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PATENT SPECIFICATION

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(72) Inventor DIETMAR ROMER

(54) PHARMACEUTICAL COMPOSITIONS

(71) We, SANDOZ LTD., of Lichstrasse 35, Basle, Switzerland, a Swiss Body Corporate, 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:—

The present invention relates to a new pharmaceutical composition.

The invention provides a pharmaceutical composition incorporating as active ingredients.

(a) N - acetyl - *p* - aminophenol.

(b) 3 - methylthio - 10 - (2 - (1 - methyl - 2 - piperidyl)ethyl)phenothiazine, or a water-soluble, pharmaceutically acceptable salt thereof, and

(c) caffeine.

The new composition may be produced by mixing the active constituents indicated above, optionally with one or more pharmaceutically acceptable diluents or carriers.

N - Acetyl - *p* - aminophenol, for which the international name "Paracetamol" is hereinafter used, is characterized by pronounced analgesic and antipyretic properties, whilst its toxicity is low.

3 - Methylthio - 10 - (2 - (1 - methyl - 2 - piperidyl)ethyl)phenothiazine, hereinafter named "Thioridazine", produces a selective subduing of pathologic emotional excitation conditions, without affecting thought capacity and willfullness.

The weight ratio of ingredients (a) : (b) : (c) in the composition is suitably in the range 100 : 0.05 to 5.0 : 2.5 to 250, more suitably 100 : 0.375 to 1.5 : 12.5 to 25. Preferably, the weight ratio of ingredients (a) : (b) : (c) is 100 : 0.6 : 14.

The ratios quoted are calculated on the basis that Thioridazine is used in free base form. Naturally, if a salt is employed, the ranges will differ slightly in view of the difference in molecular weight.

Thioridazine may, for example, be present in the form of its hydrochloride.

A single dose of the composition may, for example, have the following composition:

Paracetamol	500 mg
Thioridazine	3 mg
Caffeine	70 mg

The invention also extends to galenic preparations of the composition, which are suitable for enteral or parenteral administration, e.g. capsules, tablets, dragees, suppositories and injectable solutions. In order to produce such medicinal preparations the mixture of active constituents is worked up with the usual organic or inorganic, pharmacologically inert adjuvants. Examples of such adjuvants are lactose, starch, magnesium stearate, stearic acid, sorbic acid, talc, methyl cellulose, alcohols, glycerin, and natural or hardened fats. The preparations may furthermore contain suitable sweetening or colouring substances and flavourings.

Example of a galenic preparation;

	Capsules
Paracetamol	0.5000 g
Thioridazine hydrochloride	0.0033 g +)
Caffeine (anhydrous)	0.0700 g
Magnesium stearate	0.0067 g
Talc	0.0230 g
Content of the capsule (for one capsule)	0.6030 g

+) Corresponds to 0.0030 g of base.

The above galenic preparation may be prepared as follows:

Thioridazine hydrochloride and caffeine are mixed, the resulting mixture is rapidly ground and again mixed, and is then combined with Paracetamol and magnesium stearate, the entire mixture is again ground slowly, and after mixing with the talc is mechanically filled into hard gelatin capsules.

The composition of the invention is indicated for use as an analgesic, and in particular in the treatment of common

headaches (with the exception of migraine), tooth aches, menstruation troubles, post-operative pains, neuralgias, sciatica and muscular pains.

An indicated suitable dose is one in which an average of 200 to 2000 mg of Paracetamol, 1 to 10 mg of Thioridazine and 50 to 500 mg of caffeine are administered daily. On appearance of pains it is preferred to administer a single dose having the above composition (500 mg of Paracetamol, 3 mg of Thioridazine, 70 mg of caffeine), for example in the form of a capsule; in case of an insufficient effect or no effect the initial dose is repeated after 1 to 2 hours, but the dose for each day should generally not exceed three single doses having the above composition.

A preparation according to the invention was tested on healthy, voluntary test persons in a physiological institute specializing in research on pain, and was compared in a double blind test with a placebo (the same preparation, but not containing the active ingredients; the test was conducted with 12 persons for the new preparation and 12 persons for the placebo. The dose of the new preparation amounted to two capsules having the composition indicated in the above Example.

The test was effected by subjecting an exposed part of the body (e.g. a hand) of the test person to heat and determining the time which elapsed before the person withdrew the exposed part because of the heat. The results obtained with the test persons treated for the preparation of the invention and the placebo were compared with each other and with a control value (ascertained on the same person before administration); the results obtained were statistically evaluated. It was found that the preparation according to the invention was significantly effective, whilst the corresponding placebo showed no significant effect. No side effects were observed.

The composition of the invention was clinically tested in three clinics (a total of 60 patients). The indications were acute pain after maxillofacial operations, common headache, acute pain after contusions and acute pains of various other origins. In 45 cases (75%) excellent and good results were obtained, whereas the number of cases of insufficient effect and failure only amounted to 15 (25%). Side effects (slight nausea) were only observed in one of the 60 cases, which points to an excellent tolerance of the composition. In this connection it is to be observed that many of the analgesics at present in use show a certain toxicity on the hematopoietic system and cause a slight euphoria which may lead the patients to toxicomania. No side effects of this nature have been observed with the new combination preparation.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition incorporating as active ingredients.
   (a) N - acetyl - *p* - aminophenol.
   (b) 3 - methylthio - 10 - (2 - (1 - methyl - 2 - piperidyl)ethyl)phenothiazine in free base form or in the form of a water-soluble, pharmaceutically acceptable salt, and
   (c) caffeine.

2. A pharmaceutical composition according to Claim 1, in which ingredient (b) is 3 - methylthio - 10 - (2 - (1 - methyl - 2 - piperidyl)ethyl) - phenothiazine hydrochloride.

3. A pharmaceutical composition according to Claim 1 or Claim 2, in which the weight ratio of ingredients (a) : (b) : (c) is in the range 100 : 0.05 to 5.0 : 2.5 to 250.

4. A pharmaceutical composition according to Claim 1 or Claim 2, in which the weight ratio of ingredients (a) : (b) : (c) is in the range 100 : 0.375 to 1.5 : 12.5 to 25.

5. A pharmaceutical composition according to Claim 1 or Claim 2, in which the weight ratio of ingredients (a) : (b) : (c) is 100 : 0.6 : 14.

6. A pharmaceutical composition according to Claim 1 or Claim 2 in unit dosage form containing 500 mg of ingredient (a), 3 mg of ingredient (b) and 70 mg of caffeine.

B. A. YORKE & Co.,
Chartered Patent Agents,
42 Upper Grosvenor Street,
London, W1X OAL,
Agents for the Applicants.

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