PATENT SPECIFICATION

NO DRAWINGS

942,889

Date of Application and filing Complete Specification Oct. 10, 1962.
No. 38359/62.
Application made in United States of America (No. 145,782) on Oct. 17, 1961.
Complete Specification Published Nov. 27, 1963.
© Crown Copyright 1963.

Index at acceptance: —~~Class~~ A5 B(1G, 1S, 2G, 2S).
International Classification: —A 61 k.

COMPLETE SPECIFICATION

Therapeutic Compositions Containing Chlordiazepoxide

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 containing chlordiazepoxide and to a process for the manufacture thereof.

One of the well known pharmacological manifestations of chlordiazepoxide is its depressant effect on animal behaviour. It has now surprisingly been found that clidinium halide, which by itself has substantially no such effect, potentiates the depressant effect of chlordiazepoxide.

The therapeutic compositions provided by the invention are, accordingly, compositions which contain as essential active ingredients chlordiazepoxide or an acid addition salt thereof with a pharmaceutically acceptable acid and clidinium halide. These compositions are useful in the treatment of gastrointestinal disorders, both organic and functional, such as peptic ulcer, hyperchlorhydria, ulcerative or spastic colon, gastritis, duodenitis, biliary dyskinesia, "nervous stomach", irritable spastic colon, anxiety states having gastrointestinal manifestations, pylorospasm, cardiospasm and other organic or functional disorders of the digestive tract.

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

The ~~radio~~ ratio of active ingredients can vary over a wide range; for example, from about 0.3 to 25 parts by weight (preferably from about 2 to 4 parts by weight) of chlordiazepoxide per part by weight of clidinium halide. A typical adult dosage of active ingredients ranges from about 2.5 to 25 mg (preferably from about 5 to 10 mg) of chlordiazepoxide and from about 1.0 to 7.5 mg (preferably about 2.5 mg) of clidinium halide. For example, a hard-shell capsule containing as active ingredients 5 mg of chlordiazepoxide hydrochloride and 2.5 mg of clidinium bromide can be administered to a a patient three or four times daily. Smaller dosages can, of course, be employed for children or 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 and clidinium halide is used herein to mean a compound of the name 1 - methyl - 3 - benziloyloxy - quinuclidinium halide and includes clidinium chloride, bromide and iodide (the bromide being preferred). These halides may be prepared as described in British Patent Specification no 694067.

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, syrups and oily suspensions, and the pharmaceutical adjuvants used in the production of these compositions 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

[*Price* 4*s.* 6*d.*]

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 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, propylene-glycol monostearate, etc.) by techniques well known to the art.

The following examples are given by way of illustration:

EXAMPLE 1

The following ingredients are blended together by mixing for 15 minutes in a container:

	mg
Chlordiazepoxide hydrochloride	5.10
Clidinium bromide - - -	2.55
Lactose - - - - - - -	162.35
Cornstarch - - - - - -	30.00
Talc - - - - - - - -	5.00

The blend is then passed through a FITZPATRICK comminuting machine and then blended for a further 5 minutes. The mixture is then filled into a hard-shell capsule.

EXAMPLE 2

The process of Example 1 is carried out using 10 mg of chlordiazepoxide and 5 mg of clidinium bromide but the same quantities of other ingredients.

EXAMPLE 3

10 mg of chlordiazepoxide hydrochloride, 5 mg of clidinium bromide, 38.45 mg of white beeswax, 96.1 mg of polyoxyethylene-sorbitan monooleate and 1105.45 mg of propylene-glycol monostearate are mixed together, heated, and shaped in the form of a rectal suppository.

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 a clidinium halide.

2) A composition as claimed in claim 1, wherein the chlordiazepoxide or acid addition salt thereof is present in a ratio of about 0.3 to 25 parts by weight per part by weight of clidinium halide.

3) A composition as claimed in claim 1 or claim 2, wherein said salt is the hydrochloride and said halide is the bromide.

4) A composition as claimed in any one of the preceding claims, wherein a compatible pharmaceutical adjuvant material is also present.

5) A therapeutic composition in 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 a clidinium halide and which also contains a vehicle for the said active ingredients comprising compatible pharmaceutical adjuvant material.

6) A composition as claimed in claim 5, which takes the form of a hard-shell capsule containing 5 mg of chlordiazepoxide, 2.5 mg of clidinium bromide and a compatible powdered solid pharmaceutical adjuvant material.

7) A therapeutic composition in 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 a clidinium halide and which also contains a vehicle for the said active ingredients comprising a compatible rectal suppository adjuvant material.

8) A process for the manufacture of capsules and suppositories, substantially as described with reference to the examples.

W. D. WHITAKER,
Patent Agent
for F. HOFFMANN-LA ROCHE & CO.
Aktiengesellschaft.

Leamington Spa: Printed for Her Majesty's Stationery Office by the Courier Press.—1963.
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.

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 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, propylene-glycol monostearate, etc.) by techniques well known to the art.

The following examples are given by way of illustration:

EXAMPLE 1

The following ingredients are blended together by mixing for 15 minutes in a container:

	mg
Chlordiazepoxide hydrochloride	5.10
Clidinium bromide - - -	2.55
Lactose - - - - - -	162.35
Cornstarch - - - - - -	30.00
Talc - - - - - - -	5.00

The blend is then passed through a FITZPATRICK comminuting machine and then blended for a further 5 minutes. The mixture is then filled into a hard-shell capsule.

EXAMPLE 2

The process of Example 1 is carried out using 10 mg of chlordiazepoxide and 5 mg of clidinium bromide but the same quantities of other ingredients.

EXAMPLE 3

10 mg of chlordiazepoxide hydrochloride, 5 mg of clidinium bromide, 38.45 mg of white beeswax, 96.1 mg of polyoxyethylene-sorbitan monooleate and 1105.45 mg of propyleneglycol monostearate are mixed together, heated, and shaped in the form of a rectal suppository.

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 a clidinium halide.

2) A composition as claimed in claim 1, wherein the chlordiazepoxide or acid addition salt thereof is present in a ratio of about 0.3 to 25 parts by weight per part by weight of clidinium halide.

3) A composition as claimed in claim 1 or claim 2, wherein said salt is the hydrochloride and said halide is the bromide.

4) A composition as claimed in any one of the preceding claims, wherein a compatible pharmaceutical adjuvant material is also present.

5) A therapeutic composition in 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 a clidinium halide and which also contains a vehicle for the said active ingredients comprising compatible pharmaceutical adjuvant material.

6) A composition as claimed in claim 5, which takes the form of a hard-shell capsule containing 5 mg of chlordiazepoxide, 2.5 mg of clidinium bromide and a compatible powdered solid pharmaceutical adjuvant material.

7) A therapeutic composition in 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 a clidinium halide and which also contains a vehicle for the said active ingredients comprising a compatible rectal suppository adjuvant material.

8) A process for the manufacture of capsules and suppositories, substantially as described with reference to the examples.

W. D. WHITAKER,
Patent Agent
for F. HOFFMANN-LA ROCHE & CO.
Aktiengesellschaft.

Leamington Spa: Printed for Her Majesty's Stationery Office by the Courier Press.—1963.
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.

* C L M S *