Lincomycin-2-phosphate antibiotic compositions and process of treatment

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ABSTRACT OF THE DISCLOSURE

Compounds of the formula

\[
\text{R}_1 \quad \text{R}_2 \quad \text{X} \quad \text{HO} \quad \text{O} \quad \text{OH} \quad \text{SCH}_3 \quad \text{O} \quad \text{p-OH} \quad \text{O} \quad \text{OH}
\]

wherein X is hydroxy, chlorine or bromine, \( \text{R}_1 \) is alkyl of \( C_{1-8} \), cycloalkyl of \( C_{4-8} \), or aralkyl of \( C_{5-12} \) and \( \text{R}_2 \) is hydrogen, alkyl of \( C_{1-8} \), cycloalkyl of \( C_{4-8} \), or aralkyl of \( C_{5-12} \) including pharmaceutically acceptable salts thereof in unit dosage form of 50 to 500 mg. with pharmaceutical carrier for oral and parenteral administration and process for therapeutic or prophylactic treatment of humans and animals hosting a lincomycin-susceptible parasite.

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of application Ser. No. 602,116, filed Dec. 16, 1966.

BRIEF SUMMARY OF INVENTION

This invention relates to lincomycin and clindamycin-2-phosphates and compounds related thereto (compounds of the Formula 1) and pharmaceutically acceptable salts thereof prepared in unit dosage form of from 50 to 500 mg. in association with a pharmaceutical carrier and a process for prophylactic and therapeutic treatment of humans and animals hosting a lincomycin-susceptible parasite.

DETAILED DESCRIPTION

This application relates to novel compositions and process of treatment and more particularly to compositions comprising, in unit dosage form, a compound of the formula

\[
\text{R}_1 \quad \text{R}_2 \quad \text{X} \quad \text{HO} \quad \text{O} \quad \text{OH} \quad \text{SCH}_3 \quad \text{O} \quad \text{p-OH} \quad \text{O} \quad \text{OH}
\]

wherein X is hydroxy, chlorine, or bromine, \( \text{R}_1 \) is alkyl of from 1 to 8 carbon atoms, cycloalkyl of from 3 to 8 carbon atoms or aralkyl of from 7 to 12 carbon atoms and \( \text{R}_2 \) is hydrogen, alkyl of from 1 to 8 carbon atoms, cycloalkyl of from 3 to 8 carbon atoms or aralkyl of from 7 to 12 carbon atoms; and including the pharmaceutically acceptable salts thereof in combination with a pharmaceutically carrier.

Typical, but not all, therapeutic compounds of this invention include the following as referred to the above Formula 1:

\[
\begin{align*}
\text{Trans n-propyl} & \quad \text{Methyl} & \quad \text{(R)-OH} \\
\text{D}- & \quad \text{Hydrogen} & \quad \text{Do.} \\
\text{D}- & \quad \text{Ethyl} & \quad \text{D.} \\
\text{D}- & \quad \text{Isopropyl} & \quad \text{D.} \\
\text{n-Butyl} & \quad \text{Cyclohexyl} & \quad \text{D.} \\
\text{D}- & \quad \text{Methyl} & \quad \text{D.} \\
\text{D}- & \quad \text{Hydrogen} & \quad \text{D.} \\
\text{D}- & \quad \text{n-Butyl} & \quad \text{D.} \\
\text{N-hexyl} & \quad \text{Methyl} & \quad \text{D.} \\
\text{D}- & \quad \text{Hydrogen} & \quad \text{D.} \\
\text{D}- & \quad \text{Ethyl} & \quad \text{D.} \\
\text{n-Butyl} & \quad \text{Cyclohexyl} & \quad \text{D.} \\
\text{n-Pentyl} & \quad \text{Methyl} & \quad \text{D.} \\
\text{D}- & \quad \text{Hydrogen} & \quad \text{D.} \\
\text{D}- & \quad \text{n-Pentyl} & \quad \text{D.}
\end{align*}
\]

In the above Formula 1, the vertical wavy line \( \sim \) is used to indicate that the group \( \text{R}_1 \) can be in position cis (below the plane of the ring) or trans (above the plane of the ring), with respect to the carbonyl group. The horizontal wavy line \( \sim \) is used to indicate that both epimers are to be included, i.e., the D-erythro configuration and L-threo configuration are intended.

Examples of alkyl are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, and octyl and isomeric forms thereof. Examples of cycloalkyl are cyclopentyl, cyclohexyl, cyclohexyl, cycloheptyl, cyclooctyl, 2-methylcyclopentyl, 2,3-dimethylcyclobutyl, 4-methylcyclobutyl, and 3-cyclopentylpropyl. Examples of aralkyl are benzyl, phenethyl, \( \alpha \)-phenylpropyl, and \( \alpha \)-naphthylmethyl.

The compounds of the Formula 1 can be prepared by the methods disclosed in copending application Ser. No. 602,116 filed Dec. 16, 1966.

Further, the invention relates to a process for therapeutic treatment of humans and animals hosting bacterial and other microparasites and the prophylactic treatment of a disease-susceptible host comprising the administration of a compound of the formula 1 or a pharmaceutically acceptable salt thereof to the host.

The compounds of the invention have essentially the same antibacterial spectrum in vivo as the antibiotic lincomycin and can be used for the same purposes as lincomycin. The compounds of the invention are particularly useful for oral administration to animals, including birds, because they lack the bitter taste of lincomycin.

The compositions of the present invention are presented for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, sterile parenteral solutions or suspensions, and oral solutions or suspensions, and oil-water emulsions containing suitable quantities of a compound of Formula 1 or its pharmaceutically acceptable salts.

For oral administration either solid or fluid unit dosage forms can be prepared. For preparing solid compositions such as tablets, the principal active ingredient is mixed with conventional ingredients such as talc, magnesium stearate, dicalcium phosphate, magnesium aluminum silicate, calcium sulfate, starch, lactose, acacia, methylcellulose, and functionally similar materials as pharmaceutical diluents or carriers. The tablets can be laminated or...
otherwise compounded to provide a dosage form affording the advantage of prolonged or delayed action or predetermined successive action of the enclosed medication. For example, the tablet can contain an inner dosage component and an outer dosage component, the latter being in the form of an envelope over the former.

Alternatively, the two component system can be utilized for preparing tablets containing two or more incompletely soluble active ingredients. Wafers are prepared in the amorphous, crystalline or amorphous crystalline form in shape and size of sucrose or other sweetener and flavor. In their simplest embodiment, capsules, like tablets, are prepared by mixing the antibiotic with an inert pharmaceutical fluid and filling the mixture into a hard gelatin capsule of appropriate size. In another embodiment, capsules are prepared by filling hard gelatin capsules with polymeric acid coated beads containing the antibiotic. Soft gelatin capsules are prepared by machine encapsulation of a slurry of the antibiotic with an acceptable vegetable oil, light liquid petrolatum or other inert oil.

Fluid unit dose forms for oral administration such as syrups, elixirs, and suspensions can also be prepared. The water-soluble forms can be dissolved in an aqueous vehicle together with sugar, aromatic flavoring agents and preservatives to form a syrup. An elixir is prepared by using hydro-alcoholic (ethanol) vehicle with suitable sweeteners such as sugar and saccharin, together with an aromatic flavoring agent.

Suspensions can be prepared of the insoluble forms with a syrup vehicle with the aid of a suspending agent such as acacia, tragacanth, methylcellulose and the like.

Topical ointments can be prepared by dispersing the antibiotic in a suitable oily ointment base such as petrolatum, lanolin, polyethylene glycols, mixtures thereof, and the like. Advantageously, the antibiotic is finely divided by means of a colloid mill utilizing light liquid petrolatum as a levigating agent prior to dispersing in the ointment base. Topical creams and lotions are prepared by dissolving the antibiotic in the oil phase prior to the emulsification of the oil phase in water.

For parenteral administration, fluid unit dosage forms are prepared utilizing the antibiotic and a sterile vehicle, water being preferred. The antibiotic, depending on the form and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the water-soluble antibiotic can be dissolved in water for injection and filtered before filling into a suitable vial or ampule and sealing. Advantageously, adjuvants such as local anesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying label of water for injection is supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in the same manner except that the antibiotic is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The antibiotic can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the antibiotic.

The term unit dosage form as used in the specification and claims refers to physically discrete units suitable as unitary doses for human subjects and animals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect associated with the required pharmaceutical diluent carrier or vehicle. The specifications for the novel unit dosage forms of this invention are dictated by and directly dependent on (a) the unique characteristics of the active material and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active material for therapeutic use in humans and animals, as disclosed in detail in this specification, these being features of the present invention. Examples of suitable unit dosage forms in accord with the invention are tablets, capsules, pills, troches, suppositories, powder packets, granules, wafers, cachets, teaspoonfuls, tablespoonfuls, dropperfuls, ampules, vials, segregated multiples of any of the foregoing, and other forms as herein described.

In addition to the administration of a compound of Formulas 1 and 2 as the principal active ingredient of compositions for the treatment of the conditions described herein, the said compound can be included with other types of compounds to obtain advantageous combinations of properties. Such combinations include a compound of Formula 1 with antibiotics such as spectinomycin, chloramphenicol, tetracyclines (e.g., tetracycline, oxytetracycline and chlorotetrachline), penicillin, erythromycin, novobiocin, kanamycin, streptomycin, neomycin, polymyxin, bacitracin, nystatin, and endomycin to broaden the bactericidal spectrum of the composition and for synergistic action against particular bacteria; steroids having antiinflammatory activity such as hydrocortisone, prednisolone, methylprednisolone, fluorprednisolone and the like; analogues such as aspirin, sodium salicylate, (acetysalicylic acid) anhydride, acetaminophen and salicylamide; antihistamines such as chloropheniramine maleate, diphenhydramine, promethazine, pyrilamine, and the like; sulfas such as sulfadiazine, sulfamerazine, sulfacetazine, sulfadimethoxazole, sulfamethiazole, and the like, antifungals such as undecylenic acid, sodium propionate, salicylanilide, sodium caprylate, and hexetidine; and the vitamins.

The dosage of a compound of Formula 1 for treatment depends on route of administration; the age, weight, and condition of the patient; and the particular disease to be treated. A dosage schedule of from about 50 to 500 mg., 1 to 4 times daily (every six hours), embraces the effective range for the treatment of most conditions for which the compositions are effective. For children the dosage is calculated on the basis of 6 to 8 mg./kg. by weight to be administered every six hours.

The antibiotic is compounded with a suitable pharmaceutical carrier in unit dosage form for convenient and effective administration. In the preferred embodiments of this invention, the dosage units contain a compound of Formula 1 in 50, 100, 200 and 500 mg. amounts for systemic treatment; in 0.25, 0.5, 1, 2 and 5% amounts for topical or localized treatment; and 5 to 25% w/v. for parenteral treatment. The dosage of compositions containing a compound of Formula 1 and one or more other active ingredients is to be determined with reference to the usual dosage of each such ingredient.

The following examples are illustrative of the best mode contemplated by the inventors for carrying out their invention and are not to be construed as limiting.

**EXAMPLE 1**

**Capsules**

One thousand two-piece hard gelatin capsules for oral use, each containing 200 mg. of lincomycin-2-phosphate are prepared from the following types and amounts of materials:

<table>
<thead>
<tr>
<th>Gm.</th>
<th>______________________</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lincomycin-2-phosphate</td>
<td>200</td>
</tr>
<tr>
<td>Corn starch</td>
<td>150</td>
</tr>
<tr>
<td>Talc</td>
<td>2.5</td>
</tr>
</tbody>
</table>

The materials are thoroughly mixed and then encapsulated in the usual manner.

The foregoing capsules are useful for the systemic treatment of infection in adult humans by the oral administration of 1 capsule every 4 hours.

Using the procedure above, capsules are similarly prepared containing lincomycin-2-phosphate in 50, 100, and...
500 mg. amounts by substituting 50, 100 and 500 gm. of lincomycin-2-phosphate for the 200 gm. used above.

**EXAMPLE 2**

**Capsules**

One thousand two-piece hard gelatin capsules for oral use, each containing 200 mg. of lincomycin-2-phosphate and 250 mg. of tetracycline hydrochloride, are prepared from the following types and amounts of ingredients:

- **Lincomycin-2-phosphate**: 200 Gm.
- **Tetracycline hydrochloride**: 250 Gm.
- **Talc**: 75 Gm.
- **Magnesium stearate**: 2.5 Gm.

The ingredients are thoroughly mixed and then encapsulated in the usual manner. The foregoing capsules are useful for the systemic treatment of infection in adult humans by the oral administration of 1 capsule every 6 hours.

Using the procedure above, capsules are similarly prepared containing lincomycin-2-phosphate and each of the following antibiotics in place of tetracycline by substituting 250 gm. of such other antibiotic for tetracycline: chloramphenicol, oxytetracycline, chlorotetracycline, furamycins, erythromycin, streptomycin, dihydrostreptomycin and novobiocin. When a penicillin, such as potassium penicillin G, is to be used in place of tetracycline, 230,000 units per capsule is employed.

Such combination products are useful for the systemic treatment of mixed infections in adult humans by the oral administration of 1 capsule every 6 hours.

**EXAMPLE 3**

**Tablets**

One thousand tablets for oral use, each containing 500 mg. of lincomycin-2-phosphate are prepared from the following types and amounts of materials:

- **Lincomycin-2-phosphate**: 500 Gm.
- **Lactose**: 125 Gm.
- **Corn starch**: 65 Gm.
- **Magnesium stearate**: 7.5 Gm.
- **Light liquid petrolatum**: 3 Gm.

The ingredients are thoroughly mixed and slugged. The slugs are broken down by forcing through a number sixteen screen. The resulting granules are then compressed into tablets, each containing 300 mg. of lincomycin-2-phosphate.

The foregoing tablets are useful for systemic treatment of infections in adult humans by oral administration of 1 tablet every 4 hours.

Using the above procedure, except for reducing the amount of lincomycin-2-phosphate to 200 gm., tablets containing 200 mg. of lincomycin-2-phosphate are prepared.

**EXAMPLE 4**

**Tablets**

One thousand oral tablets, each containing 200 mg. of lincomycin-2-phosphate and a total of 250 mg. (83.3 mg. each) of sulfadiazine, sulfamerazine, and sulfamethazine, are prepared from the following types and amounts of materials:

- **Lincomycin-2-phosphate**: 200 Gm.
- **Sulfadiazine**: 83.3 Gm.
- **Sulfamerazine**: 83.3 Gm.
- **Sulfamethazine**: 83.3 Gm.
- **Lactose**: 50 Gm.
- **Corn starch**: 50 Gm.
- **Calcium stearate**: 5.5 Gm.
- **Light liquid petrolatum**: 5 Gm.

The ingredients are thoroughly mixed and slugged. The slugs are broken down by forcing through a number sixteen screen. The resulting granules are then compressed into tablets, each containing 200 mg. of lincomycin-2-phosphate and a total of 250 mg. (83.3 mg. each) of sulfadiazine, sulfamerazine, and sulfamethazine.

The foregoing tablets are useful for systemic treatment of infections by the oral administration of 4 tablets first and then 1 every six hours.

For the treatment of urinary infections, the triple sulfas in the above formulation is advantageously replaced by 250 gm. of sulfamethathiazole or 250 gm. of sulfacetamide.

**EXAMPLE 5**

**Granules**

2367 gm. of a granulation suitable for reconstitution with water prior to use is prepared from the following types and amounts of ingredients:

- **Lincomycin-2-phosphate**: 150 Gm.
- **Tetracycline hydrochloride**: 150 Gm.
- **Lechitin**: 5 Gm.
- **Sorbosene, powdered**: 2000 Gm.
- **Flavor**: 60 Gm.
- **Sodium metabisulfite**: 2 Gm.

The tetracycline is finely divided and coated with the lecithin. The coated tetracycline, lincomycin-2-phosphate, sugar, flavor, and sodium metabisulfite are mixed together until thoroughly blended. The powder mixture is wetted with water and forced through a screen to form granules. The granules are dried and 23.67 gm. filled into 60 cc. bottles. Prior to use sufficient water is added to the granules to make 60 cc. of composition.

The foregoing composition is useful for systemic treatment of infection, particularly in children at a dose of one teaspoonful 4 times daily.

**EXAMPLE 6**

**Oral syrup**

One thousand cc. of an aqueous suspension for oral use, containing in each 5 cc. dose, one-half gram of total sulfas and 200 mg. of lincomycin-2-phosphate is prepared from the following types and amounts of ingredients:

- **Lincomycin-2-phosphate**: 40 gm.
- **Sulfadiazine**: 33.3 gm.
- **Sulfamerazine**: 33.3 gm.
- **Sulfamethazine**: 33.3 gm.
- **Citic acid**: 2 gm.
- **Benzoic acid**: 1 gm.
- **Sorosene**: 700 gm.
- **Tragacanth**: 5 gm.
- **Lemon oil**: 2 cc.
- **Deionized water, qs.**: 1000 cc.

The citric acid, benzoic acid, sorosene, tragacanth, and lemon oil are dispersed in sufficient water to make 850 cc. of solution. The lincomycin-2-phosphate and finely powdered sulfa's are stirred into the syrup until uniformly distributed. Sufficient water is added to make 1000 cc.

The composition so prepared is useful in the systemic treatment of meningitis in adult humans at a dose of 1 teaspoonful 4 times a day.

**EXAMPLE 7**

**Parenteral solution**

A sterile aqueous solution for intramuscular use, containing in 1 cc. 75 mg. of lincomycin-2-phosphate is prepared from the following types and amounts of materials:

- **Lincomycin-2-phosphate**: 75 gm.
- **Lidocaine hydrochloride**: 4 gm.
- **Methylparaben**: 2.5 gm.
- **Propylparaben**: 0.17 gm.
- **Water for injection, qs.**: 1000 cc.
The ingredients are dissolved in the water and the solution sterilized by filtration. The sterile solution is filled into vials and the vials sealed.

EXAMPLE 8

Parenteral solution

A sterile aqueous solution for intramuscular use, containing 1 cc. 250 mg. of lincomycin-2-phosphate, as the Na salt, is prepared from the following types and amounts of ingredients:

lincomycin-2-phosphate—250 gm.
Sodium hydroxide 10% solution, q.s.
Water for injection, q.s.—1000 cc.

The lincomycin-2-phosphate is added to the water and sufficient sodium hydroxide added to form a solution and the solution sterilized by filtration. The sterile solution, in the amount of 2 cc., is aseptically filled into sterile vials and frozen. The water is removed under high vacuum and the vials containing the lyophilized powder are sealed. Just prior to use, sufficient sterile water for injection to make 2 cc. of solution is added to the vial.

EXAMPLE 9

Topical ointment

One thousand gm. of 0.25% ointment is prepared from the following types and amounts of ingredients:

lincomycin-2-phosphate 875 gm.
Zinc oxide 2.5 gm.
Calamine 50 gm.
Liquid petrolatum (heavy) 50 gm.
Wool fat 750 gm.
White petrolatum, q.s. — 1000 cc.

The white petrolatum and wool fat are melted and 0.5 gm. of liquid petrolatum added thereto. The lincomycin-2-phosphate, zinc oxide and calamine are added to the remaining liquid petrolatum and the mixture chilled until the powders are finely divided and uniformly dispersed. The powder mixture is stirred into the white petrolatum mixture and stirring continued until the ointment congeals.

The foregoing ointment is usefully applied topically to the skin of mammals for the treatment of infection.

The foregoing composition can be prepared by omitting the zinc oxide and calamine.

Following the procedure above, ointments are similarly prepared containing lincomycin-2-phosphate in 0.5, 1, 2 and 5% amounts by substituting 5, 10, 20, and 50 gm. of lincomycin-2-phosphate for the 2.5 gm. used above.

EXAMPLE 10

Cream

One thousand gm. of a vaginal cream are prepared from the following types and amounts of ingredients:

lincomycin-2-phosphate 250 gm.
Prednicarone sodium 10 gm.
Sodium citrate 4.5 gm.
Polyethylene glycol 4000 120 gm.
Calcium stearate 0.05 gm.
Powdered sucrose 5000 gm.

The ingredients are dissolved in the water and the solution sterilized by filtration. The sterile solution is filled into vials and the vials sealed.

EXAMPLE 11

Ointment, ophthalmic

One thousand gm. of an ophthalmic ointment containing 0.5% lincomycin-2-phosphate are prepared from the following types and amounts of ingredients:

lincomycin-2-phosphate 5 gm.
Bacitracin 12.2 gm.
Polymyxin B sulfate (10,000 units/mg.) 1 gm.
Light liquid petrolatum 250 gm.
Wool fat 700 gm.
White petrolatum, q.s. — 1000 gm.

The antibiotics are finely divided by means of an air micronizer and added to the light liquid petrolatum. The mixture is passed through a colloid mill to uniformly distribute the antibiotics. The wool fat and white petrolatum are melted together, strained, and the temperature adjusted to 45–50° C. The liquid petrolatum slurry is added and the ointment stirred until congealed. Suitably, the ointment is packaged in one dram ophthalmic tubes.

The foregoing ointment is usefully applied to the eye for treatment of localized infection in humans and other animals.

Advantageously, the foregoing composition can contain 5 gm. (0.5%) of methylprednisolone for the treatment of inflammation, and, alternatively, the bacitracin and polymyxin B sulfate can be omitted.

EXAMPLE 12

Eye-ear drops

One thousand cc. of a sterile aqueous solution for eye or ear use containing 10 mg. of lincomycin-2-phosphate and 10 mg. of prenisolone succinate sodium in each cc. is prepared from the following types and amounts of ingredients:

lincomycin-2-phosphate 10 gm.
Prednisolone succinate sodium 10 gm.
Sodium citrate 4.5 gm.
Polyethylene glycol 4000 120 gm.
Myristyl-γ-picolinium chloride 0.2 gm.
Polyvinylpyrrolidone 1 gm.
Deionized water, q.s. — 1000 cc.

The ingredients are dissolved in the water and the resulting solution is sterilized by filtration. The solution is aseptically filled into sterile dropper containers.

The composition so prepared is useful in the topical treatment of inflammation and infection of the eye and ear as well as other sensitive tissues of the animal body.

EXAMPLE 13

Troches

Ten thousand troches are prepared from the following types and amounts of ingredients:

lincomycin-2-phosphate 100 gm.
Neomycin sulfate 50 gm.
Polymyxin B sulfate (10,000 units/mg.) 1 gm.
Ethyl aminobenzoate 50 gm.
Calcium stearate 150 gm.
Powdered sucrose, q.s. — 5000 gm.
The powdered materials are mixed thoroughly and then compressed into half gram troches following the usual techniques for the preparation of compressed tablets. The troches are held in the mouth and allowed to dissolve slowly to provide treatment for the mouth and throat.

**EXAMPLE 14**

Suppository, rectal

One thousand suppositories, each weighing 2.5 gm. and containing 100 mg. of lincomycin-2-phosphate are prepared from the following types and amounts of ingredients:

- Lincomycin-2-phosphate: 150 Gm.
- Polybromin B sulfate (10,000 units/mg.): 1.25
- Ethyl aminobenzoate: 1
- Zinc oxide: 62.5
- Propylene glycol: 162.5
- Polyethylene glycol 4000, q.s.: 2500

The lincomycin-2-phosphate, polybromin B sulfate, 6-methylprednisolone, ethyl aminobenzoate, and zinc oxide are added to the propylene glycol and the mixture is mixed until the powders are finely divided and uniformly dispersed. The polyethylene glycol 4000 is added and the propylene glycol dispersion added slowly with stirring. The suspension is poured into unchilled molds at 40°C. The composition is allowed to cool and solidify and then removed from the mold and each suppository foil wrapped. The foregoing suppositories are inserted rectally for local treatment of inflammation and infection.

Alternatively, the foregoing composition can be prepared omitting the steroid.

**EXAMPLE 15**

Mastitis ointment

One thousand gm. of an ointment for the treatment of mastitis in dairy cattle is prepared from the following types and amounts of ingredients:

- Lincomycin-2-phosphate: 50 Gm.
- Prednisolone acetate: 0.5
- Light liquid petrolatum: 300
- Chlorobutanol, anhydrous: 5
- Polysorbate 80: 5
- 2% aluminum monostearate-petrolatum oil: 400
- White petrolatum, q.s.: 1000

The lincomycin-2-phosphate and prednisolone acetate are melted with the liquid petrolatum until finely divided and uniformly dispersed. The chlorobutanol, polysorbate 80, petrolatum oil, and white petrolatum are heated to 120°F. to form a melt and the liquid petrolatum dispersion stirred in. With continued stirring the dispersion is allowed to cool (and congeal) to room temperature and is filled into disposable mastitis syringes in 10 gm. doses.

**EXAMPLE 16**

**Animal feed**

One thousand gm. of a feed mix is prepared from the following types and amounts of ingredients:

- Lincomycin-2-phosphate: 10 Gm.
- Soybean meal: 400
- Fish meal: 400
- Wheat germ oil: 50
- Sorghum molasses: 140

The ingredients are mixed together and pressed into pellets. The composition can be fed to laboratory animals, i.e., rats, mice, guinea pigs, and rabbits for prophylaxis during shipping.

For larger animals, the composition can be added to the animal's regular feed in an amount calculated to give the desired dose of lincomycin-2-phosphate.

**EXAMPLE 17**

Following the procedure of each of the preceding Examples 1 and 3, each member selected from the group consisting of sodium novobiocin, calcium novobiocin, chlorotetracycline hydrochloride, oxytetracycline hydrochloride, tetracycline, tetracycline hydrochloride, and tetracycline phosphate complex is added in 50, 100, and 250 gm. amounts to provide a combination having a wider spectrum of therapeutic effectiveness in the treatment of infectious diseases resulting from mixed organisms susceptible to lincomycin-2-phosphate as indicated in the present specification and the above indicated antibiotics as already well known to the medical art.

**EXAMPLE 18**

Following the procedure of the preceding Examples 1 through 16, inclusive, each member selected from the group consisting of lincomycin-2-phosphate, hemiammonium salt, (S)-chloro-7-deoxylincomycin-2-phosphate, (S)-chloro-7-deoxy-1'-dimethyllincomycin-2-phosphate, (S)-chloro-7-deoxy-4'-propyl-3'pentyl-1'-dimethyllincomycin-2-phosphate, (S)-chloro-7-deoxy-4'-propyl-3'-pentyl-1'-dimethyllincomycin-2-phosphate, calcium salt, or (S)-chloro-7-deoxy-4'-propyl-3'-pentyl-1'-dimethyllincomycin-2-phosphate, magnesium salt is substituted in an equivalent amount for the lincomycin-2-phosphate shown in the example to provide similar therapeutic properties.

**EXAMPLE 19**

Following the procedure of the preceding Examples 1 through 5, 9 through 11, and 13 through 16, inclusive, each member selected from the group consisting of (S)-chloro-7-deoxylincomycin-2-phosphate, calcium salt, (S)-chloro-7-deoxylincomycin-2-phosphate, magnesium salt, (S)-chloro-7-deoxy-1'-dimethyllincomycin-2-phosphate, calcium salt, or (S)-chloro-7-deoxy-1'-dimethyllincomycin-2-phosphate, magnesium salt is substituted in an equivalent amount for the lincomycin-2-phosphate shown in the example and provides similar therapeutic properties. What is claimed is:

1. An antibacterial composition comprising, in unit dosage form, from about 50 to 300 mg. of a compound of the formula:

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R1
N = O
R2
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wherein X is hydroxy, chlorine or bromine, R1 is alkyl of C1-8, cycloalkyl or C6-8, or aralkyl of C8-12, and R2
1. A composition of claim 1 wherein the concentration of the compound of the formula is from about 0.25% v/v to about 25% w/w.

2. A composition of claim 1 wherein the concentration of the compound of the formula is from about 5% v/v to about 25% w/w, and wherein the pharmaceutically acceptable vehicle for parenteral administration is a sterile vehicle for parenteral administration.

3. A process for treating a bacterial disease in humans and animals which comprises administering to the bacterial host an antibacterial therapeutic amount of a compound of the formula:

4. A process according to claim 3 wherein the compound of the formula is administered in unit dosage form in an amount of from about 50 to about 500 mg. of said compound in association with a pharmaceutical carrier.

5. A process according to claim 4 wherein the compound of the formula is administered in unit dosage form in an amount of from about 50 to about 500 mg. of said compound in association with a pharmaceutical carrier.

6. A process of prophylactic treatment for the prevention of bacterial disease comprising the administering to a disease-susceptible human or animal host a prophylactic antibacterial amount of a compound of the formula:

7. A process according to claim 6 wherein the compound of the formula is administered in unit dosage form in an amount of from about 50 to about 500 mg. of said compound in association with a pharmaceutical carrier.

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