936,501

PATENT SPECIFICATION

NO DRAWINGS

936,501

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International Classification:—A61k.

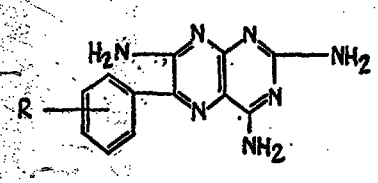
COMPLETE SPECIFICATION

Improvements in or relating to Novel Diuretic Compositions

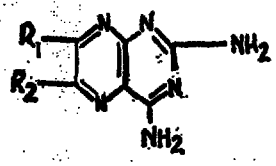
We, SMITH KLINE & FRENCH LABORATORIES, of 1500 Spring Garden City, City of Philadelphia, Zone 1, Commonwealth of Pennsylvania, United States of America, a corporation organized under the laws of the Commonwealth of Pennsylvania, one of the United States of America, do hereby declare the invention, for 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 relates to novel pharmaceutical compositions having diuretic or hypotensive activity.

In our specification No. 932,256 (to which the present application is an addition) there is described and claimed a pharmaceutical composition adapted for oral or parenteral administration having diuretic activity containing either a compound having the formula:

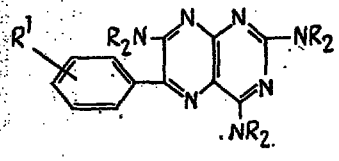


in which R is hydrogen, lower alkyl, lower alkoxyl or halogen, or a compound having the formula:

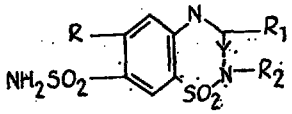


in which R_1 and R_2 are hydrogen, methyl or ethyl, in association with one or more pharmaceutical carriers therefor.

According to the present invention there is provided a pharmaceutical composition having diuretic or hypotensive activity, in dosage unit form, comprising a pteridine compound having the basic formula:



in which R is a lower alkyl having not in excess of 3 carbon atoms or hydrogen and R^1 is hydrogen, a lower alkyl having not in excess of 3 carbon atoms, trifluoromethyl, halo or a lower alkoxy having not in excess of 3 carbon atoms and a thiazide compound having the basic formula:



in which R is fluoro, chloro or trifluoromethyl, Y is a single or double bond, R_1 is hydrogen, dichloromethyl, monochloromethyl, benzylmercaptomethyl or benzyl and R_2 is hydrogen or a lower alkyl having not in excess of 3 carbon atoms.

It has been observed that one of the major drawbacks of the orally effective diuretic, in particular the thiazide type of diuretic is that there is an enhancement of potassium excreted. This excess potassium loss is the cause of fatigue and mental confusion, side effects observed when these diuretics are administered.

The novel diuretic compositions of this invention which comprise a mixture of 2,4,7-triamino-6-arylpteridines, particularly the 2,4,7-triamino-6-phenylpteridines and a thiazide diuretic unexpectedly restrict the loss

[Price 4s. 6d.]

of potassium caused by the thiazide-like diuretics and eliminate the side effects such as fatigue and mental confusion.

In accordance with this invention it has also been surprisingly discovered that the 2,4,7-triamino - 6 - arylpteridines and the thiazide diuretics act synergistically in the compositions of this invention. Thus the diuretic effect of the composition was found to be consistently greater than might be expected from a mere summation of the diuretic effects due to the two classes of diuretics, pteridine and thiazide, when used individually in a dosage equal to the sum of the dosages of the said two different classes of diuretics. The diuretic effect was also found to be consistently greater than the effect obtained when either of the two classes of diuretics, pteridine and thiazide were used alone in a dosage equal to the sum of the dosages of the two different classes of diuretics in the composition.

Exemplary of the thiazide derivatives which may be used are chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, benzoylflumethiazide, trichloromethiazide, or benzthiazide ("Urese"), or methyclothiazide.

Advantageously the pteridine ingredients are those represented by Formula I in which R_2 is hydrogen and R_1 is hydrogen, a lower alkyl group having not in excess of 3 carbon atoms, preferably methyl, a lower alkoxy group having not in excess of 3 carbon atoms, preferably methoxy, or halogen and the thiazide ingredients are those represented by Formula II in which R is fluoro, chloro or trifluoromethyl, Y is a single or double bond and R_1 is hydrogen dichloromethyl, monochloromethyl, benzylmercaptomethyl or benzyl and R_2 is methyl or hydrogen together with a pharmaceutical carrier.

Most advantageously the pharmaceutical composition of this invention in dosage unit form comprises 2,4,7 - triamino - 6 - phenylpteridine and a thiazide compound selected from those generically referred to as chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, benzydroflumethiazide (3-benzyl - 3,4 - dihydro - 6 - trifluoromethyl-7 - sulfamyl - 1,2,4 - benzothiadiazine - 1,1-dioxide), methyclothiazide (6 - chloro -3-chloromethyl - 2 - methyl - 7 - sulfamyl-3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1-dioxide), trichloro methiazide (3 - dichloromethyl - 6 - chloro - 7 - sulfamyl - 3,4-dihydro - 1,2,4 - benzothiadiazine - 1,1-dioxide) or benzthiazide (6 - chloro - 3-benzylmercaptomethyl - 7 - sulphonyl - 1,2,4-benzothiadiazine - 1,1 - dioxide) combined with a nontoxic pharmaceutical carrier.

Advantageously the triaminopteridines and thiazides as represented by the above formulae will be administered in a preparation comprising a pharmaceutical carrier and will be present in an amount to produce diuresis and/or blood pressure lowering (hypotension) in the animal organism. Preferably the preparation will contain the triaminopteridine in an amount of from 5 mg. to 250 mg., advantageously from 10 mg. to 100 mg., per dosage unit. The thiazide component is present in the preparation preferably in an amount of from about 1 mg. to about 500 mg., advantageously from about 2 mg. to about 250 mg. per dosage unit depending on the potency of the thiazide component.

These compositions when administered orally one to four times a day have been found to give an enhanced diuretic activity over the individual doses of the pteridine or thiazide components. Alternatively the dosage units can be combined in sustained release form as desired to be administered orally once or twice daily.

The pharmaceutical carrier may be, for example, either a solid or a liquid. Exemplary of solid carriers are lactose, magnesium stearate, terra alba, sucrose, talc, stearic acid, gelatin, agar, pectin or acacia. Exemplary of liquid carriers are peanut oil, olive oil, sesame oil and water. Similarly, the carrier or diluent may include a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tabletted, placed in a hard gelatin capsule or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg. to about 1 gm. If a liquid carrier is used, the preparation may be in the form of a soft gelatin capsule or a liquid suspension.

In veterinary practice, the compositions can be given *per se* or as an additive to the feed or drinking matter of the animals. These compositions are made following the conventional techniques of the pharmaceutical chemist involving mixing, granulating and compressing when necessary or variously mixing and dissolving the ingredients as appropriate to the desired end product. Exemplary of clinical conditions which may be treated with these compositions are hypertension in dogs, gut edema in swine and udder edema in cows.

The following examples are not limiting but are illustrative of the novel pharmaceutical compositions of this invention.

EXAMPLE 1

Ingredients	Amounts
2,4,7-Triamino-6-phenylpteridine	5 mg.
Hydrochlorothiazide	25 mg.
Calcium Sulfate, Dihydrate	125 mg.
Sucrose	25 mg.
Starch	15 mg.
Talc	5 mg.
Stearic Acid	3 mg.

benzydroflumethiazide

The sucrose, calcium sulfate 2,4,7-triamino-6-phenyypteridine and hydrochlorothiazide, are thoroughly mixed and granulated with hot 10% gelatin solution. The wetted mass is passed through a No. 6 mesh screen directly onto drying trays. The granules are dried at 120° F. and passed through a No. 20 mesh screen. These granules are then mixed with the starch, talc and stearic acid, passed through a No. 60 mesh screen and then compressed into tablets.

EXAMPLE 2

Ingredients	Amounts
2,4,7-Triamino-6-phenylpteridine	10 mg.
Flumethiazide	500 mg.
Magnesium Stearate	5 mg.
Lactose	50 mg.

Screen the ingredients, mix and fill into a No. 0 hard gelatin capsule. Three capsules are administered orally to an edematous patient daily.

EXAMPLE 3

Ingredients	Amounts
2,4,7-Triamino-6-phenylpteridine	25 mg.
Trichloromethiazide	2 mg.
Magnesium Stearate	5 mg.
Lactose	320 mg.

The ingredients are screened and filled into a No. 1 capsule. Four capsules are administered daily.

EXAMPLE 4

Ingredients	Amounts
2,4,7-Triamino-6-phenylpteridine	100 mg.
Hydroflumethiazide	100 mg.
Lactose	150 mg.

The ingredients are mixed and filled into a hard gelatin capsule then administered orally twice a day.

EXAMPLE 5

Ingredients	Amounts
2,4,7-Triamino-6-phenylpteridine	75 mg.
Benzthiazide	50 mg.
Lactose	75 mg.

The ingredients are mixed and filled into a hard gelatin capsule then administered orally twice a day.

EXAMPLE 6

Ingredients	Amounts
2,4,7-Triamino-6-phenylpteridine	25 mg.
Benzydroflumethiazide	5 mg.
Magnesium Stearate	5 mg.
Lactose	300 mg.

The ingredients are mixed and filled into a hard gelatin capsule then administered orally three times a day.

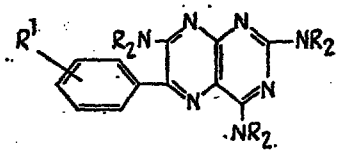
EXAMPLE 7

Ingredients	Amounts
2,4,7-Triamino-6-phenylpteridine	10 mg.
Methyclothiazide	2.5 mg.
Talc.	150 mg.

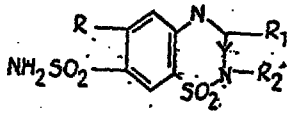
The ingredients are mixed, screened and filled into capsules, then administered orally to edematous patients b.i.d.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition having diuretic or hypotensive activity, in dosage unit form, comprising a pteridine compound having the basic formula:



in which R is a lower alkyl having not in excess of 3 carbon atoms or hydrogen and R^1 is hydrogen, a lower alkyl having not in excess of 3 carbon atoms, trifluoromethyl, halo or a lower alkoxy having not in excess of 3 carbon atoms and a thiazide compound having the basic formula:



in which R is fluoro, chloro or trifluoromethyl, Y is a single or double bond, R_1 is hydrogen, dichloromethyl, monochloromethyl, benzylmercaptomethyl or benzyl and R_2 is hydrogen or a lower alkyl having not in excess of 3 carbon atoms.

2. A pharmaceutical composition as set forth in Claim 1 in which pteridine compound is 2,4,7-triamino-6-phenylpteridine.

3. A pharmaceutical composition as set forth in Claims 1 or 2 in which the pteridine compound is present in an amount of from 5 mg. to 250 mg., preferably from 10 mg. to 100 mg., per dosage unit and the thiazide compound is present in an amount from 1 mg. to 500 mg., preferably from about 2 mg. to about 250 mg., per dosage unit.

4. A pharmaceutical composition as set forth in any of Claims 1 to 3 in which the thiazide compound is chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, benzydroflumethiazide, trichloromethiazide, benzthiazide or methyclothiazide.

The sucrose, calcium sulfate 2,4,7-triamino-6-phenyypteridine and hydrochlorothiazide, are thoroughly mixed and granulated with hot 10% gelatin solution. The wetted mass is passed through a No. 6 mesh screen directly onto drying trays. The granules are dried at 120° F. and passed through a No. 20 mesh screen. These granules are then mixed with the starch, talc and stearic acid, passed through a No. 60 mesh screen and then compressed into tablets.

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2,4,7-Triamino-6-phenylpteridine	10 mg.
Flumethiazide	500 mg.
Magnesium Stearate	5 mg.
Lactose	50 mg.

Screen the ingredients, mix and fill into a No. 0 hard gelatin capsule. Three capsules are administered orally to an edematous patient daily.

EXAMPLE 3

Ingredients	Amounts
2,4,7-Triamino-6-phenylpteridine	25 mg.
Trichloromethiazide	2 mg.
Magnesium Stearate	5 mg.
Lactose	320 mg.

The ingredients are screened and filled into a No. 1 capsule. Four capsules are administered daily.

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Ingredients	Amounts
2,4,7-Triamino-6-phenylpteridine	100 mg.
Hydroflumethiazide	100 mg.
Lactose	150 mg.

The ingredients are mixed and filled into a hard gelatin capsule then administered orally twice a day.

EXAMPLE 5

Ingredients	Amounts
2,4,7-Triamino-6-phenylpteridine	75 mg.
Benzthiazide	50 mg.
Lactose	75 mg.

The ingredients are mixed and filled into a hard gelatin capsule then administered orally twice a day.

EXAMPLE 6

Ingredients	Amounts
2,4,7-Triamino-6-phenylpteridine	25 mg.
Benzydroflumethiazide	5 mg.
Magnesium Stearate	5 mg.
Lactose	300 mg.

The ingredients are mixed and filled into a hard gelatin capsule then administered orally three times a day.

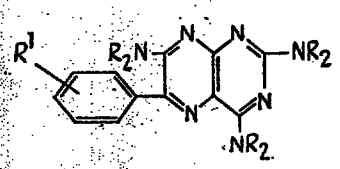
EXAMPLE 7

Ingredients	Amounts
2,4,7-Triamino-6-phenylpteridine	10 mg.
Methyclothiazide	2.5 mg.
Talc.	150 mg.

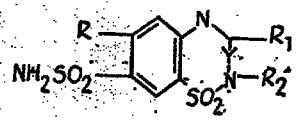
The ingredients are mixed, screened and filled into capsules, then administered orally to edematous patients b.i.d.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition having diuretic or hypotensive activity, in dosage unit form, comprising a pteridine compound having the basic formula:



in which R is a lower alkyl having not in excess of 3 carbon atoms or hydrogen and R^1 is hydrogen, a lower alkyl having not in excess of 3 carbon atoms, trifluoromethyl, halo or a lower alkoxy having not in excess of 3 carbon atoms and a thiazide compound having the basic formula:



in which R is fluoro, chloro or trifluoromethyl, Y is a single or double bond, R_1 is hydrogen, dichloromethyl, monochloromethyl, benzylmercaptomethyl or benzyl and R_2 is hydrogen or a lower alkyl having not in excess of 3 carbon atoms.

2. A pharmaceutical composition as set forth in Claim 1 in which pteridine compound is 2,4,7-triamino-6-phenylpteridine.

3. A pharmaceutical composition as set forth in Claims 1 or 2 in which the pteridine compound is present in an amount of from 5 mg. to 250 mg., preferably from 10 mg. to 100 mg., per dosage unit and the thiazide compound is present in an amount from 1 mg. to 500 mg., preferably from about 2 mg. to about 250 mg., per dosage unit.

4. A pharmaceutical composition as set forth in any of Claims 1 to 3 in which the thiazide compound is chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, benzydroflumethiazide, trichloromethiazide, benzthiazide or methyclothiazide.

5. A pharmaceutical composition as set forth in any preceding claim, wherein the active ingredients are in association with a pharmaceutical carrier.

6. A pharmaceutical composition substantially as hereinbefore described with reference to any one of Examples 1 to 7.

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