PATENT SPECIFICATION

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COMPLETE SPECIFICATION

Therapeutic Compositions useful in the Treatment of Angina Pectoris

We, F. HOFFMANN-LA ROCHE & Co. AKTIENGESELLSCHAFT, a Swiss Company of 124—184, Grenzacherstrasse, Basle, Switzerland, 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 therapeutic compositions and to a process for the manufacture thereof.

The therapeutic compositions provided by the invention are compositions which contain as essential active ingredients chlordiazepoxide, or an acid addition salt thereof with a pharmaceutically acceptable acid, and pentaerythritol tetranitrate. These compositions are useful in the treatment of angina pectoris. Heretofore nitroglycerine has been the drug of choice for eliminating or reducing the number and extent of the angina attacks. However, a disadvantage of nitroglycerine therapy lies in the short duration of action of the nitroglycerine. Other drugs which have a longer duration of action (e.g. pentaerythritol tetranitrate) have been employed, but these drugs have less activity than nitroglycerine in the treatment of angina pectoris.

It has been found that chlordiazepoxide when used in combination with pentaerythritol tetranitrate markedly enhances the activity of the pentaerythritol tetranitrate in reducing the number and extent of angina attacks. This is surprising since chlordiazepoxide alone exhibits no known effects on the heart.

The pharmaceutically acceptable acid addition salts of the chlordiazepoxide base which can be used include mineral acid salts (e.g., the hydrochloride, hydrobromide, hydroiodide, sulphate, nitrate, and phosphate) and organic acid salts (e.g., the aryl-sulphonates such as benzene- and toluene-sulphonates, the citrate, tartrate, acetate and lactate). The hydrochloride salt or the free base is preferred.

The ratio of active ingredients can vary over a wide range; for example, from 0.4 to 30 (preferably 1 to 6) parts by weight of pentaerythritol tetranitrate per part by weight of chlordiazepoxide or pharmaceutically acceptable acid addition salt thereof. A typical adult dosage of active ingredients ranges from 2 mg to 25 mg (preferably from 5 mg to 10 mg) of chlordiazepoxide or pharmaceutically acceptable acid addition salt thereof and from 10 mg to 60 mg (preferably from 10 mg to 30 mg) of pentaerythritol tetranitrate. For example, a hard-shell capsule containing as active ingredients 5 mg of chlordiazepoxide hydrochloride and 20 mg of pentaerythritol tetranitrate can be administered to a patient three or four times daily. Smaller dosages can, of course, be employed for elderly or debilitated patients. The ranges mentioned are not critical and dosages outside these ranges can be employed.

It will be understood that chlordiazepoxide is used herein to mean the basic compound 7-chloro - 2 - methylamino - 5 - phenyl -3H - 1,4-benzodiazepine 4-oxide.

The compositions of the invention are prepared by mixing together the two active components and, optionally, pharmaceutical adjuvants, and forming the resulting mixtures into suitable dosage forms. Compositions suitable for oral administration are the known pharmaceutical forms such as pressed or coated tablets, capsules, oily suspensions, and the pharmaceutical adjuvants used in the production of these formulations are those well known to the pharmacist's art, as are also the means of formulation. Suitable oral compositions are capsules and tablets in which the active ingredients are mixed with inert fillers (e.g. dicalcium phosphate or lactose) in the presence of disintegrating agents (e.g., maize starch) and lubricating agents (e.g., calcium stearate or talc). Oily suspensions for oral use may be formulated in a suitable vegetable oil (e.g., arachis oil) which may contain suitable

[*Price 4s. 6d.*]

sweetening agents and preservatives. The compositions of the invention can also be used in rectal suppository form by mixing them with suppository adjuvant material (e.g., fatty acid esters of glycerine or glycols such as cocoa-butter and propylene-glycol monostearate) by techniques well known in the art.

The following Examples are given by way of illustration of the compositions of the invention and the manner in which they may be prepared.

EXAMPLE 1

A tablet is formed from the following ingredients:

Ingredients	mg/tablet
Chlordiazepoxide	5.0
Pentaerythritol tetranitrate	20.0
Lactose	72.0
Corn starch	38.0
Calcium stearate	2.0

In this Example, 58.0 mg of a mixture of pentaerythritol tetranitrate containing 35% pentaerythritol tetranitrate and 65% of an inactive clay base, designated SDM—35 from the Atlas Chemical Company, are used.

The chlordiazepoxide, the pentaerythritol tetranitrate, the lactose and half of the corn starch are blended together in a Pony mixer and then granulated together with a corn starch paste made up from the remainder of the corn starch in about 0.11 ml of water. The granulation is then dried, the calcium stearate added and mixed therewith, and the resulting mixture compressed into tablets using a tablet compressing machine.

The tablets are then coated with a sugar coating in a conventional manner by first applying a barrier of a shellac/alcohol solution and then applying the sugar coating. Alternatively, the tablets can be used without the sugar coating.

EXAMPLE 2

A hard-shelled capsule is made up from the following ingredients:

Ingredients	mg/capsule
Chlordiazepoxide hydrochloride	10
Pentaerythritol tetranitrate	20
Dicalcium phosphate (U.S.P.)	60
Talc	7
Magnesium stearate	3

In this Example 58.0 mg of a mixture of pentaerythritol tetranitrate containing 35% pentaerythritol tetranitrate and 65% of an inactive clay base, designated SDM—35 from the Atlas Chemical Company are used.

The ingredients are blended together in a Pony mixer and the resulting mixture inserted into a hard-shelled capsule using a conventional capsule filling machine.

EXAMPLE 3

A suppository is formed from the following ingredients:

Ingredients	mg/suppository
Chlordiazepoxide hydrochloride	25
Pentaerythritol tetranitrate	30 (84 mg of 35% pentaerythritol tetranitrate in a clay base
Carnauba wax	20
Fatty base (Wecobee M, being a glyceride of coconut ~~fattyacids~~ fatty acids)	1,520

The ingredients are mixed together by first melting the carbauba wax and the fatty base to 85° C, stirring this mixture well and allowing it to cool to 45° C. Then the chlordiazepoxide hydrochloride and the pentaerythritol tetranitrate powders are added, the resulting mixture is stirred well and poured into a chilled mould. The hardened suppository is then wrapped with aluminium foil to protect it from moisture.

WHAT WE CLAIM IS:—

1) A therapeutic composition which contains as essential active ingredients chlordiazepoxide, or an acid addition salt thereof with a pharmaceutically acceptable acid, and pentaerythritol tetranitrate.

2) A composition as claimed in claim 1, wherein the pentaerythritol tetranitrate is present in a ratio of 0.4 to 30 parts by weight per part by weight of chlordiazepoxide or pharmaceutically acceptable acid addition salt thereof.

3) A composition as claimed in claim 1 or claim 2, wherein the pentaerythritol tetranitrate is present in a ratio of 1 to 6 parts by weight per part by weight of chlordiazepoxide or pharmaceutically acceptable acid addition salt thereof.

4) A composition as claimed in any one of claims 1 to 3 inclusive, wherein said salt is the hydrochloride.

5) A composition as claimed in any one of claims 1 to 4 inclusive, wherein a compatible pharmaceutical adjuvant material is also present.

6) A therapeutic composition in shaped unit dosage form for oral administration which contains as essential active ingredients chlordiazepoxide (or an acid addition salt thereof with a pharmaceutically acceptable acid) and pentaerythritol tetranitrate and which also contains compatible pharmaceutical adjuvant material.

7) A composition as claimed in claim 6, which takes the form of a hard-shell capsule containing 5 mg of chlordiazepoxide hydrochloride and 20 mg of pentaerythritol tetranitrate and a compatible solid pharmaceutical adjuvant material.

8) A therapeutic composition in shaped unit dosage form suitable as a rectal suppository, which contains as essential active ingredients chlordiazepoxide (or an acid addition salt thereof with a pharmaceutically acceptable acid) and pentaerythritol tetranitrate and which also contains a compatible rectal suppository adjuvant material.

9) A process for the manufacture of the therapeutic compositions claimed in any one of claims 1 to 8 inclusive, substantially as described with reference to the Examples.

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