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(19)

(54) PHARMACEUTICAL COMPOSITIONS CONTAINING BISCHROMONYLOXY COMPOUNDS

(71) We, FISONS LIMITED, a British Company, of Fison House, 9 Grosvenor Street, London, W.1, 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 concerns pharmaceutical compositions.

In our British Patent No. 1,144,905 there are described and claimed certain substituted bis-chromonyl compounds and compositions containing them which may be administered orally, parenterally or by inhalation in the treatment of various conditions, including asthma.

We have now found that certain of the compounds and compositions claimed in British Patent No. 1,144,905 are surprisingly of use in the treatment in man of disorders of the gastro-intestinal tract, in which disorders allergic or immune reactions play a contributory part.

Accordingly, this invention provides a composition for the administration of 1,3 - bis(2 - carboxychromon - 5 - yloxy)propan - 2 - ol or a pharmaceutically acceptable salt, alkyl C 1 to 10 ester, or a mono- or di-alkyl C 1 to 10 amide or an unsubstituted amide thereof to a patient having such a disorder of the gastro-intestinal tract, the composition being in the form of a tablet; a dragee; a powder (other than a powder wherein the active ingredient has an effective particle size, as measured by Coulter counter, under 10 microns); a sterile solution or suspension other than one in water containing a concentration of active ingredient of 0.5% by weight or less); a syrup; or a suppository.

Suitable pharmaceutically acceptable salts include, for example, ammonium, alkali metal (e.g. sodium, potassium and lithium); alkaline earth metal (e.g. magnesium and calcium), and amine (e.g. mono- di- or tri-alkyl C 1 to 6 amine, piperadine, and trialkanol C 1 to 6 amine) salts. Esters which may be mentioned include the di-ethyl ester and suitable amides include the di-ethyl amide.

Where the composition takes the form of a syrup, solution, suspension or powder, it may conveniently be presented contained in a hard or soft capsule as appropriate.

Where the condition affects the rectum, administration may be by way of suppository, enema or other conventional vehicle for administration to the rectum. Where the condition affects another part of the gastro-intestinal tract then administration may be oesphageally.

In order to produce suitable compositions the drug is worked up with suitable inorganic or organic pharmaceutically acceptable adjuvants or excipients. Examples of such adjuvants are:

for tablets or dragees: binders, for example cellulosic materials, e.g. microcrystalline cellulose and methyl cellulose; disintegrating agents, for example starches, e.g. maize starch; stabilisers, e.g. against hydrolysis of the active ingredients; flavouring agents, for example sugars such as lactose; fillers; stearates; and inorganic diluents, e.g. talc,

for syrups, suspensions or dispersions: a liquid vehicle in which the active ingredient may be dissolved or suspended, e.g. water; and suspending agents, e.g. cellulose derivatives, gums etc.,

for powders: diluents, e.g. lactose; glidants, e.g. stearates; inorganic materials, e.g. silica or talc; stabilisers and dispersing agents and

for suppositories: natural or hardened oils, waxes etc.

The composition may also contain further adjuvants, for example a composition for forming tablets may contain lubricants and glidants to assist in tabletting, e.g. magnesium stearate, or wetting agents to assist in granulation, e.g. dioctyl sodium sulphosuccinate. The composition may also if desired contain a pharmaceutically acceptable dye or colourant, and may, if desired, be coated using conventional film or sugar coating techniques.

If desired the composition may be formulated in sustained release form using techniques *per se* or as an enteric coated composition to make the drug available at the

appropriate part of the gastro-intestinal tract.

The active ingredient may alternatively be formulated as an aqueous or predominantly aqueous (e.g. a water: chloroform (400:1)) solution containing from 0.001 to 0.01% by weight of the active ingredient.

The dosage to be administered will of course vary with the condition to be treated with its severity and with its location. However in general a unit dosage form of from about 20 to 250, preferably of 20 to 100 (e.g. of 25 to 35) mg of the drug administered 2 to 4 times a day (i.e. a daily dosage of 40 to 1,000 mg) is found to be satisfactory. The administration preferably takes place about 30 minutes before the patient takes food.

Conditions which may be treated by the compositions of the invention include Crohn's disease (a condition of the small, and sometimes also of the large, intestine), atrophic gastritis (a condition of the stomach, ulcerative colitis (a condition of the rectum), coeliac disease (a condition of the small intestine), and peptic ulceration (a condition of the stomach and duodenum).

WHAT WE CLAIM IS:—

1. A composition for the administration of 1,3 - bis(2 - carboxychromon - 5 - yloxy)-propan - 2 - ol or a pharmaceutically acceptable salt, alkyl C 1 to 10 ester, or a mono- or di-alkyl C 1 to 10 amide or an unsubstituted amide thereof to a patient having a disorder of the gastro-intestinal tract, the composition comprising the active ingredient in association with a pharmaceutically acceptable diluent, carrier or excipient and being in the form of a tablet, a dragee, a syrup or a suppository.

2. A composition suitable for the administration of 1,3 - bis(2 - carboxychromon - 5 - yloxy)propan - 2 - ol or a pharmaceutically acceptable salt, alkyl C 1 to 10 ester, or a mono- or di-alkyl C 1 to 10 amide or an unsubstituted amide thereof to a patient having a disorder of the gastro-intestinal tract, the composition being in the form of a powder (other than a powder wherein the active ingredient has an effective particle size, as measured by Coulter Counter, under 10 microns), or a sterile solution or suspension (other than one in water containing a concentration of active ingredient of 0.5% by weight or less).

3. A composition as claimed in either of claim 1 or claim 2 in the form of a syrup, solution, suspension or powder, contained in a hard or soft capsule.

4. A composition as claimed in any of claims 1 to 3 in a sustained release or enteric coated solid form.

5. A composition for the administration of 1,3 - bis(2 - carboxychromon - 5 - yloxy)-propan - 2 - ol or a pharmaceutically acceptable salt, alkyl C 1 to 10 ester, or a mono- or di-alkyl C1 to 10 amide or an unsubstituted amide thereof to a patient having a disorder of the gastro-intestinal tract, in unit dosage form containing from 20 to 250 mg of active ingredient.

6. A composition as claimed in claim 5 containing from 20 to 100 mg of active ingredient.

7. A composition as claimed in claim 6 containing from 25 to 35 mg of active ingredient.

8. A composition as claimed in any of claims 1 to 7, wherein the pharmaceutically acceptable salt is an ammonium, alkali metal, alkaline earth metal or amine salt.

9. A composition as claimed in claim 8, wherein the pharmaceutically acceptable salt is the di-sodium salt.

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Reference has been directed in pursuance of Section 9, subsection (1) of the Patents Act, 1949 to Patent No. 1,144,905.

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The dosage to be administered will of course vary with the condition to be treated with its severity and with its location. However in general a unit dosage form of from about 20 to 250, preferably of 20 to 100 (e.g. of 25 to 35) mg of the drug administered 2 to 4 times a day (i.e. a daily dosage of 40 to 1,000 mg) is found to be satisfactory. The administration preferably takes place about 30 minutes before the patient takes food.

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1. A composition for the administration of 1,3 - bis(2 - carboxychromon - 5 - yloxy)-propan - 2 - ol or a pharmaceutically acceptable salt, alkyl C 1 to 10 ester, or a mono- or di-alkyl C 1 to 10 amide or an unsubstituted amide thereof to a patient having a disorder of the gastro-intestinal tract, the composition comprising the active ingredient in association with a pharmaceutically acceptable diluent, carrier or excipient and being in the form of a tablet, a dragee, a syrup or a suppository.

2. A composition suitable for the administration of 1,3 - bis(2 - carboxychromon - 5 - yloxy)propan - 2 - ol or a pharmaceutically acceptable salt, alkyl C 1 to 10 ester, or a mono- or di-alkyl C 1 to 10 amide or an unsubstituted amide thereof to a patient having a disorder of the gastro-intestinal tract, the composition being in the form of a powder (other than a powder wherein the active ingredient has an effective particle size, as measured by Coulter Counter, under 10 microns), or a sterile solution or suspension (other than one in water containing a concentration of active ingredient of 0.5% by weight or less).

3. A composition as claimed in either of claim 1 or claim 2 in the form of a syrup, solution, suspension or powder, contained in a hard or soft capsule.

4. A composition as claimed in any of claims 1 to 3 in a sustained release or enteric coated solid form.

5. A composition for the administration of 1,3 - bis(2 - carboxychromon - 5 - yloxy)-propan - 2 - ol or a pharmaceutically acceptable salt, alkyl C 1 to 10 ester, or a mono- or di-alkyl C1 to 10 amide or an unsubstituted amide thereof to a patient having a disorder of the gastro-intestinal tract, in unit dosage form containing from 20 to 250 mg of active ingredient.

6. A composition as claimed in claim 5 containing from 20 to 100 mg of active ingredient.

7. A composition as claimed in claim 6 containing from 25 to 35 mg of active ingredient.

8. A composition as claimed in any of claims 1 to 7, wherein the pharmaceutically acceptable salt is an ammonium, alkali metal, alkaline earth metal or amine salt.

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