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PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Novel Therapeutic Compositions and a Process for the Manufacture thereof

We, F. HOFFMAN-LA ROCHE & Co., AKTIENGESELLSCHAFT, a Swiss Company of 124-128 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 and a process for the manufacture thereof. More particularly, the invention is concerned with novel therapeutic compositions having improved antidepressant properties and with a process for the manufacture thereof.

7-Chloro-2-methylamino- 5-phenyl-3H-1,4-benzodiazepine 4-oxide (otherwise known as chlordiazepoxide) and its medicinally acceptable acid addition salts are known substances which have pronounced sedative activity. Moreover, 5-(3-dimethylamino-propylidene)-dibenzo[a,d]*cyclo*hepta [1,4]diene (otherwise known as amitriptyline) and its medicinally acceptable acid addition salts are known to have antidepressant properties.

It has now been found in accordance with the present invention that when 7-chloro-2-methylamino- 5-phenyl-3H-1,4-benzodiazepine 4-oxide or a medicinally acceptable acid addition salt thereof and 5-(3-dimethylamino-propylidene)- dibenzo[a,d]*cyclo*hepta [1,4]diene or a medicinally acceptable acid addition salt thereof are embodied into a suitable pharmaceutical dosage form, the resulting composition exhibits an antidepressant activity which is superior to that exhibited by pharmaceutical compositions containing either of these active ingredients as the sole active ingredient. Furthermore, despite the fact that an enhancement in antidepressant activity is achieved when the aforesaid active ingredients are administered in combination, no usual side effects are observed. On the other hand, the administration of the 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide or a medicinally acceptable acid addition salt thereof in combination with 5-(3-dimethylamino-propylidene)- dibenzo[a,d]*cyclo*hepta [1,4]diene or a medicinally acceptable acid addition salt thereof appears to minimize the side effects which normally attend the administration of the latter ingredient alone.

Accordingly, the novel therapeutic compositions provided by the present invention contain as essential active ingredients (a) 7-chloro-2-methylamino- 5-phenyl-3H-1,4-benzodiazepine 4-oxide or a medicinally acceptable acid addition salt thereof and (b) 5-(3-dimethylamino-propylidene)- dibenzo[a, d]*cyclo*hepta [1,4]diene or a medicinally acceptable acid addition salt thereof.

The novel compositions can be made into suitable dosage forms (e.g. for enteral or parenteral administration) and can contain pharmaceutically acceptable adjuvant materials.

As will be evident from the foregoing, the 7-chloro- 2-methylamino- 5-phenyl- 3H-1,4-benzodiazepine 4-oxide ingredient can be present in the compositions in the form of the free base or in the form of a medicinally acceptable acid addition salt of the free base. Such salts include, for example, salts of the base with conventional medicinally acceptable inorganic acids (e.g. hydrochloric acid, sulphuric acid, phosphoric acid or nitric acid) and with conventional medicinally acceptable organic acids (e.g. benzoic acid, citric acid, malic acid, maleic acid, tartaric acid or salicyclic acid). The preferred compositions of the invention contain 7-chloro-2-methylamino-5-phenyl- 3H-1,4-benzodiazepine 4-oxide in the form of the free base.

Further, the 5-(3-dimethylamino-propylidene)-dibenzo[a,d]*cyclo*hepta[1,4]diene in-

[Price 4s. 6d.]

gredient can be present in the form of the free base or in the form of a medicinally acceptable acid addition salt of the free base. Examples of such salts are those with an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, sulphuric acid, nitric acid or phosphoric acid) or with an organic acid (e.g. acetic acid, benzoic acid, lactic acid, malic acid, maleic acid or salicyclic acid). The preferred compositions of the invention contain a medicinally acceptable acid addition salt of the base, more preferably 5-(3-dimethylamino- propylidene)- dibenzo[a,d] *cyclo*hepta[1,4]diene hydrochloride, as an active ingredient. When the 5-(3-dimethylamino- propylidene)- dibenzo[a,d]*cyclo*hepta [1,4]diene free base is used, it is, however, advisable first to make an adsorbate since the base is a liquid at room temperature.

The ratio of the active ingredients present in the compositions of this invention can be varied within rather wide limits. For example, in bulk dosage form the present compositions can contain a ratio of from 0.25 to 5.0 parts by weight of 5-3-dimethylamino- propylidene)- dibenzo[a,d]*cyclo*hepta [1,4]diene (or such amount of a medicinally acceptable acid addition salt thereof as will yield from 0.25 to 5.0 parts by weight of said diene) for each part by weight of 7-chloro-2-methylamino- 5-phenyl-3H-1,4-benzodiazepine4-oxide (or for such an amount of a medicinally acceptable acid addition salt thereof as will yield one part by weight of said oxide).

In unit dosage form, the compositions of this invention will generally contain 2.5 mg to 30 mg of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide or an equivalent amount of a medicinally acceptable acid addition salt thereof and from 2.5 mg to 75 mg of 5-(3-dimethylamino-propylidene)-dibenzo[a,d]*cyclo*hepta[1,4]diene or an equivalent amount of a medicinally acceptable acid addition salt thereof, with the proviso that in any such dosage form the weight of 5-(3-dimethylamino-propylidene)-dibenzo[a,d]*cyclo*hepta[1,4]diene or an equivalent quantity of the medicinally acceptable acid addition salt thereof is not less than 0.25 times or not more than 5.0 times the weight of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide ingredient. Preferred compositions of the invention in unit dosage form contain from 5.0 mg to 10 mg of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide and about 10 mg of 5-(3-dimethylamino-propylidene)-dibenzo[a,d]*cyclo*heptal[1,4]diene hydrochloride. Other preferred compositions of this invention contain either about 5 mg of 7-chloro- 2-methylamino- 5-phenyl- 3H-1,4-benzodiazepine 4-oxide and about 12.5 mg of 5-(3-dimethylamino-propylidene)-dibenzo [a,d]*cyclo*hepta[1,4] diene hydrochloride or about 10 mg of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide and about 25 mg of 5-(3-dimethylamino-propylidene)-dibenzo[a,d]*cyclo*hepta[1,4]diene hydrochloride. In the dosage forms aforesaid it is generally desirable to provide an excess (for example 2% or 3%) of the active ingredients.

The therapeutic compositions of this invention are readily manufactured by mixing together the active ingredients aforesaid. Alternatively, the active ingredients aforesaid can be mixed together in the presence of pharmaceutically acceptable adjuvant or excipient materials. In either case, the resulting compositions can be made up into suitable dosage forms (e.g. compressed or coated tablets for oral administration). Moreover, the compositions can be formulated into solutions, syrups or oily suspensions. In addition, the compositions of the invention can be provided in the form of hard shell capsules. If desired, the compositions of this invention can be made up into a dosage form suitable for parenteral administration. In general, the methods and techniques by which the various dosage forms are prepared are conventional procedures.

In formulating the compositions of this invention into the aforementioned dosage forms, one can use, as optional ingredients, any of the various adjuvants or excipients ordinarily employed in formulating pharmaceutical products. Thus, for example, where compositions of the invention are to be provided in the form of tablets, these optional ingredients include, for example, fillers such as, coprecipitated (aluminium hydroxide)/calcium carbonate), dicalcium phosphate and lactose, disintegrating agents such as, maize starch, lubricating agents such as talc or calcium stearate. On the other hand, where the compositions of this invention are to be provided in the form of solutions, syrups or suspensions in oil conventional adjuvants and excipients such as, for example, water, sugar syrup or vegetable oils (e.g. arachis oil), which may contain suitable edible suspending agents, sweetening agents and preservatives, are used.

In general, the frequency with which the compositions of this invention are administered will vary depending upon the amounts of the medicaments present therein and the needs and requirements of the patient as diagnosed by the prescribing physician. under ordinary circumstances, however, up to two tablets or capsules containing about 10.0 mg of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide or an equivalent amount of medicinally acceptable acid addition salt thereof and about 25.0 mg of 5-(3-dimethylamino- propylidene)- dibenzo[a,d]*cyclo*hepta[1,4]diene or an equivalent amount of a medicinally acceptable acid

addition salt thereof can be administered every six hours. On the other hand, up to two tablets or capsules containing about 5.0 mg of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide or an equivalent amount of a medicinally acceptable acid addition salt thereof and 12.5 mg of 5-(3-dimethylamino- propylidene)- dibenzo[a,d]*cyclo*hepta[1,4]diene or an equivalent amount of a medicinally acceptable acid addition salt thereof can be administered every three hours. In the case of children aged from 6 to 12 years or in the case of debilitated patients, less frequent administration of such tablets or capsules may be more appropriate. On the other hand, in the case of patients who are experiencing more severe symptoms of depression, more frequent administration of such tablets and capsules can be prescribed.

It will be appreciated from the foregoing that the therapeutic compositions of this invention are of widespread use in the treatment of depression whether simple, acute, psychoneurotic, chronic or involutional. The compositions have been found to be particularly effective in the treatment of patients showing symptoms of apathy, despondency, fatigue, agitation and restlessness. However, at the same time, such highly desirable results are achieved without unduly increasing the incidence of undesirable side effects. In fact, a definite decrease in side effects (for example, a noted decrease in sedation) has been noted when the active ingredients aforesaid are administered in combination.

The following Example, in which all parts are parts by weight unless otherwise stated, illustrate the invention:

Example 1

11.6 parts of 5-(3-dimethylamino-propylidene)-dibenzo[a,d]*cyclo*hepta[1,4]diene hydrochloride, 5.1 parts of 7-chloro-2-methylamino- 5-phenyl- 3H-1,4-benzodiazepine 4-oxide, 121.05 parts of dicalcium phosphate, 25.0 parts of microcrystalline cellulose, 16.0 parts of corn starch and 1.25 parts of calcium stearate were mixed in a suitable vessel. The mixture thus obtained was passed through a FITZPATRICK mill using a No. 1A screen, knives forward. The ground mixture was thereafter remixed and slugged, following which the slugs were passed through a FITZPATRICK mill using a No. 12 screen, knives forward, operating at a medium speed. The mixture was thereafter remixed and compressed at a tablet weight of 180 mg.

The tablets thus obtained contained 11.6 mg of 5-(3-dimethylamino-propylidene)-dibenzo[a,d]*cyclo*hepta [1,4]diene hydrochloride (equivalent to 10.0 mg of the free base with a 3% excess) and 5.1 mg (that is, 5.0 mg plus a 2% excess) of 7-chloro-2-methylamino- 5-phenyl- 3H-1,4-benzodiazepine 4-oxide.

Example 2

A mixture of 11.6 parts of 5-(3-dimethylamino- propylidene)- dibenzo[a,d]*cyclo*hepta [1,4]diene hydrochloride, 10.2 parts of 7-chloro-2-methylamino- 5-phenyl-3H-1,4-benzodiazepine 4-oxide, 115.95 parts of dicalcium phosphate, 25.0 parts of microcrystalline cellulose, 16.0 parts of corn starch and 0.625 parts of calcium stearate was passed through a FITZPATRICK mill using a No. 1A screen, knives forward. The ground mixture was subsequently remixed and slugged, following which the slugs were passed through a FITZPATRICK mill using a No. 12 mesh screen, knives forward, operating at medium speed. 0.625 Parts of calcium stearate were thereafter added to the mixture, which was then compressed at a tablet weight of 180 mg.

The tablets thus obtained contained 11.6 mg of 5-(3-dimethylamino-propylidene)-dibenzo[a,d]*cyclo*hepta[1,4]diene hydrochloride (equivalent to 10.0 mg of the base with a 3% excess) and 10.2 mg (that is 10.0 mg plus a 2% excess) of 7-chloro-2-methylamino- 5-phenyl- 3H-1,4-benzodiazepine 4-oxide.

Example 3

A mixture of 29.15 parts of 5-(3-dimethylamino-propylidene)- dibenzo[a,d]-*cyclo*hepta [1,4]diene hydrochloride, 10.2 parts of 7-chloro-2-methylamino- 5-phenyl-3H-1,4-benzodiazepine 4-oxide and 65.0 parts of corn starch was passed through a FITZPATRICK mill through a No. 00 screen using hammers. 143.65 Parts of dicalcium phosphate were subsequently added to the mixture, which was then passed once again through the FITZPATRICK mill using a No. 00 screen and hammers. The ground mixture was subsequently remixed and granulated with a 50% polyvinylpyrrolidone solution. While still wet, the granulate was passed through a FITZPATRICK mill using a No. 7 screen, knives forward, operating at a slow speed, then dried overnight at a temperature of about 110°F. When dry, the granulation was passed through a FITZPATRICK mill using a No. 14 screen, knives forward, operating at a medium speed. Thereafter, 2.0 parts of calcium stearate were added and the mixture was compressed at a tablet weight of 280 mg.

The tablets thus obtained contained 29.15 mg of 5-(3-dimethylamino-propylidene)-dibenzo[a,d]*cyclo*hepta [1,4]diene hydrochloride (equivalent to 25.0 mg of the base with a 3% excess) and 10.2 mg (that is, 10.0 mg plus a 2% excess) of 7-chloro-2-methylamino- 5-phenyl- 3H-1,4-benzodiazepine 4-oxide.

Example 4

A mixture of 14.57 parts of 5-(3-dimethylamino-propylidene)- dibenzo[a,d]*cyclo*hepta

[1,4]diene hydrochloride, 5.1 parts of 7-chloro-2-methylamino- 5-phenyl-3H-1,4-benzodiazepine 4-oxide, 33.0 parts of microcrystalline cellulose and 22.0 parts of corn starch was passed through a FITZPATRICK mill using a No. 000 screen. 143.83 Parts of corn starch were then added and the mixture was passed through a FITZPATRICK mill using a No. 1 screen, knives forward. When this operation was completed, 1.5 parts of calcium stearate were added to the mixture, which was then slugged and the slugs subsequently passed through a FITZPATRICK mill using a No. 12 screen, knife edges forward, operating at medium speed. The mixture obtained was remixed and compressed at a tablet weight of 220 mg.

The tablets thus obtained contained 14.57 mg of 5-(3-dimethylamino-propylidene)-dibenzo[a,d]*cyclo*hepta [1,4]diene hydrochloride (equivalent to 12.5 mg of base plus a 3% excess) and 5.1 mg (that is, 5.0 mg plus a 2% excess) of 7-chloro-2-methylamino- 5-phenyl- 3H-1,4-benzodiazepine 4-oxide.

Example 5

A mixture of 29.15 parts of 5-(3-dimethylamino- propylidene)- dibenzo[a,d]*cyclo*hepta [1,4]diene hydrochloride, 10.2 parts of 7-chloro-2-methylamino -5-phenyl-3H-1,4-benzodiazepine 4-oxide and 65.0 parts of corn starch was milled, 143.65 parts of dibasic calcium phosphate were added thereto, then the mixture was milled once again. The resulting powdery mixture was granulated by mixing with a solution comprising 30.0 parts of polyvinylpyrrolidone and 30.0 parts of *iso*propanol and the wet granulate was dried at a temperature of *ca* 110°F for a period of *ca* 16 hours. The dried granulate was milled, then 2.0 parts of calcium stearate were added thereto. After mixing, the granulation was compressed at a tablet weight of 280 mg using a 3/8 inch deep concave punch. The tablets thus prepared were coated with acacia syrup, dusted with calcium sulphate to a thickness of 4.95 mm and subsequently smooth coated with sugar syrup to a thickness of 5.05 mm. Colour syrup was then added to a thickness of 5.15 mm, following which the tablets were coated with carnauba wax.

The tablets, thus obtained contained 29.15 mg of 5-(3-dimethylamino-propylidene)-dibenzo[a,d]*cyclo*hepta [1,4]diene hydrochloride (equivalent to 25.0 mg of the base with a 3% excess) and 10.2 mg (that is, 10.0 mg plus 2% excess) of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide.

Example 6

A mixture of 29.15 parts of 5-(3-dimethylamino- propylidene)- dibenzo[a,d]*cyclo*hepta [1,4]diene hydrochloride, 10.20 parts of 7-chloro-2-methylamino- 5-phenyl-3H-1,4-benzodiazepine 4-oxide, 65.00 parts of corn starch and 163.65 parts of dicalcium phosphate was milled and 2.0 parts of calcium stearate were subsequently added thereto. The mixture was then filled into No. 3 hard shell, pharmaceutical grade gelatin capsules.

Each capsule thus obtained contained 29.15 mg of 5-(3-dimethylamino-propylidene)-dibenzo[a,d]*cyclo*hepta[1,4]diene hydrochloride (equivalent to 25.0 mg of the base plus a 3% excess) and 10.2 mg (that is, 10.0 mg plus a 2% excess) of 7-chloro-2-methylamino- 5-phenyl-3H-1,4-benzodiazepine 4-oxide.

It will be appreciated that the word 'about' is used in the foregoing description and in the following claims to mean that the amounts qualified thereby can be varied by up to and including ± 5% of the specified amounts.

WHAT WE CLAIM IS:—

1. A therapeutic composition containing as essential active ingredients (a) 7-chloro-2-methylamino- 5-phenyl-3H-1,4-benzodiazepine 4-oxide or a medicinally acceptable acid addition salt thereof and (b) 5-(3-dimethylamino- propylidene)- dibenzo[a,d] *cyclo*hepta[1,4]diene or a medicinally acceptable acid addition salt thereof.

2. A composition as set forth in claim 1, wherein pharmaceutically acceptable adjuvant or excipient material is also present.

3. A composition as set forth in claim 1 or claim 2, wherein from 0.25 to 5.0 parts by weight of 5-(3-dimethylamino-propylidene)-dibenzo[a,d]*cyclo*hepta[1,4] diene or an equivalent amount of a medicinally acceptable acid addition salt thereof are present for each part by weight of 7-chloro-2-methylamino- 5-phenyl-3H-1,4-benzodiazepine 4-oxide or equivalent amount of a medicinally acceptable acid addition salt thereof.

4. A composition as set forth in claim 3 in unit dosage form for oral administration, containing from 2.5 mg to 30 mg of 7-chloro-2-methylamino- 5-phenyl-3H-1,4-benzodiazepine 4-oxide or an equivalent amount of a medicinally acceptable acid addition salt thereof and from 2.5 to 75 mg of 5-(3-dimethylamino- propylidene)- dibenzo[a,d] *cyclo*hepta[1,4]diene or an equivalent amount of a medicinally acceptable acid addition salt thereof provided that the quantity of the 5-(3-dimethylamino-propylidene)- dibenzo[a,d]*cyclo*hepta[1,4]diene ingredient is not less than 0.25 times and not more than 5.0 times the weight of the 7-chloro-2-methylamino- 5-phenyl-3H-1,4-benzodiazepine 4-oxide ingredient.

5. A composition as set forth in any one of the preceding claims, wherein the essential active ingredients are 7-chloro-2-methylamino- 5-phenyl- 3H-1,4-benzodiazepine 4-oxide and 5-(3-dimethylamino-propylidene)-

[1,4]diene hydrochloride, 5.1 parts of 7-chloro-2-methylamino- 5-phenyl-3H-1,4-benzodiazepine 4-oxide, 33.0 parts of microcrystalline cellulose and 22.0 parts of corn starch was passed through a FITZPATRICK mill using a No. 000 screen. 143.83 Parts of corn starch were then added and the mixture was passed through a FITZPATRICK mill using a No. 1 screen, knives forward. When this operation was completed, 1.5 parts of calcium stearate were added to the mixture, which was then slugged and the slugs subsequently passed through a FITZPATRICK mill using a No. 12 screen, knife edges forward, operating at medium speed. The mixture obtained was remixed and compressed at a tablet weight of 220 mg.

The tablets thus obtained contained 14.57 mg of 5-(3-dimethylamino-propylidene)-dibenzo[a,d]*cyclo*hepta [1,4]diene hydrochloride (equivalent to 12.5 mg of base plus a 3% excess) and 5.1 mg (that is, 5.0 mg plus a 2% excess) of 7-chloro-2-methylamino- 5-phenyl- 3H-1,4-benzodiazepine 4-oxide.

Example 5

A mixture of 29.15 parts of 5-(3-dimethylamino- propylidene)- dibenzo[a,d]*cyclo*hepta [1,4]diene hydrochloride, 10.2 parts of 7-chloro-2-methylamino -5-phenyl-3H-1,4-benzodiazepine 4-oxide and 65.0 parts of corn starch was milled, 143.65 parts of dibasic calcium phosphate were added thereto, then the mixture was milled once again. The resulting powdery mixture was granulated by mixing with a solution comprising 30.0 parts of polyvinylpyrrolidone and 30.0 parts of *iso*propanol and the wet granulate was dried at a temperature of *ca* 110°F for a period of *ca* 16 hours. The dried granulate was milled, then 2.0 parts of calcium stearate were added thereto. After mixing, the granulation was compressed at a tablet weight of 280 mg using a 3/8 inch deep concave punch. The tablets thus prepared were coated with acacia syrup, dusted with calcium sulphate to a thickness of 4.95 mm and subsequently smooth coated with sugar syrup to a thickness of 5.05 mm. Colour syrup was then added to a thickness of 5.15 mm, following which the tablets were coated with carnauba wax.

The tablets, thus obtained contained 29.15 mg of 5-(3-dimethylamino-propylidene)-dibenzo[a,d]*cyclo*hepta [1,4]diene hydrochloride (equivalent to 25.0 mg of the base with a 3% excess) and 10.2 mg (that is, 10.0 mg plus 2% excess) of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide.

Example 6

A mixture of 29.15 parts of 5-(3-dimethylamino- propylidene)- dibenzo[a,d]*cyclo*hepta [1,4]diene hydrochloride, 10.20 parts of 7-chloro-2-methylamino- 5-phenyl-3H-1,4-benzodiazepine 4-oxide, 65.00 parts of corn starch and 163.65 parts of dicalcium phosphate was milled and 2.0 parts of calcium stearate were subsequently added thereto. The mixture was then filled into No. 3 hard shell, pharmaceutical grade gelatin capsules.

Each capsule thus obtained contained 29.15 mg of 5-(3-dimethylamino-propylidene)-dibenzo[a,d]*cyclo*hepta[1,4]diene hydrochloride (equivalent to 25.0 mg of the base plus a 3% excess) and 10.2 mg (that is, 10.0 mg plus a 2% excess) of 7-chloro-2-methylamino- 5-phenyl-3H-1,4-benzodiazepine 4-oxide.

It will be appreciated that the word 'about' is used in the foregoing description and in the following claims to mean that the amounts qualified thereby can be varied by up to and including ± 5% of the specified amounts.

WHAT WE CLAIM IS:—

1. A therapeutic composition containing as essential active ingredients (a) 7-chloro-2-methylamino- 5-phenyl-3H-1,4-benzodiazepine 4-oxide or a medicinally acceptable acid addition salt thereof and (b) 5-(3-dimethylamino- propylidene)- dibenzo[a,d] *cyclo*hepta[1,4]diene or a medicinally acceptable acid addition salt thereof.

2. A composition as set forth in claim 1, wherein pharmaceutically acceptable adjuvant or excipient material is also present.

3. A composition as set forth in claim 1 or claim 2, wherein from 0.25 to 5.0 parts by weight of 5-(3-dimethylamino-propylidene)-dibenzo[a,d]*cyclo*hepta[1,4] diene or an equivalent amount of a medicinally acceptable acid addition salt thereof are present for each part by weight of 7-chloro-2-methylamino- 5-phenyl-3H-1,4-benzodiazepine 4-oxide or equivalent amount of a medicinally acceptable acid addition salt thereof.

4. A composition as set forth in claim 3 in unit dosage form for oral administration, containing from 2.5 mg to 30 mg of 7-chloro-2-methylamino- 5-phenyl-3H-1,4-benzodiazepine 4-oxide or an equivalent amount of a medicinally acceptable acid addition salt thereof and from 2.5 to 75 mg of 5-(3-dimethylamino- propylidene)- dibenzo[a,d] *cyclo*hepta[1,4]diene or an equivalent amount of a medicinally acceptable acid addition salt thereof provided that the quantity of the 5-(3-dimethylamino-propylidene)- dibenzo[a,d]*cyclo*hepta[1,4]diene ingredient is not less than 0.25 times and not more than 5.0 times the weight of the 7-chloro-2-methylamino- 5-phenyl-3H-1,4-benzodiazepine 4-oxide ingredient.

5. A composition as set forth in any one of the preceding claims, wherein the essential active ingredients are 7-chloro-2-methylamino- 5-phenyl- 3H-1,4-benzodiazepine 4-oxide and 5-(3-dimethylamino-propylidene)-

dibenzo[a,d]*cyclo*hepta[1,4]diene hydrochloride.

6. A composition as set forth in claim 4 or claim 5, containing from 5 mg to 10 mg of 7-chloro-2-methylamino- 5-phenyl-3H-1,4-benzodiazepine 4-oxide and about 10 mg of 5-(3-dimethylamino- propylidene)- dibenzo [a,d]*cyclo*hepta[1,4]diene hydrochloride.

7. A composition as set forth in claim 4 or claim 5, containing about 10 mg of 7-chloro-2-methylamino-5- phenyl-3H-1,4-benzodiazepine 4-oxide and about 25 mg of 5-(3-dimethylamino- propylidene)- dibenzo [a,d]*cyclo*hepta[1,4]diene hydrochloride.

8. A composition as set forth in claim 4 or claim 5, containing about 5 mg of 7-chloro-2-methylamino- 5-phenyl-3H-1,4-benzodiazepine 4-oxide and about 12.5 mg of 5-(3-dimethylamino -propylidene)- dibenzo [a,d]*cyclo*hepta[1,4]diene hydrochloride.

9. A process for the manufacture of the therapeutic compositions as set forth in any one of the preceding claims, which process comprises mixing together 7-chloro-2-methylamino- 5-phenyl- 3H-1,4-benzodiazepine 4-oxide or a medicinally acceptable acid addition salt thereof and 5-(3-dimethylamino- propylidene)- dibenzo[a,d]*cyclo*hepta [1,4]diene or a medicinally acceptable acid addition salt thereof; said mixing being carried out in the presence of pharmaceutically acceptable adjuvant materials where required.

10. A process for the manufacture of a therapeutic composition as claimed in any one of claims 1 to 8 inclusive, substantially as described with reference to the foregoing Examples.

11. Therapeutic compositions as claimed in any one of claims 1 to 8 inclusive, when manufactured by the process claimed in claim 9 or claim 10.

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