

PATENT SPECIFICATION

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(54) COMBINATION PREPARATIONS

(71) We, F. HOFFMANN-LA ROCHE & CO., AKTIENGESellschaft, a Swiss Company of 124—184 Grenzacherstrasse, 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 combination preparations.

The combination preparations provided by the present invention contain N¹-(4,5-dimethyl-3-isoxazolyl)-sulphanilamide or an alkali metal salt thereof (component A) and 2,4 - diamino - 5 - (3,4,5 - trimethoxybenzyl)-pyrimidine or a physiologically tolerable salt thereof (component B). This combination of components A and B produces a synergistic effect, component A being potentiated by component B.

Examples of alkali metal salts of the sulphonamide component are the sodium salt and the potassium salt.

25 Examples of physiologically tolerable salts of the 2,4 - diamino - 5 - (3,4,5 - trimethoxybenzyl)-pyrimidine component are acid addition salts with the usual inorganic and organic acids; for example, a halide (chloride and bromide) or the sulphate, phosphate, acetate and citrate.

30 The sulphonamide component and the pyrimidine component are normally present in the combination preparations in free form (i.e. not as a salt).

35 The weight ratio of the components A and B in the combination preparations provided by the present invention can vary within wide limits. For example, the weight ratio of component A to component B can be from 1:20

to 20:1, preferably from 1:1 to 20:1. Especially preferred are combination preparations which contain a weight ratio of component A to component B of from 5:1 to 9:1.

45 The combination preparations provided by the present invention are active against gram-positive and gram-negative bacteria, especially, for example, against *Salmonellae*, *E. coli*, *Pneumococci*, *Staphylococci*, *Streptococci*, *Pseudomonas aeruginosa* and *Pasteurellae*. They can therefore be used, for example, in veterinary medicine as a medicament for the prophylactic and therapeutic treatment of infections, especially of domestic animals such as *Artiodactylae* (pigs, goats, sheep, cows and, primarily, calves), *Perisodactylae* (horses), dogs, cats, poultry (hens and geese), fish, experimental animals and zoo animals. They can also be used as additives to feedstuffs. Thus, a further aspect of the invention is a method of providing domestic animals subject to or subjected to infection free from or resistant to such infection, which comprises administering to the animals or feeding to the animals, a veterinary preparation or a feed-stuff comprising the combination preparation.

65 In veterinary medicine, the aforementioned components A and B can be used in the form of veterinary preparations which contain them in association with a compatible veterinary carrier material. This carrier material can comprise one or more organic or inorganic carrier materials suitable for enteral or parenteral administration. The preferred form of administration is by injection, the appropriate veterinary preparation thus being an injection solution which contains the components A and B in water and an organic water-miscible solvent. Examples of suitable

water-miscible organic solvents are poly-ethyleneglycol ethers of tetrahydrofurfuryl alcohol having about three mols of ethylene oxide per mol of alcohol, dimethylformamide, dimethyl sulphoxide, dimethylacetamide, diethylacetamide, 1,2 - propyleneglycol, di-propyleneglycol and 1,3 - butyleneglycol. Glycerineformal (25% by weight 4-hydroxy-methyl-1,3-dioxolane and 75% by weight 5-hydroxy-1,3-dioxane) and polyethyleneglycols containing 2—15 ethylene oxide groups, especially diethyleneglycol, have been found to be especially well-suited water-miscible organic solvents.

The water content of such injection solutions usually amounts to 5—50% by weight, the content of water-miscible organic solvent being 30—80% by weight.

The aforementioned veterinary preparations can be sterilised and can also contain adjuvants such as preservatives, stabilisers, wetting agents, emulsifiers, salts for the modification of the osmotic properties or compounds for the adjustment to a specific pH-value.

The concentration of ingredient A (i.e. sulphonamide) in the present veterinary pre-

parations usually lies between 1% and 40%, preferably between 10% and 30%, by weight.

The aforementioned injection solutions are also useful in that they can be added to drinking water to give solutions which provide for oral medication. Such solutions are stable for several days with a concentration of components A and B which preferably lies between 0.1 and 5 wt.%. 30

When components A and B hereinbefore are used as feedstuff additives, the weight ratio can vary within wide limits depending on whether there is under consideration a ready-for use animal feedstuff or a premix (e.g. with cornmeal) or a concentrate. The final concentration of the components A and B in a ready-for-use animal feedstuff should lie at 50—1000 ppm, preferably at 250—500 ppm. Suitable concentrations in a premix are 25% or 50% by weight. 35 40 45

As basic feedstuffs there can be used single commercially available feed ingredients (e.g. cornmeal, lucerne, fish meal and soya meal) or mixtures of various ingredients (see, for example, the feed recipes given in the following Table). 50

TABLE 1

Feed recipes

Feed Ingredient	Parts by weight		
	Pre-starter Feed	Starter Feed	Grower Feed
Powdered milk	40.00	10.00	2.0
Maize	30.50	53.50	60.50
Sugar	7.00	2.00	0.50
Soya	6.00	15.50	14.00
Barley	5.00	5.00	8.00
Fish meal 63%	2.00	4.50	4.00
Fish meal 70%	2.00	2.50	3.00
Fat	2.00	2.00	—
Yeast	1.50	1.00	1.00
Lucerne	1.00	1.00	1.00
Dicalcium phosphate	1.00	1.00	1.00
Chalk	0.50	0.50	0.50
Salt	0.50	0.50	0.50
Premix*	1.00	1.00	1.50
Bran	—	—	2.50

Footnote to Table 1.

* The premix contains per kg of finished feed:

Vitamin A	12,000 I.U.
Vitamin D ₃	1,600 I.U.
Vitamin E	35 I.U.
Vitamin B ₁	5 mg
Vitamin B ₂	14 mg
Vitamin B ₁₂	50 γ
Calcium pantothenate	25 mg
Choline chloride	300 mg
Nicotinamide	60 mg

as well as trace elements.

- 5 The combination of components A and B hereinbefore is distinguished by a relatively long half-life of component A in blood plasma (especially in cows), the relatively short half-life of component B being compensated to the extent that, after the blood-level of component B falls below a therapeutically active value, component A is still present as a chemo-
10 therapeutic in an active dosage in the body for a longer time. By the administration of a maintenance dose, component B becomes active again in conjunction with the still-present and the newly-administered component A. This combination of an intermittent short-duration therapy with a potentiated sulphonamide and of a long-duration therapy with an active sulphonamide enables a relatively low dosage of the combination of components A and B to be used.

Comparison of Half-life Times

Preparation	Sulphonamide Component	Half-life Time in Cows (i.v.)
Sulphamethazine	Sulphamethazine	7 hours
Sulphadoxine/Trimethoprim	Sulphadoxine	9 hours
Components A+B hereinbefore	Isosulphafurazole	15 hours

- 25 The superior action in the treatment of infections in domestic animals of the combination of components A and B hereinbefore over prior customary preparations having a good activity will be evident from the following results obtained in an experiment in fish breeding (carps).
30 In the case of continuous feeding with feedstuff containing 620 ppm of chloramphenicol, the loss of fish in 5 pools amounted to 10—30%.
- After a 5-day feeding with a feedstuff containing 3000 ppm of a combination of components A and B, the death of fish stopped immediately and no further losses occurred.
35 The following Examples illustrate the present invention:
Example 1.
A feedstuff premix consisting of the following amounts by weight of ingredients is prepared:
40

Ingredient	(i)	(ii)
N ¹ -(4,5-Dimethyl-3-isoxazolyl)-sulphanilamide (Isosulphafurazole)	41.7%	20.8%
2,4-Diamino-5-(3,4,5-trimethoxybenzyl)-pyrimidine	8.3%	4.2%
Wheat middlings	50.0%	75.0%

(component A) and 2,4-diamino-5-(3,4,5-trimethoxybenzyl)-pyrimidine or a physiologically tolerable salt thereof (component B) in association with a compatible veterinary carrier material.

6. A veterinary preparation according to claim 5, wherein the weight ratio of component A to component B amounts to 1:20 to 20:1.

7. A veterinary preparation according to claim 5 or claim 6, wherein the weight ratio of component A to component B amounts to 1:1 to 20:1.

8. A veterinary preparation according to claim 7 wherein the weight ratio of component A to component B amounts to 5:1 to 9:1.

9. A process for the manufacture of a veterinary preparation as claimed in any one of claims 5 to 8 inclusive, which process comprises mixing a combination preparation as claimed in any one of claims 1 to 4 inclusive with a compatible veterinary carrier material.

10. A feedstuff which contains as an additive a combination preparation as claimed in any one of claims 1 to 4 inclusive.

11. A feedstuff according to claim 10, wherein said combination preparation is present in an amount of 50—1000 ppm.

12. A feedstuff according to claim 10 or claim 11, wherein said combination preparation is present in an amount of 250—500 ppm.

13. A process for the manufacture of a feedstuff as claimed in claim 10, wherein a combination preparation as claimed in any one of claims 1 to 4 inclusive is added to a basic feedstuff.

14. A method of providing domestic animals subject to or subjected to infection free from or resistant to such infection, which method comprises administering to said animals a veterinary preparation as claimed in any one of claims 5 to 8 inclusive or feeding to said animals a feedstuff as claimed in any one of claims 10 to 12 inclusive.

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The individual ingredients are successively added to a suitable mixer (planet stirrer or drum mixer) and mixed until a homogeneous distribution is ensured.

5 Example 2.

An injection solution for veterinary purposes having a low water content contains the following ingredients per litre: 204 g of N¹-(4,5 - dimethyl - 3 - isoxazolyl) - sulphanilamide, 40.8 g of 2,4-diamino-5-(3,4,5-trimethoxybenzyl)-pyrimidine, ca 31 g of pure sodium hydroxide (q.s. ad pH 8.8—9.2), 250 g of distilled water and glycerineformal q.s. ad 1000 ml.

15 This injection solution is prepared as follows: The pyrimidine ingredient is dissolved in glycerineformal with slight warming at about 35° C and with nitrogen gassing. In the water, which is boiled and cooled with nitrogen gassing, there are dissolved firstly the sodium hydroxide and then the sulphonamide ingredient. The two solutions are mixed together, the resulting solution is adjusted to pH 9.0±0.1, made up to 1000 ml with glycerineformal, filtered through Millipore (Trade Mark) 0.45 mm and filled into brown 100 ml ampoules which are finally sterilised for 20 minutes at 120° C.

WHAT WE CLAIM IS:—

30 1. A combination preparation which contains N¹ - (4,5 - dimethyl - 3 - isoxazolyl)-sulphanilamide or an alkali metal salt thereof (component A) and 2,4-diamino-5-(3,4,5-trimethoxybenzyl)-pyrimidine or a physiologically tolerable salt thereof (component B).

35 2. A combination preparation according to claim 1, wherein the weight ratio of component A to component B amounts to 1:20 to 20:1.

40 3. A combination preparation according to claim 1 or claim 2, wherein the weight ratio of component A to component B is from 1:1 to 20:1.

45 4. A combination preparation according to claim 3 wherein the weight ratio of component A to component B amounts to 5:1 to 9:1.

5. A veterinary preparation which contains N¹ - (4,5 - dimethyl - 3 - isoxazolyl)-sulphanilamide or an alkali metal salt thereof

(component A) and 2,4-diamino-5-(3,4,5-trimethoxybenzyl)-pyrimidine or a physiologically tolerable salt thereof (component B) in association with a compatible veterinary carrier material. 50

6. A veterinary preparation according to claim 5, wherein the weight ratio of component A to component B amounts to 1:20 to 20:1. 55

7. A veterinary preparation according to claim 5 or claim 6, wherein the weight ratio of component A to component B amounts to 1:1 to 20:1. 60

8. A veterinary preparation according to claim 7 wherein the weight ratio of component A to component B amounts to 5:1 to 9:1. 65

9. A process for the manufacture of a veterinary preparation as claimed in any one of claims 5 to 8 inclusive, which process comprises mixing a combination preparation as claimed in any one of claims 1 to 4 inclusive with a compatible veterinary carrier material. 70

10. A feedstuff which contains as an additive a combination preparation as claimed in any one of claims 1 to 4 inclusive. 75

11. A feedstuff according to claim 10, wherein said combination preparation is present in an amount of 50—1000 ppm.

12. A feedstuff according to claim 10 or claim 11, wherein said combination preparation is present in an amount of 250—500 ppm. 80

13. A process for the manufacture of a feedstuff as claimed in claim 10, wherein a combination preparation as claimed in any one of claims 1 to 4 inclusive is added to a basic feedstuff. 85

14. A method of providing domestic animals subject to or subjected to infection free from or resistant to such infection, which method comprises administering to said animals a veterinary preparation as claimed in any one of claims 5 to 8 inclusive or feeding to said animals a feedstuff as claimed in any one of claims 10 to 12 inclusive. 90

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