

PATENT SPECIFICATION

(11) 1322 149

NO DRAWINGS

1322 149

- (21) Application No. 11351/72 (22) Filed 10 March 1972
 (31) Convention Application No. 003558 (32) Filed 11 March 1971 in
 (33) Switzerland (CH)
 (44) Complete Specification published 4 July 1973
 (51) International Classification A61K 21/00
 (52) Index at acceptance

A5B 213 21Y 38Y 390 410 41Y 421 42Y 430 433 43Y
 441 444 446 44Y 450 451 45Y 480 481 482 483
 48Y 491 49Y 501 50Y 510 51Y 540 544 546 54Y
 552 55Y 565 56Y 576 57Y 586 58Y 606 60Y 616
 61Y 642 64Y 650 656 65Y 676 67Y
 C2C 172—193—283 175—193—286 215 220 226 22Y 247
 253 256 25Y 28X 292 29Y 30Y 321 32Y 342 34Y
 366 367 368 57Y 620 63X 790 79Y KZ

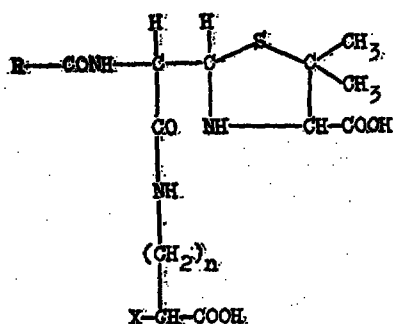


(54) PHARMACEUTICAL COMPOSITIONS

(71) We, F. HOFFMANN-LA ROCHE & CO., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzachstrasse, Basle, Switzerland, 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:—

10 The present invention is concerned with pharmaceutical compositions.

The pharmaceutical compositions provided by the present invention contain a therapeutically active penicillin and a penicilloyl acid derivative of the general formula



wherein X represents a hydrogen atom or a group of the formula R^1-NH- in which R^1 represents a hydrogen atom or a lower acyl group, n represents a whole number from 1—4 and R represents 2 - pentenyl, n - pentyl, n - heptyl, allylthiomethyl, 5 - amino - 5 - carboxypentyl, benzyl, carboxybenzyl, α - aminobenzyl, phenoxybenzyl, phenoxyethyl, α - phenoxyethyl, α - phenoxypropyl, 2,6 - dimethoxyphenyl, 2 - ethoxy - 1 - naphthyl,

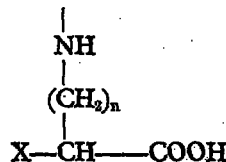
3 - carboxy - 2 - quinoxaliny, 5 - methyl - 3 - phenyl - 4 - isoxazolyl, 3 - (2 - chlorophenyl) - 5 - methyl - 4 - isoxazolyl, 3 - (2,6 - dichlorophenyl) - 5 - methyl - 4 - isoxazolyl or 2 - furoyloxyisobutyl, or a pharmaceutically acceptable salt thereof.

The present invention also provides a process for the manufacture of the pharmaceutical compositions set forth above, which process comprises mixing a therapeutically active penicillin with a penicilloyl acid derivative of formula I above or a pharmaceutically acceptable salt thereof.

Particularly preferred residues denoted by R in formula I are:

benzyl, α - aminobenzyl, phenoxyethyl, α - phenoxyethyl, 2,6 - dimethoxyphenyl, 2 - ethoxy - 1 - naphthyl and 3 - (2 - chlorophenyl) - 5 - methyl - 4 - isoxazolyl and 2 - furoyloxyisobutyl.

Preferably, in the penicilloyl acid derivatives of formula I n stands for 2, 3 or 4 and the aminocarboxylic acid moiety of the formula



is present in the L-form.

The term "lower acyl" is used in this description and in the claims appended hereto to denote the formyl group and alkanoyl groups containing up to 7 carbon atoms. The acetyl group is the preferred lower acyl group.

[Price 25p]

Price 33p

Examples of salts of the penicilloyl acid derivatives of formula I include organic ammonium salts such as the procaine, bis-benzylammonium or bisdicyclohexylammonium salts or mineral salts such as the sodium, potassium or calcium salts. Non-pharmaceutically utilisable salts can readily be converted into pharmaceutically valuable salts by an ion exchange process which is known per se.

Examples of penicilloyl acid derivatives of formula I and salts thereof which can be present in the pharmaceutical compositions provided by the present invention are:

- 15 N⁶ - (α - aminobenzyl - α - penicilloyl) - ε - amino - caproic acid,
N⁶ - (benzyl - α - penicilloyl) - ε - amino - caproic acid,
N⁶ - (phenoxymethyl - α - penicilloyl) - ε - amino - caproic acid,
- 20 N⁶ - (benzyl - α - penicilloyl) - L - lysine,
N⁶ - (benzyl - α - penicilloyl) - N³ - formyl - L - lysine,
- 25 N⁶ - (benzyl - α - penicilloyl) - N³ - acetyl - L - lysine,
N⁶ - (benzyl - α - penicilloyl) - N³ - acetyl - D - lysine,
N⁵ - (benzyl - α - penicilloyl) - N³ - butyryl - L - ornithine,
- 30 N⁴ - (benzyl - α - penicilloyl) - N³ - caproyl - D - α - γ - diamino - butyric acid,
N⁶ - (2 - pentenyl - α - penicilloyl) - L - lysine,
- 35 N⁶ - (2 - pentenyl - α - penicilloyl) - N³ - acetyl - L - lysine,
N⁶ - (2 - pentenyl - α - penicilloyl) - N³ - formyl - L - lysine,
- 40 N⁶ - (allylthiomethyl - α - penicilloyl) - L - lysine,
N⁶ - (allylthiomethyl - α - penicilloyl) - N³ - acetyl - L - lysine,
N⁶ - (allylthiomethyl - α - penicilloyl) - N³ - formyl - L - lysine,
- 45 N⁶ - (phenoxymethyl - α - penicilloyl) - N³ - acetyl - L - lysine,
N⁶ - (phenoxymethyl - α - penicilloyl) - N³ - butyryl - L - lysine,
- 50 N⁶ - (α - aminobenzyl - α - penicilloyl) - N³ - acetyl - L - lysine,
N⁶ - (2,6 - dimethoxyphenyl - α - penicilloyl) - N³ - acetyl - L - lysine,
N⁶ - (2 - ethoxy - 1 - naphthyl - α - penicilloyl) - N³ - acetyl - L - ornithine,
- 55 N⁶ - (3 - carboxy - 2 - quinoxazinyl - α - penicilloyl) - N³ - acetyl - L - lysine,
N⁶ - (5 - methyl - 3 - phenyl - 4 - oxazolyl - α - penicilloyl) - N³ - acetyl - L - lysine,
- 60 N⁶ - [3 - (2 - chlorophenyl) - 5 - methyl - 4 - isoxazolyl - α - penicilloyl] - N³ - acetyl - L - lysine,

N⁵ - [3 - (2,6 - dichlorophenyl) - 5 - methyl - 4 - isoxazolyl - α - penicilloyl] - N³ - formyl - L - ornithine and
6 - [[(R) - 1 - (2 - furoyloxy) - isobutyl] - α - penicilloylamino] - caproic acid,

and pharmaceutically acceptable salts thereof.

The penicilloyl acid derivatives of formula I are known or can be manufactured in a manner known per se; see, for example, U.K. Patent Specification No. 1,201,977.

Any therapeutically active penicillin can be present in the therapeutic compositions provided by this invention. Examples of such penicillins are benzylpenicillin, α - phenoxyethylpenicillin, sodium 2,6 - dimethoxyphenylpenicillin monohydrate, sodium 3 - (2 - chlorophenyl) - 5 - methyl - 4 - isoxazolylpenicillin monohydrate and α - aminobenzylpenicillin.

The expression "therapeutically active penicillin" used in this description and in the accompanying claims also includes pharmaceutically acceptable salts of penicillins; for example, those salts which are mentioned earlier in connection with the salts of the penicilloyl acid derivatives of formula I and also hydrated forms.

In a preferred embodiment of the present invention, the residue denoted by R in the penicilloyl acid derivative of formula I is the same as in the therapeutically active penicillin contained in the pharmaceutical composition. In this manner, the profile of the penicilloyl acid derivative is similar to a certain degree to the profile of the therapeutically active penicillin present in the pharmaceutical composition.

Preferred pharmaceutical compositions provided by the present invention contain:

- benzylpenicillin and N⁶ - (benzyl - α - penicilloyl) - aminocaproic acid,
phenoxymethylpenicillin and N⁶ - (phenoxymethyl - α - penicilloyl) N³ - acetyl - L - lysine,
sodium 2,6 - dimethoxyphenylpenicillin monohydrate and N⁶ - (phenoxymethyl - α - penicilloyl) - N³ - formyl - L - lysine,
- α - aminobenzylpenicillin and N⁶ - (α - aminobenzyl - α - penicilloyl) - ε - aminocaproic acid, and
sodium 3 - (2 - chlorophenyl) - 5 - methyl - 4 - isoxazolylpenicillin monohydrate and N⁶ - [3 - (2 - chlorophenyl) - 5 - methyl - 4 - isoxazolyl - α - penicilloyl] - ε - aminocaproic acid and
sodium [(R) - 1 - (2 - furoyloxy) - 3 - methylbutyl]penicillin and calcium 6 - [[(R) - 1 - (2 - furoyloxy) - isobutyl] - α - penicilloylamino]caproate.

The pharmaceutical compositions provided by the present invention can be primarily used where a penicillin treatment is indicated, especially where a penicillin allergy exists or is suspected. Furthermore, they can be used for the prophylactic treatment of penicillin allergies.

The dosage of the pharmaceutical compositions provided by the present invention is decided individually and is in proportion to the amount of therapeutically active penicillin which is therapeutically necessary and the amount of penicilloyl acid derivative of formula I which is necessary to prevent the formation of harmful penicilloyl-specific antigen-antibody complexes. For normal oral penicillin therapy, dosages of 250—625 mg per medication can be administered and the pharmaceutical compositions provided by the present invention preferably contain such an amount of therapeutically active penicillin for oral administration. In the case of parenteral administration, the individual doses can, for example, amount to up to 2 g. The amount of penicilloyl acid derivative of formula I in the present pharmaceutical compositions preferably amounts to 200 mg to 1250 mg and is in proportion primarily to the ratio between penicilloylamine and therapeutically active penicillin, and also to the nature and intensity of the penicillin-allergic reaction which is already present or is to be expected in the patient. The amount of penicilloyl acid derivative of formula I can also be varied as a function of the nature of the therapeutically active penicillin. The ratio of therapeutically active penicillin to penicilloyl acid derivative of formula I can consequently vary within a wide range. For example, the ratio of penicilloyl acid derivative of formula I to therapeutically active penicillin can vary from 0.01:1 to 10:1 parts by weight; a preferred range being 0.01:1 to 2:1 and especially 0.1:1 to 2:1 parts by weight.

The pharmaceutical compositions provided by the present invention can be present in a form which is usual for pharmaceutical compositions. For example, the active ingredients can be mixed with conventional organic or inorganic inert pharmaceutical carriers which are suitable for parenteral or enteral administration. Examples of such carriers are water, gelatine, gum arabic, lactose, starches, magnesium stearate, talc, vegetable oils, polyalkyleneglycols, and petroleum jelly. The pharmaceutical compositions can be made up in solid form (e.g. as tablets, dragées, suppositories or capsules), in semi-solid form (e.g. as salves) or in liquid form (e.g. as solutions, suspensions or emulsions). The pharmaceutical compositions may be sterilised and/or may contain adjuvants such as preserving, stabilising, wetting or emulsifying agents, salts for vary-

ing the osmotic pressure or buffers. They can also contain other therapeutically valuable substances.

The following Examples illustrate the present invention; the percentages given being by weight:

Example 1

Ampoules for the preparation of intramuscular injection solutions containing benzyl-penicillin and N⁶ - (benzyl - α - penicilloyl) - N³ - formyl - L - lysine are manufactured as follows:

110 g of N⁶ - (benzyl - α - penicilloyl) - N³ - formyl - L - lysine calcium and 330 g of penicillin G potassium are dissolved in 800 ml of water which contains 0.1% methyl - p - hydroxy - benzoate and 0.01% propyl - p - hydroxy - benzoate. The solution is brought to a volume of 1 litre with distilled water, filtered sterile, divided into 500 ampoules and lyophilised.

Example 2

In an analogous manner to that described in Example 1, there are manufactured ampoules each containing 625 mg of penicillin G and 200 mg of benzyl - penicilloyl - ϵ - amino - caproate.

Example 3

In an analogous manner to that described in Example 1, there are manufactured ampoules each containing 600 mg of penicillin V and 200 mg of N⁶ - (phenoxy-methyl - α - penicilloyl) - N³ - acetyl - L - lysine sodium.

Example 4

In an analogous manner to that described in Example 1, there are manufactured ampoules each containing 150 mg of calcium 6 - [[(R) - 1 - (2 - furoxyloxy) - isobutyl] - α - penicilloylamino]caproate and 420 mg of furoxyloxyisobutyl - penicillin sodium.

The calcium 6 - [[(R) - 1 - (2 - furoxyloxy) - isobutyl] - α - penicilloylamino]caproate may be obtained as follows:

91.8 g of 6 - aminocaproic acid and 6.8 g of imidazole are treated in 700 ml of water at 0°—5°C, with stirring, with 31.5 g of [(R) - 1 - (2 - furoxyloxy) - isobutyl] - penicillin sodium. Within 2 hours, the pH of the mixture is held at 9.9—10.3 by means of a 3-M potassium carbonate solution. The mixture is then extracted with ethyl acetate, acidified to pH 4.3 by adding 3-N sulfuric acid and the organic phase is separated, washed with water and saturated sodium chloride solution, dried over sodium sulfate and concentrated under reduced pressure at 20°C. The residue is dissolved in 200 ml of acetone and added, with stirring to a suspension of 5.2 g of calcium hydroxide in 200 ml of ice-water. After 5 minutes, the

5

10

15

20

208 mg

60 mg

magnes

3 mg

17 mg

38

35

-4-

49

50

5

60

65

~~~~~



75

80

香



10

- mixture is filtered through a charcoal filter; the filtrate is freed from acetone under reduced pressure at 20°C and the lyophilisate (36 g) is dissolved in 140 ml of water and treated with 1000 ml of isopropanol. After separation from an impure first fraction, the solution is concentrated to a third of its volume at 20°C under reduced pressure and the precipitate formed is separated by filtration. The precipitate is dried for 16 hours at 40°C under reduced pressure. There are obtained 21 g of calcium 6 - [(R) - 1 - (2 - furoyloxy) - isobutyl] -  $\alpha$  - penicilloyl-amino]caproate melting at 267°—270°C (with decomposition);  $[\alpha]_D^{25} = +73.8^\circ$  (c=0.8 in water).

#### Example 5

A capsule for oral administration contains the following ingredients:

- |    |                                                      |        |
|----|------------------------------------------------------|--------|
| 20 | ampicillin trihydrate                                | 208 mg |
|    | N <sup>6</sup> - (benzyl - $\alpha$ - penicilloyl) - |        |
|    | L - lysine calcium                                   | 60 mg  |
|    | lactose                                              | 72 mg  |
|    | magnesium stearate                                   | 3 mg   |
| 25 | talc                                                 | 17 mg  |

- The magnesium stearate, talc and N<sup>6</sup> - (benzyl -  $\alpha$  - penicilloyl) - N<sup>3</sup> - formyl - L - lysine calcium are homogeneously mixed and passed through a sieve of 0.3 mm mesh width. Thereafter, the ampicillin trihydrate is homogeneously admixed, the mixture passed through a sieve of mesh width 0.5 mm and again mixed. The mixture is subsequently filled into gelatine capsules.

#### Example 6

- In an analogous manner to that described in Example 5, there are manufactured capsules for oral administration each containing 200 mg of ampicillin and 100 mg of sodium - N<sup>6</sup> - ( $\alpha$  - amino - benzyl -  $\alpha$  - penicilloyl) - 6 - amino - caproate.

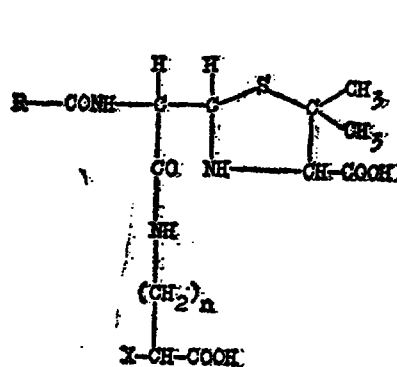
- The sodium - N<sup>6</sup> - ( $\alpha$  - aminobenzyl -  $\alpha$  - penicilloyl) - 6 - amino - caproate can be obtained as follows:

- 26 g of 6 - amino - caproic acid in 345 ml 1-N aqueous sodium hydroxide are treated, over a period of 10 minutes with stirring at 10°C, with 58 g of ampicillin trihydrate. Stirring is continued for another 20 minutes, whereupon the solution is placed on 1 kg of Amberlite (Registered Trade Mark) IR 120 and eluted with water. The aqueous solution is then lyophilised and the residue is dissolved in ethanol and precipitated by adding ethyl acetate. The precipitated material is reacted in methanolic solution with 2-N sodium ethylcaproate in ethyl acetate and precipitated with ether. By treatment with charcoal and crystallisation from methanol/ether, there is obtained the sodium salt of N<sup>6</sup> - ( $\alpha$  - aminobenzyl -  $\alpha$  -

penicilloyl) - 6 - amino - caproic acid melting at 157°—160°C;  $[\alpha]_D^{25} = +30.3^\circ$  (1.0 in water).

#### WHAT WE CLAIM IS:—

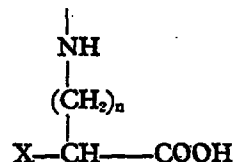
- 1) A pharmaceutical composition containing a therapeutically active penicillin and a penicilloyl acid derivative of the general formula



wherein X represents a hydrogen atom or a group of the formula R<sup>1</sup>-NH- in which R<sup>1</sup> represents a hydrogen atom or a lower acyl group, n represents a whole number from 1—4 and R represents 2 - pentenyl, n - pentyl, n - heptyl, allylthiomethyl, 5 - amino - 5 - carboxypentyl, benzyl, carboxybenzyl,  $\alpha$  - aminobenzyl, phenoxybenzyl, phenoxymethyl,  $\alpha$  - phenoxyethyl,  $\alpha$  - phenoxypropyl, 2,6 - dimethoxyphenyl, 2 - ethoxy - 1 - naphthyl, 3 - carboxy - 2 - quinoxaliny, 5 - methyl - 3 - phenyl - 4 - isoxazolyl, 3 - (2 - chlorophenyl) - 5 - methyl - 4 - isoxazolyl, 3 - (2,6 - dichlorophenyl) - 5 - methyl - 4 - isoxazolyl or 2 - furoyloxyisobutyl,

or a pharmaceutically acceptable salt thereof.

- 2) A pharmaceutical composition in accordance with claim 1, wherein n in formula I stands for 2, 3 or 4 and the amino acid moiety of the formula



is present in the L-form.

- 3) A pharmaceutical composition in accordance with claim 1 or claim 2, wherein the ratio of the penicilloyl acid derivative of formula I to the therapeutically active penicillin amounts to 0.01:1 to 10:1 parts by weight.

- 4) A pharmaceutical composition in accordance with claim 3, wherein the ratio of the penicilloyl acid derivative of formula I to

the therapeutically active penicillin amounts to 0.01:1 to 2:1 parts by weight.

5 5) A pharmaceutical composition in accordance with any one of claims 1—4, wherein R in the compound of formula I is benzyl,  $\alpha$  - aminobenzyl, phenoxyethyl,  $\alpha$  - phenoxyethyl, 2,6 - dimethoxyphenyl, 2 - ethoxy - 1 - naphthyl or 3 - (2 - chlorophenyl) - 5 - methyl - 4 - isoxazolyl.

10 6. A pharmaceutical composition in accordance with any one of claims 1 to 4 inclusive, wherein R in the compound of formula I is 2 - furoyloxyisobutyl.

15 7) A pharmaceutical composition in accordance with any one of claims 1 to 6 inclusive, wherein the residue denoted by R in the penicilloyl acid derivative of formula I is the same as in the therapeutically active penicillin.

20 8) A pharmaceutical composition in accordance with any one of claims 1 to 7 inclusive containing benzylpenicillin and N<sup>6</sup> - (benzyl -  $\alpha$  - penicilloyl) - aminocaproic acid.

25 9) A pharmaceutical composition in accordance with any one of claims 1 to 7 inclusive containing phenoxymethylpenicillin and N<sup>6</sup> - (phenoxymethyl -  $\alpha$  - penicilloyl) - N<sup>2</sup> - acetyl L - lysine.

30 10 A pharmaceutical composition in accordance with any one of claims 1 to 7 inclusive containing sodium 2,6 - dimethoxyphenylpenicillin monohydrate and N<sup>6</sup> - (phenoxymethyl -  $\alpha$  - penicilloyl) - N<sup>2</sup> - formyl - L - lysine.

11) A pharmaceutical composition in accordance with any one of claims 1 to 7 inclusive containing  $\alpha$  - aminobenzylpenicillin and N<sup>6</sup> - ( $\alpha$  - aminobenzyl -  $\alpha$  - penicilloyl) -  $\epsilon$  - aminocaproic acid. 35

12) A pharmaceutical composition in accordance with any one of claims 1 to 7 inclusive containing sodium 3 - (2 - chlorophenyl) - 5 - methyl 4 - isoxazolylpenicillin monohydrate and N<sup>6</sup> - [3 - (2 - chlorophenyl) - 5 - methyl - 4 - isoxazolyl -  $\alpha$  - penicilloyl] -  $\epsilon$  - aminocaproic acid. 40 45

13) A pharmaceutical composition in accordance with any one of claims 1 to 7 inclusive containing sodium [(R) - 1 - (2 - furoyloxy) - 3 - methylbutyl]penicillin and calcium 6 - [(R) - 1 - (2 - furoyloxy) - isobutyl] -  $\alpha$  - penicilloylamino] - caproate. 50

14) A process for the manufacture of the pharmaceutical compositions set forth in any one of claims 1 to 12 inclusive, which process comprises mixing a therapeutically active penicillin with a penicilloyl acid derivative of formula I in claim 1 or a pharmaceutically acceptable salt thereof. 55

For the Applicants,  
CARPMAELS & RANSFORD,  
Chartered Patent Agents,  
24, Southampton Buildings,  
Chancery Lane,  
London, WC2A 1AZ.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1973.  
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

