PATENT SPECIFICATION

953,102

953,102

Date of Application and filing Complete Specification: December 7, 1962. *No.* 46262/62

Application made in United States of America (No. 161270) *on December 21, 1961.*

Complete Specification Published: March 25, 1964.

© *Crown Copyright* 1964.

Index at Acceptance:—**A5 B** (2A, 2C, 2D, 2G, 2S).

International Classification:—A 61 k.

COMPLETE SPECIFICATION

NO DRAWINGS

Therapeutic Compositions useful for inducing Sleep

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:—

This invention relates to novel therapeutic compositions useful for the inducement of sound sleep and the preparation thereof.

The compositions of the present invention comprise mixtures of 3,3-diethyl-5-methyl-piperidinedione-(2,4) with 7-chloro-2-methylamino-5-phenyl-3H-1, 4-benzodiazepine 4-oxide or a medicinally acceptable acid addition salt thereof. They are especially well suited for use in the treatment of patients with sleep problems associated with anxiety, tension or other common emotional disturbances. These compositions, therefore, fill a long existing need in the treatment of patients with heart diseases or other chronic ailments, in the treatment of neuropsychiatric patients and in the treatment of patients in pre- and postoperative states. The 3,3-diethyl-5-methyl-piperidinedione-(2,4) ingredient is a non-narcotic, sedative-hypnotic which possesses high therapeutic activity and, at the same time, manifests low toxicity. The other main ingredient, namely 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide or a medicinally acceptable acid addition salt thereof, has no hypnotic properties in therapeutic doses but has been found, in accordance with the invention to cause sleep-inducing potentiation of the 3,3-diethyl-5-methyl-piperidinedione-(2,4).

Moreover, in some animal species, particularly in the dog, administration of the 3,3-diethyl-5-methyl-piperidinedione-(2,4) ingredient appears to induce an initial phase of excitation which is followed by a sedation phase and, finally, a hypnotic phase, and it has been found that admixing with 7-chloro-2-methylamino-5-phenyl-3H-1, 4-benzodiazepine 4-oxide does not result in potentiation of the excitation phase. In fact, surprisingly the initial excitation appears to be suppressed.

Thus, the present invention provides therapeutically active compositions comprising a mixture of 3,3-diethyl-5-methyl-piperidinedione-(2,4) with 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide or, if desired, a medicinally acceptable acid addition salt thereof. As the 3,3-diethyl-5-methyl-piperidinedione-(2,4) ingredient is somewhat unstable in an acid environment, the use of an acid addition salt of 7-chloro-2-methylamino-5-phenyl-3H-1, 4-benzodiazepine 4-oxide as the other active ingredient should be accompanied by a sufficient quantity of alkali (for example, an alkaline filler such as coprecipitated aluminium hydroxide/calcium carbonate) to render the finished product basic, or at least neutral, in reaction. In general, any one of many medicinally acceptable acid addition salts of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide can be used. These include salts of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide with conventional mineral acids (such as hydrochloric acid, hydrobromic acid, nitric acid, phosphoric acid) and with conventional organic acids (such as benzoic acid, *para*-toluene-sulphonic acid, acetic acid, citric acid, maleic acid, tartaric acid and lactic acid). In the preferred compositions, however, 7-chloro-2-methylamino-5-phenyl-3H-1, 4-benzodiazepine 4-oxide or its hydrochloric acid salt is used.

The compositions of the invention are

[Price 4s. 6d.]

prepared simply by intimately mixing the two active components. The mixture may then be embodied in a suitable shaped unit dosage form for internal administration. Suitable dosage forms include capsules, pressed or coated tablets, syrups and oily suspensions. The methods by which such dosage forms are obtained are well known in the art.

In addition to the active ingredients, the compositions of this invention may contain various adjuvants conventionally used in the formulation of pharmaceutical preparations. Examples of adjuvants employed in compositions in encapsulated or tablet form are fillers such as coprecipitated aluminium hydroxide / calcium carbonate, dicalcium phosphate or lactose in the presence of disintegrating agents (such as maize starch) and lubricating agents such as talc and calcium stearate. The compositions may, moreover, be produced in the form of suspensions in oil; for example, in a vegetable oil such as arachis oil. Such suspensions may contain sweetening agents and preservatives of the type normally employed in the art.

The ratio of the active components comprising the products of this invention can be varied within rather wide limits. For example, the products may contain from 4 to 120 parts by weight of 3,3-diethyl-5-methyl-piperidinedione-(2,4) for each part by weight of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide or for each part by weight of a salt thereof. The preferred products of the invention, however, contain from 15 parts by weight to 25 parts by weight of 3,3-diethyl-5-methyl-piperidinedione-(2,4) for each part by weight of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide or salt thereof.

A typical adult dosage of the active ingredients comprising the present compositions may vary within the range of from 175 mg to 225 mg of 3,3-diethyl-5-methyl-piperidinedione-(2,4) with from 8 mg to 12 mg of 7-choro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide or salt thereof. For example, a hard-shell capsule containing 200 mg of 3,3-diethyl-5-methyl-piperidinedione-(2,4) and 10 mg of 7-chloro-2-methylamino-5-phenyl-3H-1, 4-benzodiazepine 4-oxide or salt thereof, may be administered to the patient at bedtime. In cases of severe insomnia, a second capsule may be prescribed. Smaller doses may, of course, be recommended in particular cases; for example, in the treatment of children and debilitated patients. It should be fully understood, however, that the dosages set forth herein are by way of example only.

The following Examples are illustrative of the invention:

Example 1

1020 g of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide, 20,400 g of 3,3-diethyl-5-methyl-piperidinedione-(2,4), 400 g of coprecipitated aluminium hydroxide/calcium carbonate, 5400 g of starch, 1500 g of talc and 1280 g of lactose were intimately mixed in a suitable container. The mixture was then passed through a FITZPATRICK comminuting machine and the milled powder was mixed and reblended. The powdery mixture was then passed into hard-shell capsules.

Example 2

200 parts by weight of 3,3-diethyl-5-methyl-piperidinedione-(2,4) and 20 parts by weight of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide were first intimately admixed. 65.0 parts by weight of coprecipitated aluminium hydroxide/calcium carbonate were added to the resulting mixture. This mixture was granulated with a mixture of 5 parts by weight of gelatin and 5 parts by weight of corn starch. Thereafter, the granulate obtained was mixed with 3.6 parts by weight of corn starch, 4.0 parts by weight of talc and 0.4 parts by weight of magnesium stearate. The product was then compressed into tablets by conventional means.

WHAT WE CLAIM IS:—

1. A therapeutic composition useful for inducing sleep comprising a mixture of 3,3-diethyl-5-methyl-piperidinedione-(2,4) with 7 - chloro - 2 - methylamino - 5 - phenyl - 3H-1,4-benzodiazepine 4-oxide or a medicinally acceptable acid addition salt thereof.

2. A composition as claimed in claim 1 wherein from 4 to 120 parts by weight of 3,3-diethyl-5-methyl-piperidinedione-(2,4) are present for each part by weight of 7 - chloro - 2 - methylamino - 5 - phenyl - 3H-1,4-benzodiazepine 4-oxide or medicinally acceptable acid addition salt thereof.

3. A composition as claimed in claim 2, wherein from 15 to 25 parts by weight of 3,3-diethyl-5-methyl-piperidinedione-(2,4) are present for each part by weight of 7 - chloro - 2 - methylamino - 5 - phenyl - 3H-1,4-benzodiazepine 4-oxide or medicinally acceptable acid addition salt thereof.

4. A composition as claimed in claim 1, claim 2 or claim 3, wherein said salt is the hydrochloric acid salt.

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

6. A therapeutic composition in shaped unit dosage form for internal administration comprising a mixture of 3,3-diethyl-5-methyl-piperidinedione-(2,4) with 7-chloro-2-methylamino - 5 - phenyl - 3H - 1, 4 - benzodiazepine 4-oxide or a medicinally acceptable acid addition salt thereof and a com-

prepared simply by intimately mixing the two active components. The mixture may then be embodied in a suitable shaped unit dosage form for internal administration. Suitable dosage forms include capsules, pressed or coated tablets, syrups and oily suspensions. The methods by which such dosage forms are obtained are well known in the art.

In addition to the active ingredients, the compositions of this invention may contain various adjuvants conventionally used in the formulation of pharmaceutical preparations. Examples of adjuvants employed in compositions in encapsulated or tablet form are fillers such as coprecipitated aluminium hydroxide / calcium carbonate, dicalcium phosphate or lactose in the presence of disintegrating agents (such as maize starch) and lubricating agents such as talc and calcium stearate. The compositions may, moreover, be produced in the form of suspensions in oil; for example, in a vegetable oil such as arachis oil. Such suspensions may contain sweetening agents and preservatives of the type normally employed in the art.

The ratio of the active components comprising the products of this invention can be varied within rather wide limits. For example, the products may contain from 4 to 120 parts by weight of 3,3-diethyl-5-methyl-piperidinedione-(2,4) for each part by weight of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide or for each part by weight of a salt thereof. The preferred products of the invention, however, contain from 15 parts by weight to 25 parts by weight of 3,3-diethyl-5-methyl-piperidinedione-(2,4) for each part by weight of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide or salt thereof.

A typical adult dosage of the active ingredients comprising the present compositions may vary within the range of from 175 mg to 225 mg of 3,3-diethyl-5-methyl-piperidinedione-(2,4) with from 8 mg to 12 mg of 7-choro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide or salt thereof. For example, a hard-shell capsule containing 200 mg of 3,3-diethyl-5-methyl-piperidinedione-(2,4) and 10 mg of 7-chloro-2-methylamino-5-phenyl-3H-1, 4-benzodiazepine 4-oxide or salt thereof, may be administered to the patient at bedtime. In cases of severe insomnia, a second capsule may be prescribed. Smaller doses may, of course, be recommended in particular cases; for example, in the treatment of children and debilitated patients. It should be fully understood, however, that the dosages set forth herein are by way of example only.

The following Examples are illustrative of the invention:

Example 1

1020 g of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide, 20,400 g of 3,3-diethyl-5-methyl-piperidinedione-(2,4), 400 g of coprecipitated aluminium hydroxide/calcium carbonate, 5400 g of starch, 1500 g of talc and 1280 g of lactose were intimately mixed in a suitable container. The mixture was then passed through a FITZPATRICK comminuting machine and the milled powder was mixed and reblended. The powdery mixture was then passed into hard-shell capsules.

Example 2

200 parts by weight of 3,3-diethyl-5-methyl-piperidinedione-(2,4) and 20 parts by weight of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide were first intimately admixed. 65.0 parts by weight of coprecipitated aluminium hydroxide/calcium carbonate were added to the resulting mixture. This mixture was granulated with a mixture of 5 parts by weight of gelatin and 5 parts by weight of corn starch. Thereafter, the granulate obtained was mixed with 3.6 parts by weight of corn starch, 4.0 parts by weight of talc and 0.4 parts by weight of magnesium stearate. The product was then compressed into tablets by conventional means.

WHAT WE CLAIM IS:—

1. A therapeutic composition useful for inducing sleep comprising a mixture of 3,3-diethyl-5-methyl-piperidinedione-(2,4) with 7 - chloro - 2 - methylamino - 5 - phenyl - 3H-1,4-benzodiazepine 4-oxide or a medicinally acceptable acid addition salt thereof.

2. A composition as claimed in claim 1 wherein from 4 to 120 parts by weight of 3,3-diethyl-5-methyl-piperidinedione-(2,4) are present for each part by weight of 7 - chloro - 2 - methylamino - 5 - phenyl - 3H-1,4-benzodiazepine 4-oxide or medicinally acceptable acid addition salt thereof.

3. A composition as claimed in claim 2, wherein from 15 to 25 parts by weight of 3,3-diethyl-5-methyl-piperidinedione-(2,4) are present for each part by weight of 7 - chloro - 2 - methylamino - 5 - phenyl - 3H-1,4-benzodiazepine 4-oxide or medicinally acceptable acid addition salt thereof.

4. A composition as claimed in claim 1, claim 2 or claim 3, wherein said salt is the hydrochloric acid salt.

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

6. A therapeutic composition in shaped unit dosage form for internal administration comprising a mixture of 3,3-diethyl-5-methyl-piperidinedione-(2,4) with 7-chloro-2-methylamino - 5 - phenyl - 3H - 1, 4 - benzodiazepine 4-oxide or a medicinally acceptable acid addition salt thereof and a com-

* C L M S *

patible pharmaceutical adjuvant material.

7. A process for the manufacture of the therapeutic compositions claimed in any one of claims 1 to 6 inclusive, substantially as described with reference to the Examples.

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

Berwick-upon-Tweed: Printed for Her Majesty's Stationery Office by The Tweeddale Press Ltd.—1964
Published at The Patent Office, 25 Southampton Buildings, London, W.C.2. from which copies may be obtained.

