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(54) ANTI-HYPERTENSIVE 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:—

The present invention relates to a pharmaceutical composition comprising as active agents

a) 4 - (2 - hydroxy - 3 - isopropylamino-propoxy)indole, and

b) clopamide.

Clopamide is the common name for the compound N - (cis - 2,6 - dimethylpiperidyl-1) - 4 - chloro - 3 - sulphamoyl - benzamide. Active agents a) or b) may be in free base form or an acid addition salt form. Clopamide is preferably used in the free base form. 4 - (2 - hydroxy - 3 - isopropylamino - propoxy)indole is preferably used in the form of the hydrogen maleate. The compositions may include conventional pharmaceutical carriers or diluents. Such compositions may be produced in conventional manner. The compositions may be in the form of tablets or capsules as mentioned hereinafter in the Examples.

The combination of active agents a) and b) is indicated in tests to provoke good antihypertensive activity, and to be well tolerated with few undesirable side effects, associated with the properties of active agents a) and b) alone, e.g. headaches, sleep disturbances, or insomnia.

An indicated preferred weight ratio of active agent a) to b) calculated on the free base moiety thereof is from 1:5 to 12.5:1, especially 1:1 to 3:1. A particularly convenient ratio is 2:1. An indicated daily dosage of active agent a) is from 7.5 to 60 mg. The daily dose may conveniently be administered unit dosage forms 2 to 3 times daily or in sustained release form. Each unit dose may contain for example a total of 2 to 20 mg or 2 to 15 mg of active agents a) and b). In one preferred composition a unit dose contains 10 mg active agent a) and 5 mg active agent b).

The compositions of the invention will now be described in more detail by way of the following Examples.

EXAMPLE 1

Tablets

4 - (2 - hydroxy - 3 - isopropylaminopropoxy) indole hydrogen maleate	(1)	7.34 mg
Clopamide as base		2.50 mg
Polyvinyl pyrrolidone		4.0 mg
Magnesium stearate		1.0 mg
Talc		6.0 mg
Mannitol		99.16 mg
For a tablet of		120.00 mg

(1) corresponds to 5 mg of base

EXAMPLE 2

Effervescent tablets

4 - (2 - hydroxy - 3 - isopropylaminopropoxy) indole hydrogen maleate	(2)	22.02 mg
Clopamide as base		10.0 mg
Sodium bicarbonate		1000.0 mg
Citric acid		1400.0 mg
Crystalline sugar		1417.98 mg
Polyethylene glycol 6000		150.0 mg
For an effervescent tablet of		4000.00 mg

(2) corresponds to 15 mg of base

[Price 33p]

EXAMPLE 3

Capsule

4 - (2 - hydroxy - 3 - iso-propylaminopropoxy) indole hydrogen maleate [3]	14.68	mg
Clopamide as base	5.0	mg
Microcrystalline cellulose	50.0	mg
Talc	10.0	mg
Mannitol	120.32	mg
For a capsule of	200.00	mg

[3] corresponds to 10 mg of base

EXAMPLE 4

Tablets

4 - (2 - hydroxy - 3 - iso - propylaminopropoxy) indole hydrogen maleate [4]	3.67	mg
Clopamide as base	2.50	mg
Polyvinyl pyrrolidone	4.0	mg
Magnesium stearate	1.0	mg
Talc	6.0	mg
Mannitol	102.83	mg
For a tablet of	120.00	mg

[4] corresponds to 2.5 mg of base

EXAMPLE 5

Effervescent tablets

4 - (2 - hydroxy - 3 - iso - propylaminopropoxy) indole hydrogen maleate [5]	14.68	mg
Clopamide as base	10.0	mg
Sodium bicarbonate	1000.0	mg
Citric acid	1400.0	mg
Crystalline sugar	1425.32	mg
Polyethylene glycol 6000	150.0	mg
For an effervescent tablet of	4000.00	mg

[5] corresponds to 10 mg of base

EXAMPLE 6

Capsule

4 - (2 - hydroxy - 3 - iso - propylaminopropoxy) indole hydrogen maleate [6]	7.34	mg
Clopamide as base	5.0	mg
Microcrystalline cellulose	50.0	mg
Talc	10.0	mg
Mannitol	127.66	mg
For a capsule of	200.00	mg

[6] corresponds to 5 mg of base

WHAT WE CLAIM IS:—

1. A pharmaceutical composition comprising as active agents
   a) 4 - (2 - hydroxy - 3 - isopropylamino-propoxy)indole, and
   b) clopamide.
2. A composition according to claim 1 wherein the weight ratio of active agent a) to b) is from 1:5 to 12.5:1.
3. A composition according to claim 2 wherein the weight ratio of active agent a) to active agent b) is from 1:1 to 3:1.
4. A composition according to any preceding claim in unit dosage form.
5. A composition according to claim 4 wherein the weight of active agent a) is from 2.5 to 15 mg per unit dosage.
6. A composition according to claim 4 containing a total of 2 to 20 mg active agents a) and b).
7. A composition according to claim 4 containing 10 mg active agent a) and 5 mg active agent b).
8. A pharmaceutical composition according to claim 1 substantially as hereinbefore described with reference to any one of the Examples.

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EXAMPLE 3

Capsule

4 - (2 - hydroxy - 3 - iso-propylaminopropoxy) indole hydrogen maleate [3]	14.68	mg
Clopamide as base	5.0	mg
Microcrystalline cellulose	50.0	mg
Talc	10.0	mg
Mannitol	120.32	mg
For a capsule of	200.00	mg

[3] corresponds to 10 mg of base

EXAMPLE 4

Tablets

4 - (2 - hydroxy - 3 - iso - propylaminopropoxy) indole hydrogen maleate [4]	3.67	mg
Clopamide as base	2.50	mg
Polyvinyl pyrrolidone	4.0	mg
Magnesium stearate	1.0	mg
Talc	6.0	mg
Mannitol	102.83	mg
For a tablet of	120.00	mg

[4] corresponds to 2.5 mg of base

EXAMPLE 5

Effervescent tablets

4 - (2 - hydroxy - 3 - iso - propylaminopropoxy) indole hydrogen maleate [5]	14.68	mg
Clopamide as base	10.0	mg
Sodium bicarbonate	1000.0	mg
Citric acid	1400.0	mg
Crystalline sugar	1425.32	mg
Polyethylene glycol 6000	150.0	mg
For an effervescent tablet of	4000.00	mg

[5] corresponds to 10 mg of base

EXAMPLE 6

Capsule

4 - (2 - hydroxy - 3 - iso - propylaminopropoxy) indole hydrogen maleate [6]	7.34	mg
Clopamide as base	5.0	mg
Microcrystalline cellulose	50.0	mg
Talc	10.0	mg
Mannitol	127.66	mg
For a capsule of	200.00	mg

[6] corresponds to 5 mg of base

WHAT WE CLAIM IS:—

1. A pharmaceutical composition comprising as active agents
   a) 4 - (2 - hydroxy - 3 - isopropylamino-propoxy)indole, and
   b) clopamide.
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3. A composition according to claim 2 wherein the weight ratio of active agent a) to active agent b) is from 1:1 to 3:1.
4. A composition according to any preceding claim in unit dosage form.
5. A composition according to claim 4 wherein the weight of active agent a) is from 2.5 to 15 mg per unit dosage.
6. A composition according to claim 4 containing a total of 2 to 20 mg active agents a) and b).
7. A composition according to claim 4 containing 10 mg active agent a) and 5 mg active agent b).
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