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(54) STERILE INJECTABLE SOLUTIONS OF PYRITINOL SALTS

(71) We, MERCK PATENT GESELLSCHAFT MIT BESCHRANKTER HAFTUNG, a German body corporate, of 61 Darmstadt, Frankfurter Strasse 250, Germany, 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 sterile injectable aqueous solutions of pyritinol salts.

Pyritinol, which is bis - (3 - hydroxy - 4 - hydroxymethyl - 2 - methyl - pyridyl - (5) methyl)-disulphide, is a drug which is administered both orally and parenterally as an aqueous solution of a salt thereof, particularly its dihydrochloride monohydrate (pyrithioxine) or sulphate. The usual dose is approximately 150 to 200 mg. Before infusion, the dosage solution is generally diluted to at least 20 ml volume, preferably 250 to 500 ml, using a suitable infusion fluid such as physiological saline solution or glucose solution.

Although the physiologically acceptable salts of pyritinol are soluble in water, it is not easy to prepare stable aqueous solutions thereof. Thus, when stored in ampoules, ordinary aqueous solutions show perceptable turbidity after 4 to 6 weeks and progressive crystalline deposition occurs after longer storage, with the result that the preparations are then unsuitable for parenteral administration, particularly for intravenous injections or infusions. Hitherto, therefore, it has been necessary, in the parenteral administration of pyritinol salts, to manufacture lyophilised dry amopules from which the aqueous injectable solution could be prepared shortly before use. Dry ampoules, however, have a number of disadvantages. They are more difficult to make and more complicated to use.

We have now found that stable solutions of physiologically acceptable salts of pyritinol can be made by including in the solutions certain organic acids and amines, in particular nitrogen-heterocyclic compounds.

According to the invention, there is provided a sterile injectable aqueous solution which comprises a physiologically acceptable salt of pyritinol, from 0.1 to 25% by weight of one or more physiologically acceptable organic acids each containing from 1 to 6 carbon atoms and from 0.1 to 25% by weight of one or more physiologically acceptable amines or physiologically acceptable salts thereof.

The organic acids are preferably present in an amount from 3 to 20% by weight. Suitable acids include monocarboxylic acids such as formic acid, dicarboxylic acids such as malonic acid or adipic acid, hydroxy acids such as lactic acid, tartaric acid, citric acid, and glutamic acid, and enol compounds such as ascorbic acid. Other lower fatty acids such as acetic acid can also be used, but their smell is a disadvantage. One, two or more organic acids may be present in the solution.

The amine(s) is/are preferably present in an amount from 0.2 to 3% by weight. Suitable amines are, in particular, N-heterocyclic compounds, especially those containing a pyridine or pyrimidine ring, and diethanolamine. It is preferred to select the heterocyclic compound from vitamin B_1, vitamin B_6, 1 - benzyl - 3 - ethyl - 6,7 - dimethodxy - isoquinoline, the physiologically acceptable acid addition salts of these three, and nicotinamide. Suitable acid addition salts include vitamin B_1 dihydrochloride, vitamin B_6 hydrochloride and eupaverine

hydrochloride. Vitamin B_6 hydrochloride (pyridoxine hydrochloride) is particularly preferred.

Functional derivatives of these N-heterocyclic compounds can also be used. For example, the acyl derivatives of vitamin B_1, pyridoxal or pyridoxamine are suitable and are preferably used in the form of one of their physiologically acceptable acid addition salts, particularly the hydrochlorides.

If necessary, the pH of the solutions of the invention can be adjusted by adding an amount of a strong base, such as sodium or potassium hydroxide; the solutions preferably have a pH of from 2.1 to 3.0. The solutions can also contain one or more preservatives. The nature and quantity of the acids and amines should, of course, be such that none of the resulting salts crystallise out of solution.

When solutions of the invention are stored in ampoules they do not show any precipitation or turbidity even after prolonged storage. Ampoules of the solution preferably contain from 150 to 200 mg of the pyritinol salt in the solution, per ampoule.

The solutions may suitably contain one or more preservatives, such as benzyl alcohol, p-hydroxybenzoic acid methyl ester, p-hydroxybenzoic acid isopropyl ester or sorbic acid. The amount of preservative added is conventional and is usually from 0.1 to 1% by weight.

The pyritinol content (measured as the base) of the solutions of the invention is advantageously from 2 to 10% by weight. In addition to the preferred dihydrochloride monohydrate (pyrithioxine), other physiologically acceptable salts of pyritinol can be used in the manufacture of the solution according to the invention, for example salts of other mineral acids such as the hydrobromide, sulphate or nitrate, or phosphates and salts of organic carboxylic or sulphonic acids such as methane or ethane sulphonate.

Whilst there are many methods of preparing the solutions of the invention, the following general method has been found to be very satisfactory:

Pyritinol in the form of its dihydrochloride monohydrate is dissolved cold in about half the available water. The organic acid is then added, followed by the amine compound in the form of a concentrated aqueous solution. If required, the pH is adjusted with a strong base. The volume is then made up to 95% of its final value with water, after which the preservative and the remaining volume of water are added. If the preservatives used are p-hydroxy-benzoic acid esters, they are advantageously first dissolved with heating in a little water to form an aqueous solution which is then added to the mixture. When the solution is prepared, its pH is measured. It is then passed through a sterilisation filter layer under aseptic conditions and filtered until it is free from fibres. It is then poured into ampoules with preliminary and subsequent fumigation with an inert gas. The inert gas may, for example, be nitrogen or argon.

In order that the invention may be more fully understood, the following Examples of solutions of the invention are given by way of illustration only.

Example 1 (for 2 ml. ampoule)
200 mg Pyrithioxine
160 mg Tartaric acid
10 mg Vitamin B_1-hydrochloride
10 mg Vitamin B_6-hydrochloride
97.4 mg 27% caustic soda
20 mg Benzyl alcohol.
Water q.s. for 2 ml.

Example 2 (for 2 ml. ampoule)
150 mg Pyrithioxine
140 mg Formic acid (98—100%)
16 mg Vitamin B_1 hydrochloride
82.5 mg 32% Caustic soda
20 mg Benzyl alcohol.
Water q.s. for 2 ml.

Example 3 (for 2 ml. ampoule)
200 mg Pyrithioxine
100 mg 90% Lactic acid
50 mg Vitamin B_6 hydrochloride
8.5 mg Diethanolamine
20 mg Benzyl alcohol.
Water q.s. for 2 ml.

Example 4 (for 2 ml. ampoule)
150 mg Pyrithioxine
60 mg 1 - Benzyl - 3 - ethyl - 6,7 - dimethoxy - isoquinoline - hydro - chloride
140 mg Citric acid
82.5 mg 32% Caustic soda
20 mg Benzyl alcohol.
Water q.s. for 2 ml.

Example 5 (for 5 ml ampoule)
200 mg Pyrithioxine
400 mg Tartaric acid
10 mg Vitamin B_1 hydrochloride
10 mg Vitamin B_6 hydrochloride
253.5 mg 32% Caustic soda solution
50 mg Benzyl alcohol.
Water q.s. for 5 ml.

Example 6 (for 5 ml. ampoule)
150 mg Pyrithioxine
350 mg Formic acid (98—100%)
40 mg Vitamin B_1 hydrochloride
230 mg 32% Caustic soda solution
50 mg Benzyl alcohol.
Water q.s. for 5 ml.

Example 7 (for 5 ml. ampoule)
150 mg Pyrithioxine
40 mg Tartaric acid
40 mg Vitamin B_6 hydrochloride
20 mg Nicotinamide
93 mg Diethanolamine
50 mg Benzyl alcohol.
Water q.s. for 5 ml.

Example 8 (for 5 ml. ampoule)
150 mg Pyrithioxine
150 mg 1 - Benzyl - 3 - ethyl - 6,7 - dimethoxy - isoquinoline hydro - chloride
136.25 mg 32% Caustic soda solution
5 mg p-Hydroxybenzoic acid methyl ester
350 mg Citric acid.
Water q.s. for 5 ml.

WHAT WE CLAIM IS:—

1. A sterile injectable aqueous solution which comprises a physiologically acceptable salt of pyritinol, from 0.1 to 25% by weight of one or more physiologically acceptable organic acids each containing from 1 to 6 carbon atoms and from 0.1 to 25% by weight of one or more physiologically acceptable amines or physiologically acceptable salts thereof.

2. A solution according to claim 1 wherein the amine(s) is/are N-heterocyclic compound(s).

3. A solution according to claim 1 wherein the amine(s) is/are a physiologically acceptable pyridine derivative.

4. A solution according to claim 1 wherein the amine(s) is/are selected from vitamin B_1, vitamin B_6, 1 - benzyl - 3 - ethyl - 6,7 - dimethoxy-isoquinoline, diethanolamine and physiologically acceptable salts thereof, and nicotinamide.

5. A solution according to claim 4 wherein the amine is vitamin B_6 hydrochloride.

6. A solution according to any of claims 1 to 5 wherein the organic acid(s) is/are selected from formic, malonic, adipic, lactic, tartaric, citric, glutamic and ascorbic acids.

7. A solution according to any of claims 1 to 6 wherein the pyritinol salt is pyrithioxine.

8. A solution according to any of claims 1 to 7 which also contains an amount of sodium or potassium hydroxide such that the pH of the solution is from 2.1 to 3.0.

9. A solution according to any of claims 1 to 8 which also contains a preservative.

10. A sterile injectable aqueous solution substantially as herein described in any of Examples 1 to 8.

11. An ampoule containing a solution as claimed in any preceding claim.

12. An ampoule containing a solution as claimed in any of claims 1 to 9 which ampoule contains from 150 to 200 mg of the pyritinol salt in the solution.

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Example 7 (for 5 ml. ampoule)
150 mg Pyrithioxine
40 mg Tartaric acid
40 mg Vitamin B_6 hydrochloride
20 mg Nicotinamide
93 mg Diethanolamine
50 mg Benzyl alcohol.
Water q.s. for 5 ml.

Example 8 (for 5 ml. ampoule)
150 mg Pyrithioxine
150 mg 1 - Benzyl - 3 - ethyl - 6,7 - dimethoxy - isoquinoline hydro - chloride
136.25 mg 32% Caustic soda solution
5 mg p-Hydroxybenzoic acid methyl ester
350 mg Citric acid.
Water q.s. for 5 ml.

WHAT WE CLAIM IS:—

1. A sterile injectable aqueous solution which comprises a physiologically acceptable salt of pyritinol, from 0.1 to 25% by weight of one or more physiologically acceptable organic acids each containing from 1 to 6 carbon atoms and from 0.1 to 25% by weight of one or more physiologically acceptable amines or physiologically acceptable salts thereof.

2. A solution according to claim 1 wherein the amine(s) is/are N-heterocyclic compound(s).

3. A solution according to claim 1 wherein the amine(s) is/are a physiologically acceptable pyridine derivative.

4. A solution according to claim 1 wherein the amine(s) is/are selected from vitamin B_1, vitamin B_6, 1 - benzyl - 3 - ethyl - 6,7 - dimethoxy-isoquinoline, diethanolamine and physiologically acceptable salts thereof, and nicotinamide.

5. A solution according to claim 4 wherein the amine is vitamin B_6 hydrochloride.

6. A solution according to any of claims 1 to 5 wherein the organic acid(s) is/are selected from formic, malonic, adipic, lactic, tartaric, citric, glutamic and ascorbic acids.

7. A solution according to any of claims 1 to 6 wherein the pyritinol salt is pyrithioxine.

8. A solution according to any of claims 1 to 7 which also contains an amount of sodium or potassium hydroxide such that the pH of the solution is from 2.1 to 3.0.

9. A solution according to any of claims 1 to 8 which also contains a preservative.

10. A sterile injectable aqueous solution substantially as herein described in any of Examples 1 to 8.

11. An ampoule containing a solution as claimed in any preceding claim.

12. An ampoule containing a solution as claimed in any of claims 1 to 9 which ampoule contains from 150 to 200 mg of the pyritinol salt in the solution.

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