Singapore

PATENT SPECIFICATION

NO DRAWINGS

1,028,745

1,028,745

Date of Application and filing Complete Specification June 17, 1963.
No. ~~240/9/63.~~ 24050/63.
Application made in United States of America (No. 207035) on July 2, 1962.
Complete Specification Published May 4, 1966.
© Crown Copyright 1966.

Index at acceptance: —A5 B(2S, 2Z)
Int. Cl.: —A 61 k 3/40

COMPLETE SPECIFICATION

Pharmaceutical Preparations Containing Corticosteroids

We, MERCK & Co., INC., a corporation duly organized and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, 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 is concerned with a combination of therapeutic agents for the treatment of corticoid-responsive syndromes.

In its broad concept the invention contemplates pharmaceutical preparations which contain both an anti-inflammatory corticosteroid and an agent which is active as an antiserotonin, *i.e.*, a serotonin antagonist (see Physiol. Rev., pp 277—334 (1958) at pages 308—313). A preferred steroid is dexamethasone and a ~~prefered~~ antiserotonin is cyproheptadine, but other agents having their respective therapeutic activities may be employed, as will be explained.

The importance of this combination resides in the discovery that the addition of the antiserotonin unexpectedly reduces the amount of the corticosteroid required to produce the desired therapeutic effect. The presence of the antiserotonin in the combination may be said to have a "steroid sparing" effect in that the same beneficial therapeutic effect is obtained with a smaller amount of steroid than would be required if the antiserotonin were absent.

The antiinflammatory corticosteroids have well recognized utility in a host of human ailments such as bronchial asthma and various allergies and dematoses but it is also known that their use often is accompanied with undesirable side reactions. The patient taking one of these steroids secures welcome relief from the principal ailment for which the steroid is indicated, but the undesirable physiological reactions which are elicited frequently are so severe that the dosage of the steroid has to be reduced to an insufficient amount. These adverse side reactions include adrenocortical insufficiency; protein catabolism with negative nitrogen balance, osteoporosis, activation and complications, including perforation and hemorrhage of peptic ulcer; aggrevation of infection; increased blood pressure, rounding of the face; ~~hirsutief~~; acne, abdominal ~~stiae~~; petechiae and purpura; amenorrhea; insomnia; and psychic disturbances.

For example, many dermatoses are not improved by any treatment other than with a steroid such as dexamethasone. The dermatoses which are particularly distressing are those which involve excessive itching such as dermatitis venenata, seborrheic dermatitis ~~reopens~~, erythema multiforme and purpitic pityriasis rosea. Although the antiinflammatory corticosteroids offer the therapeutic treatment of choice, the accompanying side effects are often intolerable as one or more of the adverse symptoms enumerated above will appear.

An important feature of the present combination is that it unexpectedly makes possible a reduction in the amount of steroid required and, thereby, a reduction or elimination of the side effects which otherwise would emerge. Although the antiserotonin to be administered with the steroid, in accordance with the present invention, is not a steroid itself, it exerts wnat may be called a steroid sparing phenomenon in that a smaller amount of the steroid can be administered than would be required if the steroid alone were administered.

The preferred anti-inflammtory corticosteroid is the known dexamethasone and especially its phosphate, but the invention contemplates as well cortisone, hydrocortisone, and their various known derivatives such as 9α - fluoro - 11β,17α - dihydroxyprogesterone, 9α - fluoro - 11 - keto - 17α - hydroxypro-

[Price 4s. 6d.]

gesterone, the Δ^1 analogs, such as 11β,17α,21-trihydroxy - 1,4 - pregnadiene - 3,20 - dione and its esters; the 2 - methyl derivatives such as 2 - methyl - 11β,17α,21 - trihydroxy-4 - pregnene - 3,20 - dione, 2 - methyl-11β,17α,21 - trihydroxy - 1,4 - pregnadiene - 3,20 - dione, 17α,21 - dihydroxy - 1,4 - pregnadiene - 3,11,20 - trione and their esters such as the acetates, hemisuccinates and the phosphates.

The preferred antiserotonin is cyproheptadine, i.e. 1 - methyl - 4 - (5 - dibenzo - [a,e]-cycloheptatrienylidene) - piperidine, which is disclosed and claimed in U.S. Patent No. 3014911 and the corresponding U.K. Patent 931555, but the other compounds covered by the patent may also be used.

If cyproheptadine and dexamethasone, which are the preferred ingredients, are to be compounded in tablet form, each tablet preferably would contain 4 mg. of cyproheptadine and 0.25 mg of the dexamethasone. However, the tablet could contain from 2 mg. to 6 mg. of cyproheptadine and from 0.15 to 0.50 mg. of dexamethasone. This same range and preferred amounts would apply if the ingredients were to be put up in capsule form.

If cyproheptadine and dexamethasone were to be made up in liquid form for use they should be in such concentration that one, two or three teaspoonful of the liquid would supply the active ingredients within the above range and preferably in the amounts stated to be preferred. In liquid form it would be desirable that the dexamethasone be present as the phosphate or acetate or other soluble therapeutic form.

These pharmaceutical tablets, capsules and liquids would be prepared by conventional manufacturing techniques. The usual flavouring agents and adjuncts would be added.

If instead of cyproheptadine, another one of the compounds claimed in U.S. Patent 3,014,911 is used, the same range of its use would be used. If instead of dexamethasone, another antiinflammatory steroid is substituted, the amount to be used would be based on its known activity relative to dexamethasone. Thus, if the substituted steroid is prednisone, which is about one-sixth as active as dexamethasone, six times as much of it would be ~~,ieu8it hovea chdtlsr 24f~~

The Examples which follow will serve to further illustrate the invention.

Example I

Compressed tablets are made as follows:

Ingredients Used	Weight for 100 Tablets
Dexamethasone	25.0 mg.
Cyproheptadine	400.0 mg.
Lactose Powder	14.3 gm.
Calcium Phosphate	3.2 gm.
Starch, Potato	2.0 gm.
Magnesium Strearate	150.0 gm.
Distilled water to Q.S. to granulate	

The dexamethasone, cyproheptadine, lactose powder, calcium phosphate and starch are combined and mixed together for 10 minutes, after which the material is put through a high speed comminutor and again mixed for 10 minutes. Enough water is added for granulation and the granulation is obtain by passage through a slow speed comminutor. The granulation is placed on a tray and dried at about 115° C. for about 10 hours. After again comminuting at a medium speed the magnesium stearate is added and the ingredients are mixed. The mixture is then compressed into 100 tablets so that each contain 0.25 mg. of dexamethasone and 4.0 mg. of cyproheptadine.

Example II

100 Tablets are made as in Example I but 200 mg. of cyproheptadine is used.

Example III

100 Tablets are made as in Example I but 600 mg. of ~~cyproheptadiene~~ is used.

Example IV

In like manner to that of the previous Examples, tablets containing more or less of the dexamethasone within the range 0.15 to 0.50 mg., are made.

An initial dosage would involve one tablet, three times a day, containing 0.25 mg. of dexamethasone and 4 mg. of cyproheptadine, and it would be increased or decreased according to the need of the patient as judged by the physician. Or the physician may elect to change to a tablet within the ranges defined above, having in mind that the smallest amount of dexamethasone administered over the day is to be established by observed titration of the patient. This enables the physician to take fullest advantage of the steroid sparing effect of the steroid-antiserotonin combination of the invention.

WHAT WE CLAIM IS:—

1. A pharmaceutical preparation in unit dosage form comprising an anti-inflammatory corticosteroid and an anti-serotonin, the

gesterone, the Δ^1 analogs, such as 11β,17α,21-trihydroxy - 1,4 - pregnadiene - 3,20 - dione and its esters; the 2 - methyl derivatives such as 2 - methyl - 11β,17α,21 - trihydroxy-4 - pregnene - 3,20 - dione, 2 - methyl-11β,17α,21 - trihydroxy - 1,4 - pregnadiene - 3,20 - dione, 17α,21 - dihydroxy - 1,4 - pregnadiene - 3,11,20 - trione and their esters such as the acetates, hemisuccinates and the phosphates.

The preferred antiserotonin is cyproheptadine, i.e. 1 - methyl - 4 - (5 - dibenzo - [a,e]-cycloheptatrienylidene) - piperidine, which is disclosed and claimed in U.S. Patent No. 3014911 and the corresponding U.K. Patent 931555, but the other compounds covered by the patent may also be used.

If cyproheptadine and dexamethasone, which are the preferred ingredients, are to be compounded in tablet form, each tablet preferably would contain 4 mg. of cyproheptadine and 0.25 mg of the dexamethasone. However, the tablet could contain from 2 mg. to 6 mg. of cyproheptadine and from 0.15 to 0.50 mg. of dexamethasone. This same range and preferred amounts would apply if the ingredients were to be put up in capsule form.

If cyproheptadine and dexamethasone were to be made up in liquid form for use they should be in such concentration that one, two or three teaspoonful of the liquid would supply the active ingredients within the above range and preferably in the amounts stated to be preferred. In liquid form it would be desirable that the dexamethasone be present as the phosphate or acetate or other soluble therapeutic form.

These pharmaceutical tablets, capsules and liquids would be prepared by conventional manufacturing techniques. The usual flavouring agents and adjuncts would be added.

If instead of cyproheptadine, another one of the compounds claimed in U.S. Patent 3,014,911 is used, the same range of its use would be used. If instead of dexamethasone, another antiinflammatory steroid is substituted, the amount to be used would be based on its known activity relative to dexamethasone. Thus, if the substituted steroid is prednisone, which is about one-sixth as active as dexamethasone, six times as much of it would be ~~,ieu8it hovea chdtlsr 24f~~

The Examples which follow will serve to further illustrate the invention.

EXAMPLE I

Compressed tablets are made as follows:

Ingredients Used	Weight for 100 ~~Tablets~~
Dexamethasone	25.0 mg.
Cyproheptadine	400.0 mg.
Lactose Powder	14.3 gm.
Calcium Phosphate	3.2 gm.
Starch, Potato	2.0 gm.
Magnesium Strearate	2.0 gm.
Distilled water to Q.S. to granulate	150.0 gm.

The dexamethasone, cyproheptadine, lactose powder, calcium phosphate and starch are combined and mixed together for 10 minutes, after which the material is put through a high speed comminutor and again mixed for 10 minutes. Enough water is added for granulation and the granulation is obtain by passage through a slow speed comminutor. The granulation is placed on a tray and dried at about 115° C. for about 10 hours. After again comminuting at a medium speed the magnesium stearate is added and the ingredients are mixed. The mixture is then compressed into 100 tablets so that each contain 0.25 mg. of dexamethasone and 4.0 mg. of cyproheptadine.

EXAMPLE II

100 Tablets are made as in Example I but 200 mg. of cyproheptadine is used.

EXAMPLE III

100 Tablets are made as in Example I but 600 mg. of ~~cyproheptadiene~~ is used.

EXAMPLE IV

In like manner to that of the previous Examples, tablets containing more or less of the dexamethasone within the range 0.15 to 0.50 mg., are made.

An initial dosage would involve one tablet, three times a day, containing 0.25 mg. of dexamethasone and 4 mg. of cyproheptadine, and it would be increased or decreased according to the need of the patient as judged by the physician. Or the physician may elect to change to a tablet within the ranges defined above, having in mind that the smallest amount of dexamethasone administered over the day is to be established by observed titration of the patient. This enables the physician to take fullest advantage of the steroid sparing effect of the steroid-antiserotonin combination of the invention.

WHAT WE CLAIM IS:—

1. A pharmaceutical preparation in unit dosage form comprising an anti-inflammatory corticosteroid and an anti-serotonin, the

* C L M S *

steroid being present in a smaller amount than would be required to produce a desired therapeutic effect if the anti-serotonin were absent.

2. A pharmaceutical preparation in unit dosage form comprising dexamethasone and cyproheptadine, the dexamethasone being present in a smaller amount than would be required to produce a desired therapeutic effect if the anti-serotonin were absent.

3. A pharmaceutical preparation in unit dosage form comprising from 0.15 to 0.50 mg. of dexamethasone and from 2 to 6 mg. of cyproheptadine.

4. A pharmaceutical preparation in unit dosage form comprising 0.25 mg. of dexamethasone and from 2 to 6 mg. of cyroheptadine.

5. A pharmaceutical preparation of unit dosage form comprising 0.25 mg. of dexamethasone and 4 mg. of cyproheptadine.

6. A pharmaceutical preparation as claimed in any one of claims 1—5, in the form of a tablet, liquid, or capsule.

7. A pharmaceutical preparation substantially as hereinbefore described with reference to any one of the foregoing Examples.

For the Applicants,
D. YOUNG & CO.,
Chartered Patent Agents,
9, Staple Inn, London, W.C.1.

Leamington Spa: Printed for Her Majesty's Stationery Office by the Courier Press.—1966.
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2. from which copies may be obtained.

20 SEP 1967

I CERTIFY THOSE TO BE A TRUE COPY OF THE SPECIFICATION AS ACCEPTED.

21/9/67

ACTING FOR COMPTROLLER,
THE PATENT OFFICE,
25 Southampton Buildings, London, W.C.2.

* C L M S *