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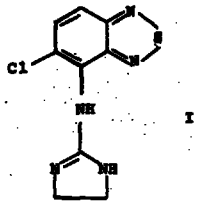
(72) Inventors ERWIN EICHENBERGER and PETER NEUMANN

(19)

(54) A PHARMACEUTICALLY ACTIVE BENZOTHIADIAZOLE DERIVATIVE

(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:—

This invention concerns novel pharmaceutical compositions containing the 2,1,3 - benzothiadiazole derivative of the formula I,



I

which is 5 - chloro - 4 - (2 - imidazolin - 2 - ylamino) - 2,1,3 - benzothiadiazole.

This compound is known and is disclosed in U.S.P. 3,843,668, wherein the compound is stated to be anti-tremor and anti-rigor agent as indicated by an inhibition of the tremor induced by 2,6 - dichlorophenyl acetamidoylureide and by an inhibition of the tremor induced by Thalamonal.

The compound now has been found to be an especially active orally administrable myotonolytic, for example for the treatment of spastic conditions of different etiology (neurological, inflammatory, and rheumatic), and muscle relaxant.

Standard tests indicate this activity for example, in rabbits on i.e. administration of from 0.001 to 0.1 mg/kg animal body weight of the compound a significant muscle relaxing effect is observed in accordance with the method of Teschendorf et al, Arch. Exp. Pharmacol. *266*, 467—468 (1970).

The present invention accordingly provides an oral myotonolytic or muscle relaxant composition in unit dosage form containing per unit dose from 0.25 mg to 2 mg of the compound of formula I as defined above or an equivalent amount of a pharmaceutically acceptable acid addition salt form thereof, in association with a pharmaceutical carrier or diluent. Preferably the unit dosage form contains 2 mg, or up to 1.8 mg, or up to 1.5 mg, of the free base of the compound of formula I or the equivalent amount of pharmaceutically acceptable acid addition salt.

These unit dosage forms may be administered 2 to 4 times a day. The compositions may already be in the final form ready for administration, for example in the form of integral solid dosage forms, e.g. a tablet. The composition may be packaged to facilitate administration of a unit dosage form.

The compositions may contain multiple unit dosages. For example a tablet may be formulated with a break line such that it may be broken into two halves. In such cases the term "unit dosage form" refers to the weight of compound of formula I in any portion thereof, adapted to be separated before administration.

As indicated above the compound may be administered orally in the form of tablets, powders, granules, capsules, suspensions, sirups and elixirs, or parenterally in the form of injectable solutions or suspensions. Aside from the compound of formula I the compositions may contain pharmaceutically inert organic or inorganic adjuvants, optionally granulating agents, binding agents, lubricants, dispersing agents, wetting agents and preservatives. Moreover, the pharmaceutical compositions may contain colourin, flavouring and sweetening substances. Adjuvants for the production of tablets may be calcium carbonate, lactose, microcrystalline cellulose, mannitol, or talc. Starch and alginic acid or microcrystalline cellulose may be used as granulating and disintegrating agents, starch, polyvinylpyrrolidone and gelatine may be used as binding agents, and magnesium stearate, stearic acid, colloidal silicon dioxide and talc as lubricants. Tablet formulations may be coated or uncoated, with the coating being applied in a manner *per se* and having the purpose of delaying the disintegration and adsorption in the gastrointestinal tract, thus providing a retarded effect over a longer period. Suitable

suspending agents for the production of liquid administration forms are especially methyl cellulose, tragacanth and sodium alginate. Suitable wetting agents are e.g. polyoxyethylene stearate and polyoxyethylene sorbitan - monooleate. Furthermore, preservatives such as p-hydroxy - benzoic acid alkyl ester may be used. Capsule formulations may contain the compound of formula I on its own or together with an inert solid diluent, for example calcium phosphate, starch, lactose, mannitol, colloidal silicon dioxide and microcrystalline cellulose.

Solid preparations are preferred, especially hard-filled capsules and tablets, for reasons of easier production and favourable administration.

The compound may be administered in free base form or in pharmaceutically acceptable acid addition salt form. Such salt forms are known and include for example the hydrochloride. The free base form and said acid addition salt forms exhibit the same order of activity.

The following Examples are illustrative of compositions for use in the invention.

EXAMPLE 1

Tablet suitable for oral administration

Tablets containing the ingredients indicated below may be prepared by conventional techniques and are useful in treating spastic conditions at a dose of one or two tablets four times a day.

Ingredient	Weight (mg)
5 - chloro - 4 - (2 - imidazolin - 2 - yl - amino) - 2,1,3 - benzothiadiazolehydrochloride	0.572 mg (≃0.5 mg base)
Lactose	70.528 mg
Microcrystalline cellulose	18.0 mg
Colloidal silicon dioxide	0.45 mg
Magnesium stearate	0.45 mg
	90.0 mg

If desired the tablet may be shaped so that it may be easily divided into two.

EXAMPLE 2

Capsule suitable for oral administration

Capsules containing the ingredients indicated below may be prepared by conventional techniques and are useful in the treatment of spastic conditions at a dose of one capsule two to four times a day.

Ingredient	Weight
5 - chloro - 4 - (2 - imidazolin - 2 - yl - amino) - 2,1,3 - benzothiadiazolehydrochloride	2.288 mg (≃2 mg base)
Lactose	173.212 mg
Corn starch	120.0 mg
Colloidal silicon dioxide	1.5 mg
Magnesium stearate	3.0 mg
	300.0 mg

EXAMPLE 3

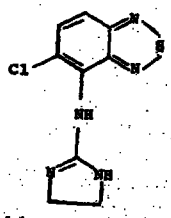
Dragées suitable for oral administration

Dragées containing the ingredients indicated below may be prepared by conventional techniques and are useful in the treatment of spastic conditions when administered at a dose of one dragée two to four times a day.

Ingredient	Weight
5 - chloro - 4 - (2 - imidazolin - 2 - yl - amino) - 2,1,3 - benzothiadiazolehydrochloride	1.725 mg (~1.5 mg base)
Polyvinyl pyrrolidone	3.6 mg
Lactose	69.825 mg
Magnesium stearate	0.9 mg
Colloidal silicon dioxide	0.45 mg
Corn starch	13.5 mg
Dragée mass	100 mg
	190 mg

WHAT WE CLAIM IS:—

1. An oral myotonolytic or muscle relaxant composition in unit dosage form containing per unit dose from 0.25 mg to 2 mg of a compound of formula I,



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which is 5 - chloro - 4 - (2 - imidazolin - 2 - ylamino) - 2,1,3 - benzothiadiazole, or an equivalent amount of a pharmaceutically acceptable acid addition salt form thereof, in association with a pharmaceutical carrier or diluent.

2. A composition according to claim 1, wherein the compound of formula I is in the form of the hydrochloride salt form.

suspending agents for the production of liquid administration forms are especially methyl cellulose, tragacanth and sodium alginate. Suitable wetting agents are e.g. polyoxyethylene stearate and polyoxyethylene sorbitan - monooleate. Furthermore, preservatives such as p - hydroxy - benzoic acid alkyl ester may be used. Capsule formulations may contain the compound of formula I on its own or together with an inert solid diluent, for example calcium phosphate, starch, lactose, mannitol, colloidal silicon dioxide and microcrystalline cellulose.

Solid preparations are preferred, especially hard-filled capsules and tablets, for reasons of easier production and favourable administration.

The compound may be administered in free base form or in pharmaceutically acceptable acid addition salt form. Such salt forms are known and include for example the hydrochloride. The free base form and said acid addition salt forms exhibit the same order of activity.

The following Examples are illustrative of compositions for use in the invention.

EXAMPLE 1

Tablet suitable for oral administration

Tablets containing the ingredients indicated below may be prepared by conventional techniques and are useful in treating spastic conditions at a dose of one or two tablets four times a day.

Ingredient	Weight (mg)
5 - chloro - 4 - (2 - imidazolin - 2 - yl - amino) - 2,1,3 - benzothiadiazolehydrochloride	0.572 mg (≃0.5 mg base)
Lactose	70.528 mg
Microcrystalline cellulose	18.0 mg
Colloidal silicon dioxide	0.45 mg
Magnesium stearate	0.45 mg
	90.0 mg

If desired the tablet may be shaped so that it may be easily divided into two.

EXAMPLE 2

Capsule suitable for oral administration

Capsules containing the ingredients indicated below may be prepared by conventional techniques and are useful in the treatment of spastic conditions at a dose of one capsule two to four times a day.

Ingredient	Weight
5 - chloro - 4 - (2 - imidazolin - 2 - yl - amino) - 2,1,3 - benzothiadiazolehydrochloride	2.288 mg (≃2 mg base)
Lactose	173.212 mg
Corn starch	120.0 mg
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Magnesium stearate	3.0 mg
	300.0 mg

EXAMPLE 3

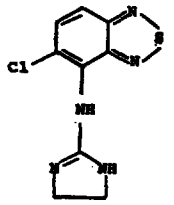
Dragées suitable for oral administration

Dragées containing the ingredients indicated below may be prepared by conventional techniques and are useful in the treatment of spastic conditions when administered at a dose of one dragée two to four times a day.

Ingredient	Weight
5 - chloro - 4 - (2 - imidazolin - 2 - yl - amino) - 2,1,3 - benzothiadiazolehydrochloride	1.725 mg (~1.5 mg base)
Polyvinyl pyrrolidone	3.6 mg
Lactose	69.825 mg
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WHAT WE CLAIM IS:—

1. An oral myotonolytic or muscle relaxant composition in unit dosage form containing per unit dose from 0.25 mg to 2 mg of a compound of formula I,



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which is 5 - chloro - 4 - (2 - imidazolin - 2 - ylamino) - 2,1,3 - benzothiadiazole, or an equivalent amount of a pharmaceutically acceptable acid addition salt form thereof, in association with a pharmaceutical carrier or diluent.

2. A composition according to claim 1, wherein the compound of formula I is in the form of the hydrochloride salt form.

3. A composition according to claim 1 or 2, which contains per unit dose from 0.25 mg to 1.5 mg of a compound of formula I or an equivalent amount of a pharmaceutically acceptable acid addition salt form.

4. A composition according to claim 1 or 2, which contains per unit dose 2 mg of a compound of formula I or an equivalent amount of a pharmaceutically acceptable acid addition salt form.

5. A composition according to any preceding claim which is a solid.

6. A composition according to claim 5 in the form of a tablet.

7. A composition according to claim 1 substantially as hereinbefore described with reference to any one of the Examples.

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