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COMPLETE SPECIFICATION

Veterinary Compositions

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:—

The present invention relates to veterinary compositions. More particularly, the invention is concerned with veterinary compositions which are useful in the prevention, control or treatment of coccidiosis and with a process for the manufacture thereof. The invention is also concerned with premixes useful in preparing said compositions and with a method for providing poultry free from or resistant to coccidiosis with the aid of said compositions.

Coccodiosis, especially poultry coccidiosis, is a major problem in the poultry industry and, if not controlled, mortality and morbidity caused thereby effect serious economic loss in the raising of poultry.

Coccidiosis is a disease caused by a protozoan parasite of microscopic size called coccidia, belonging to the genus *Eimeria*. It is specific to the host animal. Thus the finding that a coccidiostatic agent is suitable for use against one species of *Eimeria* in a host of a specific species does not necessarily carry with it the implication that it will be equally effective against other species of *Eimeria* in the same or other species of hosts. In fact, many coccidiostatic agents, while being effective against a specific species of *Eimeria* in a host animal, will not show this efficacy against other species of *Eimeria* in the same host animal.

Coccidiosis affects most animals raised commercially for food purposes. Poultry such as turkeys, ducks and chickens are particularly prone to the disease, but sheep, cattle and swine are also affected. For example, in the poultry industry, no problems are more serious and more common than those resulting from parasitic diseases such as coccidiosis. The problem is especially great in this industry since the new techniques for raising poultry require that the birds be confined to narrow environs and, thus, be raised under crowded conditions. This close proximity of the birds while being raised is conductive to coccidiosis infections and the rapid spread thereof.

Infection is caused by the invasion of the animals by the protozoan parasite, coccidia. The infection in the host animals is initiated by the ingestion, usually along with feed or water, of *Eimeria* organisms in the sporulated oocyst stage. When the ingested oocysts enter the intestine, the infectious stage of the *Eimeria* soon develops from the oocysts and causes extensive damage to the inner walls of the intestine and the cecum or "intestinal pouch". There are both chronic and acute forms or coccidiosis infection in chickens. One type called cecal coccidiosis is caused primarily by the organism *E. tenella* and results in the destruction of the cecal linings of the host. Intestinal coccidiosis in chickens results primarily from other species of *Eimeria* and is equally as serious from an economical point of view. Such species of *Eimeria* are exemplified by *E. necatrix*, *E. acervuline*, *E. maxima*, *E. brunetti*, *E. hagani*, *E. praecox* and *E. mitis*.

Other organisms, such as *E. gallopavonis*, *E. melaegrimitis*, *E. adenoeides*, *E. meleagridis*, *E. dispersa*, *E. innocua* and *E. subrotunda* cause coccidiosis infections in turkeys. *E. truncata* and *E. anseris* cause coccidiosis in ducks and geese, *E. bovis*, *E. zurnii*, *E. alabamensis* and *E. auburnensis* cause coccidiosis in cattle. *E. ahsata*, *E. parva*, *E. faurei* and *E. arloingi* cause coccidiosis in

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sheep and *E. debliecki* and *E. spinosa* cause coccidiosis in pigs. Thus, it will be apparent that the various species of *Eimeria* cause infection to a type specific to host animals.

In an outbreak of coccidiosis in poultry (e.g. chickens and turkeys) the flock becomes seriously infected with little or no forewarning and a very high mortality can result unless the birds are promptly treated. Animals that do survive these types of infections are usually of lessened economical value inasmuch as they are quite inefficient in converting feed to weight gains, grow much more slowly than normal animals and frequently appear listless.

As will be evident from the foregoing coccidiosis is also a problem in other larger animals such as lambs, sheep, calves, cattle and pigs, although it is of less concern than in the poultry industry. However, an awareness is currently developing in connection with the raising of these larger animals of the effect of coccidiosis thereon from an economical point of view, and the people concerned in the field are beginning to recognize that the problems resulting from an outbreak of coccidiosis should not be overlooked. In such an outbreak in larger animals, the herd also becomes seriously infected with little or no forewarning. It is readily apparent that even a low mortality rate in a herd of larger animals from coccidiosis has serious economic consequences due to the large loss incurred per animal unit.

A number of coccidiostatic agents are currently available for either the therapy or prevention of coccidiosis and some of these agents are effective in preventing high mortality among infected animals. Notwithstanding this, outbreaks of coccidiosis among the animals still occur due, in some cases, to the development of resistance of the *Eimeria* to known coccidiostatic agents. Furthermore, animals treated with certain known coccidiostatic agents sometimes show a lower feed efficiency and less rapid weight gains than healthy animals. Moreover, many of the known coccidiostatic agents have been found to possess a limited antococcidial species spectrum and they are also often too expensive for wide use such as in poultry husbandry, particularly in view of the high concentration levels at which they must be used in order to achieve the desired end.

Accordingly, a definite need exists for an antiparasitic composition which is effective in the treatment and control of coccidiosis caused by a broad spectrum of *Eimeria* organisms in animals but which does not suffer from the defect of lowering the feed efficiency and growth. Furthermore, a highly effective coccidiostat which is well tolerated by the host is greatly desired from the point of view of the animal raiser.

It has now been found in accordance with the present invention that the antibiotic X-537 A and its pharmaceutically acceptable salts (e.g. sodium and potassium) are useful both for the prophylaxis and therapy of coccidiosis. The antibiotic is especially useful by virtue of its high activity against *Eimeria tenella* or against multiple infections; for example, those comprising as the coccidiosis-producing organisms *E. tenella, E. necatrix, E. acervulina, E. brunetti, E. maxima* and *E. mivati*, particularly in poultry such as chickens or turkeys.

Accordingly, the veterinary compositions provided by the present invention comprise antibiotic X-537 A or a non-toxic pharmaceutically acceptable salt thereof as the active ingredient in association with a compatible carrier material; said active ingredient being present in an amount of from 0.001% to 0.0125% by weight of the composition.

The organism producing the antibiotic useful in this invention was isolated from a sample of soil collected at Hyde Park, Massachusetts, and is a member of the genus of *Streptomyces*. Lyophilized tubes of the culture labelled with the laboratory designation X-537 have been deposited in the NRRL collection, United States Department of Agriculture, Agricultural Research Service, Northern Utilization Research and Development Division, Peoria, Illinois and added to its collection as NRRL 3382. This culture has been made available to the public.

Antibiotic X-537 A, the active ingredient in the veterinary compositions of this invention, is obtained in the form of its sodium salt when the culture is grown on a variety of media in submerged cultures. The preparation of this antibiotic from NRRL 3382 is disclosed by BERGER *et al.*, Journal of the American Chemical Society, Vol. 73, pages 5295—5298 (1951).

The antibiotic which is obtained in the form of the sodium salt by extraction of the cells with butyl acetate is soluble in benzene and hot petroleum ether and practically insoluble in water. The empirical formula of the antibiotic is $C_{34}H_{54}O_8$. The free acid in *iso*propyl alcohol has a characteristic *ultra*violet absorption spectrum with maxima at 317 mμ(ε3700) and 249 mμ(ε 6400) and shows *infra*red spectrum main peaks (3% in $CHCl_3$) at 3410, 3030, 2960, 2860, 1705, 1650, 1460 cm^{-1}. It gives a positive ferric chloride reaction, it is active *in vitro* against gram-positive bacteria and mycobacteria but it is inactive against gram-negative bacteria.

The following table summarizes the antimicrobial spectrum of crystalline antibiotic X-537 A.

TABLE

Antimicrobial Spectrum of Antibiotic X—537 A

Test Organism	Plate Units per mg
Bacillus E	800
Sarcina lutea	500
Staphylococcus aureus	20
Mycobacterium phlei	20
Corynbacterium simplex	20
Bacillus cereus	120
Bacillus simplex	20
Bacillus mesentericus	50
Saccharomyces cerevisiae	0
Scopulariopsis brevicaulis	0
Gram-negatives*	0

* These organisms were *Pseudomonas aeruginosa, Aerobacillu polymyxa* and *Escherichia coli.*

The antibiotic is not toxic and shows no untoward side-effects when used at the dosages necessary to successfully control coccidiosis. The toxic dosage of the antibiotic as tested in mice and designated as the lethal dose is shown in the following table: 5

TABLE

Mode of Administration	Lethal dose (LD 100) mg/kg	Tolerated dose (LD 0) mg/kg
Oral	125	62.5
Subcutaneous	125	62.5
Intraperitoneal	62.5	50

The antibiotic can be prepared by growing the *Streptomyces* organisms in an aerated submerged culture. This can be done in either a shaken flask or in 50 gallon to 1,000 gallon stainless steel and iron fermentation tanks. The broths are adjusted to a pH which is about neutral (i.e. 6.5 to 7.5) prior to being sterilized and are then incubated at slightly elevated temperatures (e.g. 27°C to 30°C) after being inoculated with spore suspensions or vegetative growth. The broth is then filtered and the active material is extracted with a suitable solvent, preferably methanol, *n*-butanol or butyl acetate. The antibiotic activity is followed by cup-plate agar diffusion assay in which the test organism *Bacillus E* is employed. In general, the concentration of antibiotic required to produce an inhibition zone of 20 to 22 mm in diameter with any of the test organisms is considered to be 1 unit per ml. Whole broths are diluted for assay in 1% phosphate buffer, pH 6.0.

The growth of the *Streptomyces* organism can be supported on a variety of media which results in antibiotic production. Examples of suitable media are those containing complex nitrogen sources such as soyflour, fishmeal, distillers residues, and cottonseed meal. These media will support production of antibiotic with 30 to 400 units of activity. Synthetic media are generally unsatisfactory since low yields result.

The non-toxic pharmaceutically acceptable salts of antibiotic X-537 A can be prepared by conventional means. Among such salts there may be mentioned the non-toxic alkali-metal salts, alkaline-earth metal salts and organic salts. Of these, the sodium, potassium and calcium salts are preferred. The sodium salt is prepared by reaction of the antibiotic with sodium carbonate and the potassium salt is prepared by reaction of the antibiotic with potassium carbonate.

The veterinary compositions of this invention are manufactured by mixing the active ingredient (antibiotic X-57 A or a non-toxic pharmaceutically acceptable salt thereof) with a compatible carrier material, said active ingredient being used in an amount of from 0.001% to 0.0125% by weight of the composition. The compatible carrier material can comprise, for example, a feedstuff or an extender material. The term "compatible carrier material" is used to mean a material which does not function as an antiparasitic agent (e.g. a coccidiostat), is inactive with respect to the active ingredient and which may be safely ingested by the animals to be treated

The antibiotic or its non-toxic salts when administered orally as a component of the feed to coccidiosis-susceptible domestic fowl, particularly turkeys and chickens effectively controls the disease by either preventing it or curing it after it occurs. Furthermore, the treated fowl either maintain their weight or actually gain weight when compared to control fowl. Thus, the veterinary compositions of this invention not only control coccidiosis, but also aid in improving the efficiency of conversion of feed to weight gains.

The actual concentration of the active ingredient in animal feed can, of course, be adjusted to the individual needs and may vary over a wide range. The limiting criteria of concentration are that the minimum concentration is such that a sufficient amount of active ingredient is provided to effect the desired control of coccidiosis and the maximum concentration is such that the amount of composition ingested does not result in any untoward or undesirable side-effects.

Thus, for example, a feed premix or finished feed contains sufficient active ingredient to provide from 0.001% to 0.0125% by weight of the daily feed consumption. Preferably, 0.00312% to 0.00625% by weight of active ingredient is used. Generally, 0.005% of the active ingredient is sufficient for the purpose of controlling and combating coccidiosis. Amounts greater than 0.0125%, while being efficacious, do not generally show improved results.

Even though amounts over 0.00625% are efficacious for combating coccidiosis, this amount is the preferred upper range because of economics; that is to say, the cost per unit of effectiveness is lowest within this range. Amounts lower than 0.001% are not effective for combating coccidiosis. A lower limit of 0.00312% is preferred because this insures greatest effect. The most preferred amount (i.e. 0.005% by weight of the poultry daily feed consumption) is particularly efficacious since it achieves maximum effect with minimum dose. The optimum dose level will, of course, vary with the size of the animal. When using the veterinary compositions of the invention for treating or preventing coccidiosis, the active ingredient can be first compounded or blended with a feed ingredient or carrier to become a feed additive or premix, a feed concentrate, or a feed additive supplement. A feed additive, concentrate or premix is an article intended to be diluted to produce a finished feed; that is to say, a feed intended to be administered as a sole ration. A feed additive supplement is intended for consumption by an animal directly or which can be further diluted to produce a finished feed or which can be ingested and used as a supplement to other rations. Feed additive supplements, concentrates and premixes contain a relatively large percentage of active ingredient and are conveniently prepared by adding the active ingredient to a suitable carrier and mixing in a manner to give substantially uniform dispersion of the active ingredient in the carrier. Suitable carriers are solids which are inert with res-

pect to the active ingredient and which may safely be ingested by the animals to be treated. Typical of such carriers are commercial poultry feeds, ground cereal grains, grain byproducts, plant protein concentrates (soy and peanuts), fermentation byproducts, salt, limestone, inorganic compounds or mixtures thereof. Liquid dispersions can be prepared by using water or vegetable oil preferably including a surface-active agent or emulsifying agent in the liquid dispersion such as ethylenediamine tetraacetic acid and solubilizers. Any suitable carrier or extender material can function as the inert ingredient in the solid form of the veterinary compositions provided that it is inert to the active ingredient and is non-toxic insofar as the animal to which it is to be administered is concerned.

The active ingredient may be blended into a mash, pellet, or any desired form with the inert carrier or extender solid material by any convenient technique. For example the veterinary compositions can be formed by finely grinding or pulverizing the active ingredient and the inert ingredient using any commercially available grinder or pulverizer with or without the feed material being present. If the feed material is not present when the grinding or pulverizing is effected, the resultant material can be distributed in any conveniently available feed material. Typical poultry feeds with which the active ingredient of this invention can be associated can contain several ingredients; for example, they can contain high energy grain products such as corn, wheat, wheat red dog flour, milo or oatmeal, medium and low energy grain products such as oats, barley, wheat flour, middlings or standard middlings stabilized fats, vegetable protein such as soybean meal, corn gluten meal or peanut meal animal protein such as fish meal, fish solubles or meat scraps, UGF (unidentified growth factor) sources and other B-vitamin carriers such as dried milk products, dried brewers yeast, distillers dried solubles, fermentation solubles, or the like, dehydrated alfalfa meal and various special additives such as additional reboflavin, vitamin-B_{12}, calcium pantothenate, niacin, choline, vitamin-K and vitamin-E as well as stabilized vitamin-A, vitamin-D_3 (D-activated animal sterols), calcium and phosphorus supplements such as dicalcium phosphate, steamed bone meal, defluorinated phosphate, limestone, or the like, iodized salt, manganese sulphate, zinc carbonate, an antibiotic feed supplement, methionine or its hydroxy analogue and an antioxidant.

As will be evident from the foregoing, the veterinary compositions of this invention are intended for oral ingestion. They can be added to the normal feed supply of the treated animal or can be administered by other procedures such as by incorporating the same in a tablet, pill or bolus and supplying it forcibly to the animal. The administration of the active ingredient must be considered in terms of the specific animal under the husbandry practices encountered.

The present invention is also concerned with a method of providing animals (especially poultry and particularly turkeys and chickens) free from or resistant to coccidiosis. This method comprises orally administering to animals suffering from or subject to coccidiosis a therapeutically effective amount of antibiotic X-537 A or a non-toxic pharmaceutically acceptable salt thereof in an inert carrier. The antibiotic is preferably employed in the crystalline form.

In order that the invention may be more fully understood and readily carried into effect the following Examples are given by way of illustration:

EXAMPLE 1

Preparation of Crystalline Antibiotic X537 A

The *Streptomyces* organism was grown in aerated submerged culture in shaken flasks. The pH of the broth was adjusted by the addition of potassium hydroxide solution to 6.5—7.5 and then the broth was sterilized. A tank fermentation was used wherein a 5—10% inoculum consisting of 3 day old submerged growth from the aerated bottles was used in the tank. The medium contained 2% soybean flour, 2% brown sugar, 0.5% potassium hydrogen phosphate. The fermentation was carried out at 28°C under positive air pressure with air-flows of 5—10 cubic feet of air per minute per 40 to 80 gallon liquid charge. The broth was harvested after 4 to 6 days fermentation, filtered, and the antibiotic was recovered by extraction. The extraction was carried out as follows:

204 litres of broth were filtered and the wet filter cake was suspended in 100 litres of butyl acetate and the mixture was stirred overnight at room temperature. The mixture was then filtered and the water layer was separated and discarded. The butyl acetate solution, assaying 30 million *Bacillus E.* units, was concentrated in vacuo to 3 litres, washed with 10% sodium carbonate solution and dried with anhydrous sodium sulphate.

On further concentration to 300 ml and dilution with 350 ml of petroleum ether (boiling point 50°—60°C), 41 g of solid material assaying 25 million *Bacillus E* units separated. This solid material was then extracted in a SOXHLET apparatus with 4 litres of petroleum ether (boiling point 50°—60°C) for 40 hours. The extract was taken to dryness *in vacuo*, the crystalline residue suspended in petroleum ether and filtered, yielding 24.49 g assaying 500 E units per mg: total 12.25 million E units. The mother

liquor of the solid yielded an additional 5.73 g of the crystalline antibiotic.

After recrystallization from ether/(petroleum ether), this material which contained sodium was dissolved in ether and washed with dilute sulphuric acid to convert it to the free acid. Removal of the ether left an oily residue which crystallized from ethanol. Several recrystallizations from ethanol did not change the melting point which remained unsharp at 100°—109°C; $[\alpha]^{26}$ (D −7.2°) (methanol, c. 1); assay 800 E units per mg. The *ultra*violet adsorption spectrum of the free acid showed maxima at 317 mμ (ε 3700) and 249 mμ (ε 6400) in *iso*propyl alcohol The acid was soluble in organic solvents and insoluble in water, but could be obtained in crystalline condition only from alcohol, from which it appeared to crystallize with one or more molecules of solvent. With alcoholic ferric chloride a green-blue colouration was obtained. The anthrone test for carbohydrate was negative. The antibiotic reacted with ethereal diazomethane, but no crystalline product could be isolated. It contained no nitrogen or halogen, phosphorus or sulphur and on combustion left no ash.

A sample recrystallized twice from *iso*propyl alcohol also melted at 100°—109°C and was analyzed with the following results:

Analysis: Calculated for $C_{34}H_{54}O_8$: C, 69.12; H, 9.21; O, 21.67, for $C_{34}H_{54}O_8.C_3H_7OH$: C, 68.27; H, 9.60, for $C_{34}H_{54}O_8.2C_3H_7OH$: C, 67.57; H, 9.93. Found (dried at 50°C): C, 67.60; H, 9.32. Found (dried at 60°C): C, 68.24: H, 9.35, 9.26.

Example 2

Sodium Salt of Crystalline Antibiotic X-537 A

The sodium salt was prepared by shaking an ether solution of the free acid with aqueous sodium carbonate. The salt which remained in the ether was recrystallized twice from benzene/ligroin and dried. It had a melting point, taken in an open capillary tube, of 196°—197°C (decomposition). After storage in the cold, its melting point is 191°—192°C (decomposition). This was then electrometrically titrated. 0.6204 g of the sodium salt used 10.1 ml of 0.1-*N* HCl.

Upon analysis, for a calculated equivalent weight of 610.7, an equivalent weight of 604 was found.

The *ultra*violet absorption spectrum of the sodium salt in *iso*propyl alcohol showed a maximum at 308 mμ (ε 4100) and an inflection at about 245 mμ.

The *infra*red spectrum of the sodium salt shows the following peaks: (3% in $CHCl_3$) 3500—3100 (broad), 3000, 2960, 2940, 2875, 1710, 1600, 1580, 1460, 1440, 1390, 1380 cm^{-1}.

Example 3

Potassium Salt of Crystalline Antibiotic X-537 A

The potassium salt was prepared by shaking an ether solution of the free acid with aqueous potassium carbonate, drying and removing the ether *in vacuo*. The crystalline residue was recrystallized twice from petroleum and dried *in vacuo* at 100°C. The potassium salt has a melting point of 177°—178°C.

Upon analysis, the following results were obtained:

Calulated for $C_{34}H_{53}O_8K$: C, 64.94; H, 8.48; K, 6.22. Found C, 65.23, 65.55; H, 9.17, 8.94; K, 6.17, 6.24.

Example 4

This Example illustrates the utilization of the crystalline antibiotic in an animal feed. A poultry feed intended as a starter feed for broilers is prepared by blending 0.005% by weight of crystalline antibiotic X-537 A in a basic poultry ration consisting of the following ingredients:

Ingredients	Pounds per ton
Corn meal (No. 2, yellow, ground)	1123
Stabilized grease or vegetable oil	60
Soybean oil meal (low fibre 50)	480
Corn gluten meal	50
Fish meal (antioxidant treated, 60% protein)	30
Fish solubles (dried basis)	10
Meat solubles (dried basis)	140
Corn distillers dried solubles	50
Alfalfa meal (17% protein 100,00 A/lb)	30
Salt (iodized)	5
Manganese sulphate (feed grade)	0.75
Zinc carbonate or oxide	0.25
Riboflavin (grams)	3
Vitamin B_{12} (mg)	6
Calcium pantothenate (grams)	5
Niacin (grams)	30
Stabilized vitamin-A (U.S.P. units)	6,000,000
Vitamin—D_3 (I.C. Units)	650,000
Vitamin—E acetate (IU)	5,000
Vitamin—K (menadione sodium bisulphate) (grams)	2
DL-methionine or hydroxy analogue (pound)	1
Antioxidant (ethoxyquin or butylated hydroxytoluene) (lbs)	0.25

Similar feeds can be prepared containing the antibiotic at other concentrations; for example, containing from 0.001% to 0.0125% by weight of the antibiotic.

The following tests were carried out to determine the activity of the crystalline antibiotic X-537 A.

A) *Eimeria tenella* infection in laboratory chickens Test Method

This test utilizes ten chickens per drug group. Ten chickens are employed as a weight control and ten chickens as an infected control. The drug is given 24 hours in advance of the infection. One g of the test drug is mixed in a mechanical mixer with a sufficient amount of chicken feed to result in the desired dosage. The infection consists of approximately 300,000 oocysts given orally by pipette. The test lasts for eight days and then the surviving birds are autopsied and examined for gross lesions in the ceca. The test birds are rated according to the number of survivors and the number of cecal lesions. The results are expressed as average degree of infection (A.D.I.). An average degree of infection of less than 2.5 is considered to represent an activity of practical interest.

The results achieved with antibiotic X-537 A are shown in the following table:

TABLE

Drug	Dosage in feed (%)	Average degree of infection		% Mortality		Weight Gain %	
		Treated	Untreated	Treated	Untreated	Treated	Untreated
Uninfected untreated control	None	—	0.0	—	0	—	100
Infected untreated control	None	—	3.0	—	25	—	68
Crystalline antibiotic	0.00625	0.4		0		92	
X—537 A	0.00312	2.2		0		85	

As can be seen from the data in the Table, the antibiotic is effective at the dosage illustrated for the treatment of coccidiosis. It will also be noted from the data in the Table that the use of the antibiotic as a coccidiostat does not substantially adversely affect the conversion of feed to weight gain.

B) Multiple *Eimeria* infections in chickens

Test Method

The test method is the same as that for *Eimeria tenella*. The multiple *Eimeria* infection tested herein are mixtures of *E. tenella*, *E. necatrix*, *E. acervulina*, *E. brunetti*, *E. maxima* and *E. mivati* infections.

The results are shown in the following Table:

TABLE

Drug	Dosage in feed (%)	Average degree of infection		% Mortality		Weight Gain %	
		Treated	Untreated	Treated	Untreated	Treated	Untreated
Uninfected untreated control	None	—	0.0	—	0	—	100
Infected untreated control	None	—	3	—	50	—	62
Crystalline antibiotic	0.00625	0.0	—	0	—	108	—
X—537 A	0.00312	0.9	—	0	—	105	—

As can be seen from the foregoing Table the crystalline antibiotic is effective in treating multiple coccidiosis infections and is further significant in causing greater than expected efficiency of conversion of feed to weight gain in the chickens, thus indicating that there is some synergistic effect present.

WHAT WE CLAIM IS:—

1. A veterinary composition comprising antibiotic X-537 A or a non-toxic pharmaceutically acceptable salt thereof as the active ingredient in association with a compatible carrier material; said active ingredient being present in an amount of from 0.001% to 0.0125% by weight of the composition.

2. A composition as set forth in claim 1, wherein the active ingredient is present in an amount from 0.00312% to 0.00625% by weight.

3. A composition as set forth in claim 1, wherein the active ingredient is present in an amonut of 0.005% by weight.

4. A composition as set forth in any one of claims 1 to 3 inclusive, wherein the active ingredient is present in crystalline form.

5. A veterinary composition which comprises an animal feed having dispersed therein from 0.001% to 0.0125% by weight of antibiotic X-537 A or a non-toxic pharmaceutically acceptable salt thereof as the active ingredient.

6. A composition as set forth in claim 5, wherein the active ingredient is present in an amount of from 0.00312% to 0.00625% by weight.

7. A composition as set forth in claim 5, wherein the active ingredient is present in an amount of 0.005% by weight.

8. A composition as set forth in any one of claims 5 to 7 inclusive, wherein the active ingredient is present in crystalline form.

9. An animal feed having dispersed therein from 0.001% to 0.0125% by weight of antibiotic X-537 A or a non-toxic pharmaceutically acceptable salt thereof as the active ingredient.

10. An animal feed as set forth in claim 9, wherein the active ingredient is present in crystalline form.

11. A premix useful for preparing a composition as set forth in any one of claims 1 to 10 inclusive comprising antibiotic X-537 A or a non-toxic pharmaceutically acceptable salt thereof in association with a compatible carrier material; said antibiotic or salt thereof being present in an amount appropriately higher than 0.001% by weight of the premix.

12. A method for providing poultry suffering from or subject to coccidiosis free from or resistant to coccidiosis which comprises orally administering to said poultry a veterinary composition or animal feed as claimed in any one of claims 1 to 10 inclusive.

13. A method as set forth in claim 12, wherein the compatible carrier material is an animal feed.

14. A method as set forth in claim 12 or claim 13, wherein the active ingredient is present in crystalline form.

15. A process for the manufacture of a veterinary composition as claimed in claim 1, which process comprises mixing antibiotic X-537 A or a non-toxic pharmaceutically acceptable salt thereof as the active ingredient with a compatible carrier material, said active ingredient being used in an amount of from 0.001% to 0.0125% by weight of the composition.

16. A process as set for in claim 15, wherein the inert carrier is a feedstuff, an extender material or a combination of a feedstuff and an extender material.

17. A process as set forth in claim 13 or claim 16, wherein from 0.001% to 0.0125% by weight of active ingredient are used.

18. A process as set forth in claim 15 or claim 16, wherein from 0.00312% to 0.00625% by weight of active ingredient are used.

19. A process as set forth in claim 18, wherein 0.005% by weight of active ingredient are used.

20. A process as set forth in any one of claims 15 to 19 inclusive, wherein the active ingredient is used in crystalline form.

21. A process for the manufacture of a premix as claimed in claim 11, which process comprises mixing antibiotic X-537 A or a non-toxic pharmaceutically acceptable salt thereof with a compatible carrier material; said antibiotic or salt being used in an amount appropriately higher than 0.001% by weight of the premix.

22. A process for the manufacture of the compositions claimed in any one of claims 1 to 11 inclusive, substantially as hereinbefore particularly described with reference to the foregoing Examples.

23. A composition as set forth in any one of claims 1 to 11 inclusive, when manufactured by the process set forth in any one of claims 15 to 22 inclusive.

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As can be seen from the foregoing Table the crystalline antibiotic is effective in treating multiple coccidiosis infections and is further significant in causing greater than expected efficiency of conversion of feed to weight gain in the chickens, thus indicating that there is some synergistic effect present.

WHAT WE CLAIM IS:—

1. A veterinary composition comprising antibiotic X-537 A or a non-toxic pharmaceutically acceptable salt thereof as the active ingredient in association with a compatible carrier material; said active ingredient being present in an amount of from 0.001% to 0.0125% by weight of the composition.

2. A composition as set forth in claim 1, wherein the active ingredient is present in an amount from 0.00312% to 0.00625% by weight.

3. A composition as set forth in claim 1, wherein the active ingredient is present in an amonut of 0.005% by weight.

4. A composition as set forth in any one of claims 1 to 3 inclusive, wherein the active ingredient is present in crystalline form.

5. A veterinary composition which comprises an animal feed having dispersed therein from 0.001% to 0.0125% by weight of antibiotic X-537 A or a non-toxic pharmaceutically acceptable salt thereof as the active ingredient.

6. A composition as set forth in claim 5, wherein the active ingredient is present in an amount of from 0.00312% to 0.00625% by weight.

7. A composition as set forth in claim 5, wherein the active ingredient is present in an amount of 0.005% by weight.

8. A composition as set forth in any one of claims 5 to 7 inclusive, wherein the active ingredient is present in crystalline form.

9. An animal feed having dispersed therein from 0.001% to 0.0125% by weight of antibiotic X-537 A or a non-toxic pharmaceutically acceptable salt thereof as the active ingredient.

10. An animal feed as set forth in claim 9, wherein the active ingredient is present in crystalline form.

11. A premix useful for preparing a composition as set forth in any one of claims 1 to 10 inclusive comprising antibiotic X-537 A or a non-toxic pharmaceutically acceptable salt thereof in association with a compatible carrier material; said antibiotic or salt thereof being present in an amount appropriately higher than 0.001% by weight of the premix.

12. A method for providing poultry suffering from or subject to coccidiosis free from or resistant to coccidiosis which comprises orally administering to said poultry a veterinary composition or animal feed as claimed in any one of claims 1 to 10 inclusive.

13. A method as set forth in claim 12, wherein the compatible carrier material is an animal feed.

14. A method as set forth in claim 12 or claim 13, wherein the active ingredient is present in crystalline form.

15. A process for the manufacture of a veterinary composition as claimed in claim 1, which process comprises mixing antibiotic X-537 A or a non-toxic pharmaceutically acceptable salt thereof as the active ingredient with a compatible carrier material, said active ingredient being used in an amount of from 0.001% to 0.0125% by weight of the composition.

16. A process as set for in claim 15, wherein the inert carrier is a feedstuff, an extender material or a combination of a feedstuff and an extender material.

17. A process as set forth in claim 13 or claim 16, wherein from 0.001% to 0.0125% by weight of active ingredient are used.

18. A process as set forth in claim 15 or claim 16, wherein from 0.00312% to 0.00625% by weight of active ingredient are used.

19. A process as set forth in claim 18, wherein 0.005% by weight of active ingredient are used.

20. A process as set forth in any one of claims 15 to 19 inclusive, wherein the active ingredient is used in crystalline form.

21. A process for the manufacture of a premix as claimed in claim 11, which process comprises mixing antibiotic X-537 A or a non-toxic pharmaceutically acceptable salt thereof with a compatible carrier material; said antibiotic or salt being used in an amount appropriately higher than 0.001% by weight of the premix.

22. A process for the manufacture of the compositions claimed in any one of claims 1 to 11 inclusive, substantially as hereinbefore particularly described with reference to the foregoing Examples.

23. A composition as set forth in any one of claims 1 to 11 inclusive, when manufactured by the process set forth in any one of claims 15 to 22 inclusive.

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