lichtstrasse 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:—

The present invention relates to new compositions comprising three different ingredients and having pharmaceutical properties.

The present invention provides compositions containing a) one or more of the hydrogenated ergot alkaloids 9,10-dihydro-ergocristine, 9,10 - dihydro - ergocryptine, and 9,10 - dihydro - ergocornine or a physiologically acceptable acid addition salt thereof, b) rutin and c) esculin.

The proportions in which the active ingredients in the composition of the present invention may be present will vary within wide limits and they will also depend on the presentation of the composition, e.g. whether it is intended for oral administration or for injection. Preferably the active ingredients are present in the composition of the present invention in a weight ratio of a):b):c)=1:15 to 240:0.75 to 12. The actual amounts giving the optimum effect may be determined depending, e.g. on the individual preparation used, its presentation, and even the purpose and nature of the treatment.

As may be seen from the Examples 1—3, one specific suitable weight ratio of the hydrogenated ergot alkaloids, rutin and esculin is 1:60:3; another such ratio, as seen from Example 4, is 1:200:10.

Constituent (a) may be made up of any desired amounts of any one or more of the three above ergot alkaloids, but one convenient specific constituent (a) consists of equal parts of each of the three alkaloids; another specific constituent (a) consists of dihydro-ergocristine only. The ergot alkaloids may be used as free bases or in the form of their water-soluble, physiologically tolerated salts with inorganic or organic acids. Examples of such salts are the hydrochlorides, hydrobromides, sulphates, methane-, benzene- and toluene-sulphonates, fumarates and tartrates.

The compositions of matter of the invention have a synergistic effect.

The present invention also includes galenical preparations of the new compositions of matter which are suitable for enteral and parenteral administration, e.g. tablets, dragées, capsules, drops and injectable solutions. In order to produce such medicinal preparations the active mixture is worked up with the usual inorganic or organic adjuvants which are inert and physiologically acceptable; 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.

[*Price 4s. 6d.*]

EXAMPLES

1) Dragées A

dihydro-ergocristine methanesulphonate	0.00057 g*)
rutin	0.0300 g
esculin	0.0015 g
polyvinyl pyrrolidone	0.0040 g
talcum	0.0040 g
maize starch	0.0100 g
lactose	0.02893 g
stearic acid	0.0010 g
coating mass	0.020 g
for a dragée of	0.100 g

*) corresponds to 0.0005 g of the free base

2) Dragées B

equal amounts of the methanesulphonates of dihydro-ergocristine, dihydro-ergocryptine and dihydro-ergocornine	0.00057 g*)
rutin	0.030 g
esculin	0.0015 g
polyvinyl pyrrolidone	0.0040 g
talcum	0.0040 g
maize starch	0.0100 g
lactose	0.02893 g
stearic acid	0.0010 g
coating mass	0.020 g
for a dragée of	0.100 g

*) corresponds to 0.0005 g of the free bases.

3) Drop solution (for oral administration)

dihydro-ergocristine methanesulphonate	0.05785	g*)
esculin	0.150	g
rutin . 3 H_2O	3.0	g
flavouring (orange)	0.10	g
94% ethanol (weight by weight)	15.0	g
glycerin	35.0	g
propylene glycol	54.09215	g
carbon dioxide gas	to saturation	
	107.4 g=100 ml	

Every ml of drop solution contains 0.5 mg of dihydro-ergocristine, 30.0 mg of rutin and 1.5 mg of esculin; 1 ml yields about 30 drops.

*) corresponds to 0.05 g of the free base.

4) Injectable solution

dihydro-ergocristine methanesulphonate	0.3	mg
esculin	3.0	mg
rutin (content about 80%)	75	mg*)
propylene glycol	2023.7	mg
for an ampoule of 2 ml=	2102.0	mg

*) corresponds to 60 mg of pure rutin

The hydrogenated ergot alkaloids indicated above lower the central vascular tonus, have a peripheral adreno-sympathicolytic effect and therefore, dilate the peripheral vessels. They are therefore indicated for use *inter alia* in the treatment of functional and organic circulatory disorders and in the treatment of venopathias. Recent tests have furthermore shown that dihydro-ergocristine in particular, has a tonic effect on the small and medium-sized veins when administered in doses which do not influence the arterial muscles. A widening of the arteries is produced on the one hand and a toning of the veins on the other, whereby blood circulation is improved.

Rutin (rutoside) is a naturally occurring flavone glucoside which decreases the permeability of the capillaries as does vitamin P. It furthermore protects adrenalin from oxidative degradation and, therefore, increases the level of this capillary permeability reducing catecholamine in the blood. Rutin, furthermore, has diuretic properties.

Esculin [6,7 - dihydroxy - cumarin - β-D - glucopyranoside - (6)] is mainly found in the bark of horse-chestnut branches and also has a vitamin P like effect, i.e. it lowers the permeability of capillary vessels. It exihibits a coagulation inhibiting effect, as do other cumarin derivatives. Esculin furthermore improves the tonus of the veins and stimulates blood reflux.

The new compositions of matter are indicated for use in the treatment of disorders in capillary permeability and in venous circulation, especially in the case of the following illnesses:

1. Varicosis
2. Pregnancy varicosities
3. Ulcus cruris
4. Leg edemas
5. Hemorrhoids.

A suitable average daily dose contains 1.5 to 6 mg of hydrogenated ergot alkaloids, 90 to 360 mg of rutin and 4.5 to 18 mg of esculin, administered *per os* or parenterally. On peroral administration the initial dose usually amounts to 3 times 1 to 2 dragées (Example

1 or 2) or 2 to 3 times 20 to 50 drops (Example 3) daily. After 3 to 5 days of treatment the dose can usually be reduced to 3 times 1 dragée or 3 times 20 drops daily. The treatment should have a duration of at least 2 to 4 weeks, but if necessary, it may be prolonged over a period of several months.

Clinical tests show that the compositions of the invention are excellently tolerated; no side effects being ascertained.

The following Table indicates the therapeutic results of peroral treatment with 2 forms of the composition of matter (columns A and B). Column C shows results obtained using a commercial preparation Hydergine (Registered Trade Mark) which consists of dihydroergocristine, -cornine and -cryptine in a proportion of 1:1:1.

	A				B				C			
Treatment	Dihydro-ergocristine, rutin and esculin (1:60:3)				Dihydro-ergocristine, -cornine, -cryptine, rutin and esculin (1:1:1:180:9)				Dihydro-ergocristine, -cornine and -cryptine 1:1:1 (as methanesulphonate)			
Posolgy and duration of treatment	1—2 dragées A (Example 1) or 25—30 drops (Example 3) 3 times daily for 1 to 3 months				2 dragées B (Example 2) 3 times daily for 2 to 6 weeks				0.5—2 mg perorally or 0.5 mg sublingually 3 to 4 times daily for 2 weeks to 9 months			
Therapeutic indication	Number of patients	Results			Number of patients	Results			Number of patients	Results		
		Good	Satis-factory	Unsatis-factory		Good	Satis-factory	Unsatis-factory		Good	Satis-factory	Unsatis-factory
Ulcus cruris	157	97	31	29	17	13	2	2	62	23	22	17
Thrombophlebitis, post-thrombotic syndrome	35	28	5	2	32	21	10	1	85	10	36	39
Varicous symptom complex, venous insufficiency, venous edemas, post-traumatic circulation disorders	130	50	56	24	18	12	6	—	32	4	13	15
Total	322	175	92	55	67	46	18	3	179	37	71	71
in %	100%	54%	29%	17%	100%	68%	27%	5%	100%	20%	40%	40%

The superiority of the compositions of matter in the case of those indications shown in the table is statistically significant, as a great number of patients were treated—and as treatment was effected under strictly comparable conditions.

Furthermore it was surprisingly ascertained that the compositions of matter give very good results, which were hitherto not obtained, in the treatment of Ulcus cruris, which is known to have a great resistance to treatment. Thus, of a total of 174 patients suffering from this refractory disease, 110 (63%) were treated with good results and 33 (19%) with satisfactory results, whereas only 31 (18%) cases proved to be refractory.

The results obtained with the compositions of the invention in comparison with those obtained with the individual components prove the presence of a synergistic effect.

The compositions of the invention have been found to be superior to the hitherto known pharmaceuticals in the treatment of distorders of venous circulation, especially of the lower extremities. In particular, it allows successful treatment of the hitherto refractory Ulcus cruris.

WHAT WE CLAIM IS:—

1. Pharmaceutical compositions containing a) one or more of the hydrogenated ergot alkaloids 9,10 - dihydro - ergocristine, 9,10-dihydro - ergocryptine and 9,10 - dihydro-ergocornine, or a physiologically acceptable acid addition salt thereof, together with b) rutin and c) esculin.

2. A pharmaceutical composition according to Claim 1, in which the active ingredients are present in a weight ratio of a):b):c)=1:15 to 240:0.75 to 12.

3. Pharmaceutical compositions containing 9,10-dihydro-ergocristine or a physiologically acceptable acid addition salt thereof, together with rutin and esculin.

4. Pharmaceutical compositions containing equal parts by weight of 9,10-dihydro-ergocristine, -ergocryptine and -ergocornine, or a physiologically acceptable acid addition salt thereof, together with rutin and esculin.

5. Pharmaceutical compositions as claimed in any one of Claims 2 to 4, in which the quantitative ratio by weight of the hydrogenated ergot alkaloids:rutin:esculin is 1:60:3.

6. Pharmaceutical compositions according to any one of Claims 1 to 4, in unit dosage form and suitable for the administration of a daily dose of 1.5 to 6 mg. of component a), 90 to 360 mg. of component b) and 4.5 to 18 mg. of component c).

7. Pharmaceutical compositions substantially as herein described with reference to any one of Examples 1 to 4.

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5. Pharmaceutical compositions as claimed in any one of Claims 2 to 4, in which the quantitative ratio by weight of the hydrogenated ergot alkaloids:rutin:esculin is 1:60:3.

6. Pharmaceutical compositions according to any one of Claims 1 to 4, in unit dosage form and suitable for the administration of a daily dose of 1.5 to 6 mg. of component a), 90 to 360 mg. of component b) and 4.5 to 18 mg. of component c).

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