PATENT SPECIFICATION (11) 1 235 635

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NO DRAWINGS

(21) Application No. 56794/69 (22) Filed 20 Nov. 1969

(31) Convention Application No. 17656 (32) Filed 27 Nov. 1968 in

(33) Switzerland (CH)

(45) Complete Specification published 16 June 1971

(51) International Classification A 61 k 27/00

(52) Index at acceptance

A5B 332 33Y 38Y 390 391 480 482 48Y 511 51Y 542 54Y 566 56Y 586 58Y 650 651 65Y

(54) COMPOSITIONS SUITABLE FOR ADMINISTRATION TO POULTRY

(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: %

This invention relates to compositions suitable for administration to poultry both for veterinary and general feeding purposes. The compositions provided by the present invention exhibit prophylactic and curative action against coccidiosis and can be employed for the promotion of growth in poultry. The term "poultry" is used in this specification to include game birds.

Coccidiosis is a very widespread disease in poultry which occurs in the form of severe intestinal infections and often proves fatal. This disease is caused by infection with protozoa or the genus *Eimeria* such as, for example *Eimeria tenella*. The compositions in accordance with this invention are useful in the effective control of this disease. They can be used for preventing, containing or curing coccidiosis by administering them to the poultry (e.g. hens or turkeys) in prophylactically or therapeutically active amounts. They also exert a growth-promoting action on poultry and are accordingly also useful as growth-promoting agents. The compositions in accordance with this invention are also active against a wide range of pathogenic bacterial poultry infections, for example, against *St. aureus, P.multocida, S.gallinarum* or *E. coli*. This in an outstanding advantage of the compositions provided by this invention, since poultry are frequently attacked simultaneously by coccidiosis and bacterial infections. The compositions provided by this invention can thus serve for the prevention and treatment of both coccidiosis and bacterial infections.

According to the present invention there is provided a composition suitable for administration to poultry containing as active ingredients a mixture of (I) 4-sulphanilamido-2,6-dimethoxy-pyrimidine or a physiologically acceptable salt thereof, (II) 2,4-diamino-5-(3,4-dimethoxy-benzyl)-pyrimidine or a physiologically acceptable salt thereof and (III) 2,4 - diamino - 5 - (4 - chlorophenyl) - 6 - ethyl - pyrimidine or a physiologically acceptable salt thereof. The three active ingredients are for the sake of brevity referred in this specification as I, II and III and it will be appreciated that such referencesc to the physiologically aceptable salts of the compounds where appropriate.

When the present compositions containing the active ingredients I, II and III are administered to poultry in the form of feeds, the poultry maintain an undisturbed feeding rate even after infection with sporulated oocysts. The general condition of the poultry remains unaltered and no pathological manifestations are observed.

The three active ingredients aforesaid may be brought into a form which is suitable for administration to poultry by admixing them with an inert carrier or diluent and/or by admixing them with ingredients having nutritional value or which are physiologically acceptable to poultry. Thus, the active ingredients can be incorporated in uniformly and finely divided form in a liquid or powdered basic feed or dispersed in the drinking water of the poultry. As basic feeds there can be used appropriate commercial basic animal or poultry feeds. Both for the prophylactic treatment and curing of coccidiosis and also for producing growth promotion, the compositions preferably contain from 0.006 to 0.1 (preferably from 0.006 to 0.03) percent by weight of the active ingredients. Such compositions most conveniently take the form of ready-to-use feeds or drinking water. Active ingredient I preferably constitutes 2—98% (for example 50—98%) by weight of the total amount of active ingredients I, II and III. The weight

ratio of II to III is preferably from 3:1 to 1:3, more preferably 1:1. One preferred composition contains two parts of I to each part of II plus III.

In special cases it may be convenient to use smaller or larger concentrations than those mentioned earlier. A uniform distribution of the active ingredients may conveniently be achieved by any conventional method such as mixing, grinding or stirring or by spraying dilute solutions of the active ingredients (preferably in water) on to the carrier or diluent or the basic feed. The compounds I, II and III are only sparingly soluble in water so that, for the preparation of aqueous compositions, water-soluble salts are conveniently employed or an aqueous dispersion may be prepared using conventional emulsifiers. The alkali metal salts such as the sodium or potassium salts are particularly suitable as water-soluble salts of compound I. Compounds II and III form acid addition salts which may also be used for this purpose. Examples of physiologically acceptable acids which may be used for the preparation of such acid addition salts include mineral acids such as hydrochloric acid or sulphuric acid and organic acids such as acetic acid or citric acid. Emulsifiers which may be used include non-ionogenic emulsifiers such as polyoxyethylene-sorbitan monooleate or laurate or polyoxyethylene ricinoleate.

The compositions of the present invention may take the form of premixes which are suitable for adding to the basic feeds prior to feeding or to poultry drinking water. These premixes (or concentrates) may conveniently contain the active ingredients in concentrations of from 5 to 95% by weight, more preferably from 10 to 50% by weight. Suitable carriers for the premixes, include, for example, cereal grain, by-products of the milling industry, ground oil cake, distillation residues of the fermentation industry, finely divided mineral materials, ground oyster shells and silicon dioxide. Premixes can also be prepared using fats, oils, antioxidants and surface-active substances.

The active ingredients can also be added to basic feeds and feed-mixes together with other veterinary preparations. A typical example of a feed-mix is the following:

118 kg	maize meal
50 kg	barley meal
55 kg	soya meal
15 kg	animal protein
4.5 kg	dried yeast
2.5 kg	calcium carbonate
2.5 kg	calcium phosphate
1.1 kg	sodium chloride
1.4 kg	vitamin and mineral premix (containing vitamins, A, B_1, B_2, B_6, B_{12}, D_3, E, K, Ca pantothenate, nicotinic acid, folic acid, biotin, choline, Fe^{++}, Mn^{++}, Zn^{++}, Cu^{++}, I^-).

It will be appreciated that the invention also includes within its scope a method for the prevention or cure of coccidiosis in poultry which comprises feeding to poultry a composition as hereinbefore described (except a composition in the form of a premix or concentrate).

The following Examples illustrate the invention.

EXAMPLE 1

Groups of 40 weighed, two-week old chickens were fed with a feed-mix containing 80 mg per 1 kg of feed-mix of a combination of 4 - sulphanilamido - 2,6 - dimethoxy - pyrimidine, (62.5% by weight), 2,4 - diamino - 5 - (3,4 - dimethoxy - benzyl) - pyrimidine (18.75% by weight) and 2,4 - diamino - 5 - (4 - chlorophenyl) - 6 - ethyl - pyrimidine (18.75% by weight). 72 hours after beginning feeding with this feed-mix each chicken was infected *per os* with 100,000 sporulated oocysts of *Eimeria tenella*.

Control groups each of 10 weighed two-week chickens were fed with the same feed-mix to which, however, none of the foregoing compounds had been added and were likewise each infected *per os* with 100,000 sporulated oocysts. After an 8-day experimental period, the surviving chickens of both the test and control groups were killed, weighed and investigated for pathological changes. The results are summarised in the following Table:

TABLE

Active compound combination in the feed in %	Mortality in %	Caecal (intestinal) damage	Blood excretion with the droppings on 4th and 5th day p.i.	Weight development in %
Zero (untreated uninfected controls)	0	none	none	100
Zero (untreated infected controls)	50	heavy	heavy	70
0.008	0	none	none	108

Analogous results were obtained when compounds I, II and III were not employed in the ratio of 62.5:18.75:18.75 as earlier, but in the ratio of 65:22:13 or when the feed contained 60 mg/kg of the combination and the ratio of the compounds was 50:25:25 or 50:12.5:37.5.

EXAMPLE 2

A group of 250 weighed two-week old chickens was fed with feed-mixes containing either 80 mg or 120 mg per 1 kg of feed-mix of a combination of 4' - sulphanilamido - 2, 6 - dimethoxy - pyrimidine (62.5% by weight). 2,4 - diamino - 5 - (3,4 - dimethoxy - benzyl)- pyrimidine (18.75% by weight) and 2,4 - diamino - 5 - (4 - chlorophenyl) - 6 - ethyl - pyrimidine (18.75% by weight). A control group of 250 weighed two-week chickens was fed with the same feed-mix, but without the addition of the active compounds. After an 8-day experimental period, the chickens of both groups were weighed. The results are summarised in the following Table:

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Active combination in the feed in %	Weight development in %
Zero (untreated uninfected controls)	100
0.008	108
0.012	110

Analogous results were obtained when compounds I, II and III, were not employed in the ratio of 62.5:18.75:18.75 as earlier but in the ratio of 65:22:13 or when the feed contained 60 mg/kg of the combination and the ratio of compounds I, II and III was 50:25:25 or 50:12.5:37.5.

WHAT WE CLAIM IS:—

1. A composition suitable for administration to poultry containing as active ingredients a mixture of (I) 4' - sulphanilamido - 2,6 - dimethoxy - pyrimidine or a physiologically acceptable salt thereof, (II) 2,4 - diamino - 5 - (3,4 - dimethoxy - benzyl) - pyrimidine or a physiologically acceptable salt thereof and (III) 2,4 - diamino - 5 - (4 - chlorophenyl) - 6 - ethyl - pyrimidine or a physiologically acceptable salt thereof.

2. A composition as claimed in claim 1, wherein the weight ratio of I to II + III is from 2:98 to 98:2.

3. A composition as claimed in claim 1 or claim 2 wherein the weight ratio of I to II + III is from 50:50 to 98:2.

4. A composition as claimed in any one of the preceding claims, wherein the weight ratio of II to III is from 3:1 to 1:3.

5. A composition as claimed in any one of the preceding claims, wherein the weight ratio of II to III is 1:1.

6. A composition as claimed in any one of claims 1 to 5 inclusive, wherein a physiologically acceptable inert carrier or diluent is also present.

7. A composition as claimed in claim 6 containing from 0.006 to 0.1 per cent by weight of the active ingredients.

8. A composition as claimed in claim 7 con-

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2. A composition as claimed in claim 1, wherein the weight ratio of I to II + III is from 2:98 to 98:2.

3. A composition as claimed in claim 1 or claim 2 wherein the weight ratio of I to II + III is from 50:50 to 98:2.

4. A composition as claimed in any one of the preceding claims, wherein the weight ratio of II to III is from 3:1 to 1:3.

5. A composition as claimed in any one of the preceding claims, wherein the weight ratio of II to III is 1:1.

6. A composition as claimed in any one of claims 1 to 5 inclusive, wherein a physiologically acceptable inert carrier or diluent is also present.

7. A composition as claimed in claim 6 containing from 0.006 to 0.1 per cent by weight of the active ingredients.

8. A composition as claimed in claim 7 con-

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taining from 0.006 to 0.03 per cent by weight of the active ingredients.

9. A composition as claimed in claim 6 in the form of a concentrate and containing from 5% to 95% by weight of the active ingredients.

10. A composition as claimed in claim 9 containing from 10 to 50% by weight of said active ingredients.

11. A composition as claimed in any one of claims 6 to 8 inclusive, wherein the physiologically acceptable inert carrier is water containing an emulsifier.

12. A composition as claimed in any one of claims 6 to 8 inclusive or claim 11 which also contains a substance having nutritional value.

13. A process for the preparation of a composition as claimed in any one of the preceding claims, which process comprises intimately admixing said three active ingredients together, if desired, in the presence of a physiologically acceptable inert carrier or diluent.

14. A method for the prevention or cure of coccidiosis in poultry, which method comprises feeding to poultry a composition as claimed in any one of claims 1 to 8 inclusive or claims 11 or 12.

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1971.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

