CROSS VETPHARM GROUP LTD

Osmonds (Dublin), Bimeda Ireland,
Bimeda Chemicals Export,
Bimeda Inc-Le Sueur, MN.,and Kansas, MO., USA
Bimeda-MTC Animal Health Inc - Ontario, Canada
Cross Vetpharm Group Uk Ltd - Anglesey, Wales

Broomhill Road, Tallaght,
Dublin 24, Ireland.

Tel: (353)-1-4515522 / 4515011
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16 August, 2001

Dr. Lonnie Luther
Quality Assurance Support Team (HFV-102) Room 387
FDA Center for Veterinary Medicine
7500 Standish Place
Rockville, MD 20855

Dear Dr. Luther,

Please find enclosed a suitability petition submitted on behalf of Cross Vetpharm Group Limited of Ireland. Cross Vetpharm requests consideration of this suitability petition to file an ANADA for oxytetracycline 300 mg/mL injection for intravenous use in cattle.

Please call if you have questions.

Sincerely,

Anne Nallen
Anne Nallen
Head of Regulatory Affairs

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BY:_____

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OIP-0385

CP 1

SUITABILITY PETITION

IDENTIFICATION OF PETITIONER:

This Suitability Petition is submitted on behalf of Cross Vetpharm Group Limited of Ireland under Section 512 (n)(3) of the Federal Food, Drug, and Cosmetic Act.

ACTION REQUESTED:

The petitioner requests permission from the Commissioner to file an Abbreviated New Animal Drug Application (ANADA) for a generic product that contains a different concentration of the active ingredient than the approved pioneer product. The pioneer product is Boehringer Ingelheim's Medamycin®-100 (oxytetracycline hydrochloride) 100 mg/mL Injection, approved by the Food and Drug Administration under NADA 108-963. A copy of the pioneer product labeling (package insert) is provided (Attachment 1).

The ANADA will provide for the use of a product containing 300 mg oxytetracycline per mL rather than the 100 mg/mL concentration utilized by the pioneer product. Additionally, oxytetracycline is provided in the generic product as oxytetracycline amphoteric, whereas the pioneer product contains oxytetracycline hydrochloride. Both the proposed and the pioneer products are solutions delivered via intravenous injection. Both the proposed and pioneer products are provided to affected animals at the rate of 3-5 mg oxytetracycline per pound of body weight per day.

The product labeling will provide for indications, pharmacology, recommended dosages, contraindications, precautions and warnings identical to the pioneer product. Draft labeling for the proposed product is provided (Attachment II). The proposed product label differs from the pioneer product only in listing the active ingredient designation (oxytetracycline amphoteric), concentration and subsequent dosing volumes.

STATEMENT OF GROUNDS:

The proposed product contains the same active ingredient and will be labeled with the same indications, recommended dose rates, contraindications, precautions and warnings as the approved pioneer product. The route of administration (intravenous injection) and the dosage form (a true solution) are the same for the generic and pioneer products. The bioavailability and subsequent clinical effect for the generic product is expected to be similar to that of the pioneer product even in the higher concentration of active ingredient.

Current research on the complex formed between oxytetracycline and magnesium supports the similarity of bioavailability and clinical effects regardless of the starting form (hydrochloride salt or dihydrate) of the active ingredient. Since both Boehringer Ingelheim's Medamycin®-100 and Cross Vetpharm's oxytetracycline 300 mg/mL both contain sources of divalent magnesium far in excess of the 1:1 stoicheometric ratio, any effect of the starting active materials is swamped by the oxytetracycline:magnesium complexation effect. For example, the stoichiometry of the oxytetracycline: magnesium+2 complex was determined to be (1:1) independent of pH in the range of 7 to 10 and regardless of the percentage of polyethylene glycol 400 in the solution[1].

1. Tongaree S. Goldberg AM. Falagan DR. Proust RI. Pharmaceutical Development and Technology. 5(2):189-99, 2000

Furthermore, potentiometric determinations of the formation constant of oxytetracycline magnesium+2 over large pH ranges under experimental conditions pertaining to blood plasma (37^0C, NaCl0.15mol dm^{-3}). Simulations of distributions into the proton and metal complex species allow the calculations of the distribution to be calculated. "These distributions confirm that, in combination with the proton-bound faction of the four tetracyclines [including oxytetracycline:magnesium], the metal bound fraction represents more than 99% of these drugs in plasma, the extent of their free fraction commonly being less than 1%[2]. Therefore the bioavailability and clinical effects should be equivalent regardless of the starting form of the active ingredient.

As such, the sponsor will request waiver of *in vivo* bioequivalence support because bioavailability is self-evident. The sponsor intends to provide results of animal studies supporting safety issues for the more highly concentrated generic product.

ENVIRONMENTAL IMPACT:

The action of submitting this Suitability Petition and its review by the FDA - Center for Veterinary Medicine is not expected to have an environmental impact. The action requested qualifies for categorical exclusion under 21 CFR Part 25.30(h) from the requirement for an environmental assessment and, to the best of the sponsor's knowledge, no extraordinary circumstances exist.

ECONOMIC IMPACT:

An "Economic Impact" analysis of this action will be provided if requested by the Commissioner.

CERTIFICATION:

Cross Vetpharm certifies that this suitability petition contains all information known to them that is unfavorable to the petition.

Anne Nallen

27 July 2001

Anne Nallen
Head of Regulatory Affairs
Cross Vetpharm Group Ltd.,
Broomhill Road,
Tallaght,
Dublin 24,
Ireland.

Attachments

1. Pioneer Product Label
2. Proposed Product Label

2. Berthon G., Brion M. Lambs L. Journal of Inorganic Biochemistry, 19 (1) :1-18, 1983 Aug.

ATTACHMENT 1

PIONEER PRODUCT LABEL

INDICATIONS: MEDAMYCIN Oxytetracycline Hydrochloride Injection is for the treatment of diseases in beef cattle, beef calves, non-lactating dairy cattle and dairy calves caused by pathogens sensitive to Oxytetracycline HCl.

DOSAGE AND ADMINISTRATION: 3-5 mg/lb body weight per day for a maximum of 4 consecutive days. For intravenous administration only.

See package insert for complete directions and warnings.

WARNING: Discontinue treatment at least 22 days prior to slaughter. NOT for use in lactating dairy cattle.

A withdrawal period has not been established for this product in preruminating calves. Do not use in calves to be processed for veal.

CAUTION: If no improvement occurs within 24 to 48 hours, consult a veterinarian.

Do not use the drug for more than 4 consecutive days. Use beyond 4 days or dosage higher than the maximum recommended dose may result in antibiotic residue in the tissues beyond the withdrawal time.

DSL-265C 9405

Lot No.: Exp. Date:

FERMENTA ANIMAL HEALTH

MEDAMYCIN® 100

Oxytetracycline Hydrochloride Injection
Antibiotic
100 mg/mL

Sterile

FOR USE IN ANIMALS ONLY
RESTRICTED DRUG (CALIFORNIA)
USE ONLY AS DIRECTED
KEEP OUT OF REACH OF CHILDREN
NADA 108-963, Approved by FDA

NET CONTENTS: 500 mL

EACH mL CONTAINS:

Oxytetracycline HCl	100 mg
Magnesium Chloride $\cdot 6H_2O$	5.75% w/v
Water for Injection	17.0% v/v
Propylene Glycol	q.s.

With Sodium Formaldehyde Sulfoxylate, 1.3% w/v, as a preservative and Monoethanolamine and/or Hydrochloric Acid for pH adjustment.

NOTE: Solution may darken on storage but potency remains unaffected.

Storage Temperature: 59°-86°F

MEDAMYCIN® is a Registered Trademark of Fermenta Animal Health Company.

TAKE TIME OBSERVE LABEL DIRECTIONS

Marketed By:
Fermenta Animal Health Co.
Kansas City, MO 64153

3 15563 23622 4

Oxytetracycline HCl Injection
Antibiotic
NADA 108-963, Approved by FDA

For Use in Beef Cattle, Beef Calves, Non-lactating Dairy Cattle and Dairy Calves Only.

Each mL contains 100 mg Oxytetracycline HCl, 5.75% w/v Magnesium Chloride $\bullet 6H_2O$, 17.0% v/v Water for Injection, 1.3% w/v Sodium Formaldehyde Sulfoxylate as a preservative and Propylene Glycol, q.s. Monoethanolamine and/or Hydrochloric Acid may be used for pH adjustment.

DESCRIPTION: Oxytetracycline Hydrochloride Injection is a sterile ready-to-use preparation containing 100 mg/mL Oxytetracycline HCl, for administration of the broad spectrum antibiotic, Oxytetracycline, by injection.

ANTIBIOTIC ACTION OF OXYTETRACYCLINE: Oxytetracycline is effective against a wide range of gram-negative and gram-positive organisms that are pathogenic for cattle. The antibiotic is primarily bacteriostatic in effect, and is believed to exert its antimicrobial action by the inhibition of microbial protein synthesis. The antibiotic activity of Oxytetracycline is not appreciably diminished in the presence of body fluids, serum or exudates. Since the drugs in the tetracycline class have similar antimicrobial spectra, organisms can develop cross resistance among them. Oxytetracycline is concentrated by the liver in the bile and excreted in the urine and feces at high concentrations and in a biologically active form.

WARNING: Discontinue treatment with Oxytetracycline Hydrochloride Injection at least 22 days prior to slaughter of the animal. Not for use in lactating dairy animals. A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal.

CAUTION: Store at 59°- 86°F.

If no improvement occurs within 24 to 48 hours, consult a veterinarian. Do not use the drug for more than 4 consecutive days. Use beyond 4 days or doses higher than maximum recommended dose may result in antibiotic tissue residues beyond the withdrawal period.

PRECAUTIONS: The improper or accidental injection of the drug outside of the vein will cause local tissue irritation manifested by temporary swelling and discoloration at the injection site.

Shortly after injection, treated animals may have a transient hemoglobinuria (darkened urine).

Reactions of an allergic or anaphylactic nature, sometimes fatal, have been known to occur in hypersensitive animals following the injection of Oxytetracycline solutions, but such reactions are rare.

At the first sign of any adverse reaction or anaphylactic shock (noted by glassy eyes, increased salivation, grinding of teeth, rapid breathing, muscular tremors, staggering, swelling of the eyelids or collapse), the product should be discontinued. Epinephrine solution at the recommended dosage levels should be administered and a veterinarian should be called immediately.

Because bacteriostatic drugs interfere with the bactericidal action of Penicillin, do not give Oxytetracycline Hydrochloride in conjunction with Penicillin.

As with other antibiotics, use of this drug may result in over-growth of non-susceptible organisms. If any unusual symptoms occur or in the absence of a favorable response following treatment, discontinue use immediately and call a veterinarian.

GENERAL INDICATIONS FOR USE: A great many of the pathogens involved in cattle diseases are known to be susceptible to Oxytetracycline Hydrochloride therapy. Many strains of organisms, however, have shown resistance to Oxytetracycline. In the case of certain coliforms, streptococci and staphylococci, it may be advisable to conduct culture and sensitivity testing to determine susceptibility of the infecting organism to Oxytetracycline. In this manner the likelihood of successful treatment with Oxytetracycline Hydrochloride Injection solution can be determined in advance.

DISEASES FOR WHICH OXYTETRACYCLINE HYDROCHLORIDE INJECTION IS INDICATED: The use of Oxytetracycline Hydrochloride Injection is indicated in beef cattle, beef calves, non-lactating dairy cattle and dairy calves for treatment of the following disease conditions caused by one or more of the Oxytetracycline sensitive pathogens listed as follows:

Disease	Causative Organism(s) Which Show Sensitivity to Oxytetracycline HCl Injection
Bacterial Pneumonia and Shipping Fever Complex Associated with **Pasteurella** spp.	**Pasteurella** spp.
Bacterial Enteritis (scours)	**Escherichia coli**
Necrotic Pododermatitis (Foot Rot)	**Fusobacterium necrophorum**
Calf Diphtheria	**Fusobacterium necrophorum**
Wooden Tongue	**Actinobacillus lignieresii**
Wound Infections; Acute Metritis; Traumatic Injury	Caused by oxytetracycline-susceptible strains of streptococcal and staphylococcal organisms.

RECOMMENDED DAILY DOSAGES: Treat at the first clinical signs of disease.

The intravenous injection of 3 to 5 mg of Oxytetracycline Hydrochloride per pound of body weight per day (3 to 5 mL per 100 lbs of body weight) is the recommended dosage.

Severe foot-rot and the severe forms of the indicated diseases should be treated with 5 mg per pound of body weight. Surgical procedures may be indicated in some forms of Foot-Rot or other conditions.

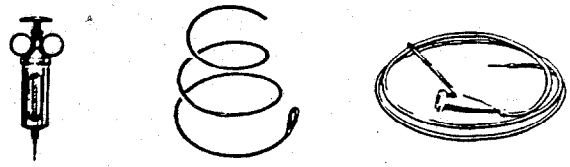
In disease treatment, the daily dose of Oxytetracycline Hydrochloride Injection should be continued 24 to 48 hours following remission of disease symptoms; however, not to exceed a total of 4 consecutive days.

DIRECTIONS FOR MAKING AN INTRAVENOUS INJECTION IN CATTLE:

Equipment Recommended

1. Choke rope—a rope or cord about 5 feet long, with a loop in one end, to be used as a tourniquet.
2. Syringe and needles; gravity flow intravenous set. (See Fig. 1.)

1. Choke rope—a rope or cord about 5 feet long, with a loop in one end, to be used as a tourniquet.
2. Syringe and needles; gravity flow intravenous set. (See Fig. 1.)



Syringe & Needle | Choke Rope | Gravity Flow Intravenous Set

FIGURE 1

3. Use new very sharp hypodermic needles, 16-gauge 1½ to 2 inches long. Dull needles will not work. Extra needles should be available in case the one being used becomes clogged.
4. Scissors or clippers.
5. 70% rubbing alcohol compound or other equally effective antiseptic for disinfecting the skin.
6. The medication to be given.

PREPARATION OF EQUIPMENT: Thoroughly clean the needles, syringe and intravenous set and disinfect them by boiling in water for twenty minutes or by immersing in a suitable chemical disinfectant such as 70% alcohol for a period of not less than 30 minutes. Warm the bottle of medication to approximately body temperature and keep warm until used.

It is recommended that the correct dose be diluted in water for injection, sodium chloride injection or other suitable vehicle immediately prior to administration. Doses up to 50 mL may be diluted in 250 mL. Larger doses may be diluted in 500 mL of one of the diluents. Adverse reactions may be minimized and the drug dose can be better regulated by this method of administration.

Avoid touching the needle with the hands at all times.

In the case of the syringe method of administration, disinfect the vial cap by wiping with 70% alcohol or other suitable antiseptic. Touching a sterile needle only by the hub, attach it to the syringe and push the plunger down the barrel to empty it of air. Puncture the rubber cap of the vial and withdraw the plunger upward in the syringe to draw up a volume of Oxytetracycline HCl Injection, 100 mg/mL of about 5 mL more than is needed for injection. Withdraw from the vial and, pointing the needle upward, remove all air bubbles from the syringe by pushing the plunger upward to the volume required.

If the injection cannot be made immediately, the tip of the needle may be covered with cotton soaked in 70% alcohol to prevent contamination.

PREPARATION OF THE ANIMAL FOR INJECTION:

1. Approximate location of vein. The jugular vein runs in the jugular groove on each side of the neck from the angle of the jaw to just above the brisket and slightly above and to the side of the windpipe. (See Figure 2 and 3.)

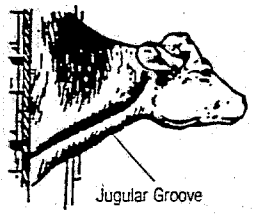


FIGURE 2

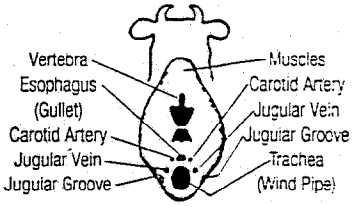


FIGURE 3

2. Method of restraint—A stanchion or chute is ideal for restraining the animal. With a halter, rope or cattle leader (nose tongs), pull the animal's head around the side of the stanchion, cattle chute or post in such a manner to form a bow in the neck (see Figure 4), then snub the head securely to prevent movement. By forming the bow in the neck, the outside curvature of the bow tends to expose the jugular vein and make it easily accessible. Caution: Avoid a tight rope or halter around the throat or upper neck which might impede blood flow. Animals that are down present no problem so far as restraint is concerned.
3. Clip hair in area where injection is to be made (over the vein in the upper third of the neck). Clean and disinfect the skin with alcohol or other suitable antiseptic.

DOSAGE FOR INJECTION: Refer to the table below for proper dosage according to body weight of the animal.

Weight of Animals, Lbs (Beef Cattle, Beef Calves, Non-Lactating Dairy Cattle, Dairy Calves)	Milligrams of Oxytetracycline Hydrochloride Per 100 Lbs of Body Weight Per Day	Daily Dosage of Oxytetracycline Hydrochloride Injection (mL)
50 lbs	300 - 500 mg	1.5 - 2.5 mL
100 lbs	300 - 500 mg	3 - 5 mL
200 lbs	300 - 500 mg	6 - 10 mL
300 lbs	300 - 500 mg	9 - 15 mL
400 lbs	300 - 500 mg	12 - 20 mL
500 lbs	300 - 500 mg	15 - 25 mL
600 lbs	300 - 500 mg	18 - 30 mL
800 lbs	300 - 500 mg	24 - 40 mL
1000 lbs	300 - 500 mg	30 - 50 mL
1200 lbs	300 - 500 mg	36 - 60 mL
1400 lbs	300 - 500 mg	42 - 70 mL

CAUTION: If no improvement is noted within 24 to 48 hours consult a veterinarian. For intravenous use only.

1. Raise the vein: this is accomplished by tying the choke rope tight around the neck, close to the shoulder. The rope should be tied in such a way that it will not come loose and so that it can be untied quickly by pulling the loose end. (See Figure 4.) In thick-necked animals, a block of wood placed in the jugular groove between the rope and the hide will help considerably in applying the desired pressure at the right point. The vein is a soft flexible tube through which blood flows back to the heart. Under ordinary conditions it cannot be seen or felt with the fingers. When the flow of blood is blocked at the base of the neck by the choke rope, the vein becomes enlarged and rigid because of the back pressure. If the choke rope is sufficiently tight, the vein stands out and can be easily seen and felt in thick-necked animals. As a further check in identifying the vein, tap it with the fingers in front of the choke rope. Pulsations that can be seen or felt with the fingers in front of the point being tapped will confirm the fact that the vein is properly distended. It is impossible to put the needle into the vein unless it is distended. Experienced operators are able to raise the vein simply by hand pressure, but the use of a choke rope is more certain.
2. Inserting the needle. This involves three distinct steps. First, insert the needle through the hide. Second, insert the needle into the vein. This may require two or three attempts before the vein is entered. The vein has a tendency to roll away from the point of the needle, especially if the needle is not sharp. The vein can be steadied with the thumb and finger of one hand. With the other hand, the needle point is placed directly over the vein, slanting it so that its direction is along the length of the vein, either toward the head or toward the heart. Properly positioned this way, a quick thrust of the needle will be followed by a spurt of blood through the needle, which indicates that the vein has been entered. Third, once in the vein, the needle should be inserted along the length of the vein all the way to the hub, exercising caution to see that the needle does not penetrate the opposite side of the vein. Continuous steady flow of blood through the needle indicates that the needle is still in the vein. If blood does not flow continuously, the needle is out of the vein (or clogged) and another attempt must be made. If difficulty is encountered, it may be advisable to use the vein on the other side of the neck.
3. While the needle is being placed in proper position in the vein, an assistant should get the medication ready so that the injection can be started without delay after the vein has been entered. Remove the rubber stopper from the bottle of intravenous solution, connect the intravenous tube to the neck of the bottle, invert the bottle and allow some of the solution to run through the tube to eliminate all air bubbles.
4. Making the injection. With needle in proper position as indicated by continuous flow of blood, release the choke rope by a quick pull on the free end. This is essential—the medication cannot flow into the vein while the vein is blocked. Immediately connect the intravenous tube to the needle, and raise the bottle. The solution will flow by gravity. (See Figure 5.) Rapid injection may occasionally produce shock. Administer slowly. The animal should be observed at all times during the injection in order not to give the solution too fast. This may be determined by watching the respiration of the animal and feeling or listening to the heart beat. If the heart beat and respiration increase markedly, the rate of injection should be immediately stopped by pinching the tube until the animal recovers approximately to its previous respiration or heart beat rate, when the injection can be resumed at a slower rate. The rate of flow can be controlled by pinching the tube between the thumb and forefinger or by raising and lowering the bottle.

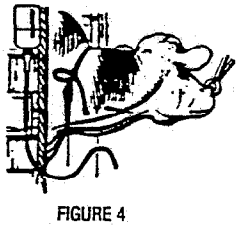


FIGURE 4

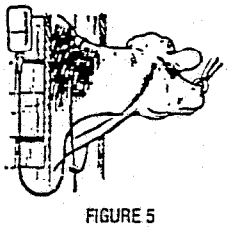


FIGURE 5

Bubbles entering the bottle through the air tube or valve indicate the rate at which the medication is flowing. If the flow should stop, this means the needle has slipped out of the vein (or is clogged) and the operation will have to be repeated. If using the syringe technique, pull back gently on the plunger: if blood flows into the syringe, the needle is in proper position. Depress the plunger slowly. If there is any resistance to the depression of the plunger, stop and repeat insertion procedure. The resistance indicates that either the needle is clogged or it has slipped out of the vein. With either method of administration, syringe or gravity flow, watch for any swelling under the skin near the needle, which would indicate that the medication is not going into the vein. Should this occur, it is best to try the vein on the opposite side of the neck. Sudden movement of the animal, especially twisting of the neck or raising or lowering the head, may sometimes cause the needle to slip out of the vein. To prevent this, tape the needle hub to the skin of the neck to hold the needle in position. Whenever there is any doubt as to the position of the needle, this should be checked in the following manner: Pinch off the intravenous tube to stop flow, disconnect the tube from the needle and re-apply pressure to the vein. Free flow of blood through the needle indicates that it is in proper position and the injection can then be continued. If using the syringe, gently pull back on the plunger. Blood should flow into the syringe.

5. Removing the needle. When the injection is complete, remove the needle with a straight pull. Then apply pressure over area of injection momentarily to control any bleeding through needle puncture, using cotton soaked in alcohol or other suitable antiseptic.

INSTRUCTIONS FOR CARE OF SICK ANIMALS: The use of antibiotics, as with most medications used in the management of diseases, is based on accurate diagnosis and adequate treatment. When properly used in the treatment of diseases caused by oxytetracycline-susceptible organisms, animals usually show a noticeable improvement within 24 to 48 hours. If improvement does not occur within this period of time, the diagnosis and treatment of animal diseases should be carried out by a veterinarian. The use of professional veterinary and laboratory services can reduce treatment costs, time and needless losses. Good management, housing, sanitation and nutrition are essential in the care of animals and in the successful treatment of disease.

PACKAGE INFORMATION: Oxytetracycline Hydrochloride Injection is available in 500 mL multidose vials containing 100 mg Oxytetracycline Hydrochloride per mL.

RESTRICTED DRUG (California)—USE ONLY AS DIRECTED

ECL-1547 9405

ATTACHMENT 2

PROPOSED PRODUCT LABEL

INDICATIONS: Tetroxy®-300 (Oxytetracycline Hydrochloride Injection) is for the treatment of diseases in beef cattle, beef calves, non-lactating dairy cattle and dairy calves caused by pathogens sensitive to Oxytetracycline HCl.

DOSAGE AND ADMINISTRATION: 3-5 mg/lb body weight per day for a maximum of 4 consecutive days. For intravenous administration only.

See attached insert for complete directions and warnings.

WARNING: Discontinue treatment at least 22 days prior to slaughter of the animal. NOT for use in lactating dairy cattle.
A withdrawal period has not been established for this product in preruminating calves. Do not use in calves to be processed for veal. Rapid intravenous administration may result in animal collapse. Oxytetracycline should be administered intravenously slowly over a period of at least 5 minutes.

0 61133 08977 5

CAUTION: If no improvement occurs within 24 to 48 hours, consult a veterinarian.
Do not use the drug for more than 4 consecutive days. Use beyond 4 days or dosage higher than the maximum recommended dose may result in antibiotic residue in the tissues beyond the withdrawal time.

TAKE TIME OBSERVE LABEL DIRECTIONS

Lot No.:

Exp. Date:

NDC # 61133-729-03

Tetroxy®-300

(Oxytetracycline Hydrochloride Injection)

Antibiotic

300 mg/mL **Sterile**

FOR USE IN ANIMALS ONLY

RESTRICTED DRUG (CALIFORNIA)

USE ONLY AS DIRECTED

KEEP OUT OF REACH OF CHILDREN

NADA 200-XXX, Approved by FDA

NET CONTENTS: 500 mL

Bimeda
Animal Health, Inc.

OPEN HERE

EACH mL CONTAINS:
Oxytetracycline base (as dihydrate) ..... 300 mg
N-Methyl 2-Pyrrolidone .... 40% w/v
Magnesium Oxide Heavy .... 2.7% w/v
Monoethanolamine .... 11.2 mg/ml
Water for Injection .... q.s.
with Sodium Formaldehyde Sulfoxylate, 0.266% w/v as a preservative and Hydrochloric Acid for pH adjustment.

NOTE: Solution may darken on storage but potency remains unaffected.

Storage Temperature 15°C-30°C (59°F-86°F).

Manufactured by:
Phoenix Scientific, Inc.
St. Joseph, MO 64503

Manufactured for:
Bimeda Animal Health, Inc.
Riverside, MO 64150

600082 Iss. 3-00

28172 bimeda tetroxy-300 133-2400 4/20/00 179 blk

SB 6-21-00
[illegible] 6-22-00
[illegible] 6-22-00
[illegible] 6-22-00
[illegible] 6/22/00 [illegible] 6-23-00

CUSTOMER PROOF • CHECK CAREFULLY!

Customer: BIMEDA **P.O. #:** STEPHANIE

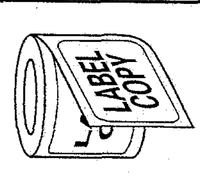
CYREL #: 28172 (ts) **Date Sent:** 3/28/00 4/20/00 5/24/00 6/1/00 6/19/00

LABEL: tetroxy-300 **UNWIND #:** 4

SIZE: 3 x 6.75

VARNISH: ☐ YES ☐ NO ☐ PATTERN ☐ FLOOD

COLORS: 179 red black



Fax Proofs are intended for proofing of content and placement only, not for exact size or color breaks.

Every effort has been taken to insure the accuracy and conformance to applicable regulations on this proof. However, please check carefully as the final liability rests with the customer.

Approved by: ______________________ **Date approved:** ______________

SB 6-21-00 dt 6-22-00 TW 6-22-00 MB 6-22-00 CB 6-23-00

NADA 200-XXX, Approved by FDA

Tetroxy®-300

(Oxytetracycline Hydrochloride Injection)

ANTIBIOTIC

Each mL contains 300 mg Oxytetracycline HCl

For Use in Beef Cattle, Beef Calves, Non-lactating Dairy Cattle and Dairy Calves Only.

DESCRIPTION

Tetroxy®-300 (Oxytetracycline Hydrochloride Injection) is a sterile ready-to-use preparation containing 300 mg/mL Oxytetracycline HCl, for administration of the broad spectrum antibiotic, Oxytetracycline, by injection.

ANTIBIOTIC ACTION OF OXYTETRACYCLINE

Oxytetracycline is effective against a wide range of gram-negative and gram-positive organisms that are pathogenic for cattle. The antibiotic is primarily bacteriostatic in effect, and is believed to exert its antimicrobial action by the inhibition of microbial protein synthesis. The antibiotic activity of Oxytetracycline is not appreciably diminished in the presence of body fluids, serum or exudates. Since the drugs in the tetracycline class have similar antimicrobial spectra, organisms can develop cross resistance among them. Oxytetracycline is concentrated by the liver in the bile and excreted in the urine and feces at high concentrations and in a biologically active form.

WARNING

Discontinue treatment at least 22 days prior to slaughter of the animal. NOT for use in lactating dairy cattle.

A withdrawal period has not been established for this product in preruminating calves. Do not use in calves to be processed for veal. Rapid intravenous administration may result in animal collapse. Oxytetracycline should be administered intravenously slowly over a period of at least 5 minutes.

CAUTION

Store between 15°C-30°C (59°F-86°F)

If no improvement occurs within 24 to 48 hours, consult a veterinarian. Do not use the drug for more than 4 consecutive days. Use beyond 4 days or doses higher than maximum recommended dose may result in antibiotic tissue residues beyond the withdrawal period.

PRECAUTIONS

The improper or accidental injection of the drug outside of the vein will cause local tissue irritation manifested by temporary swelling and discoloration at the injection site.

Shortly after injection, treated animals may have a transient hemoglobinuria (darkened urine).

Consult with your veterinarian prior to administering this product in order to determine the proper treatment required in the event of an adverse reaction. At the first sign of any adverse reaction, discontinue use of product and seek the advice of your veterinarian. Some of the reactions may be attributed either to anaphylaxis (an allergic reaction) or to cardiovascular collapse of unknown cause.

Because bacteriostatic drugs interfere with the bactericidal action of Penicillin, do not give Oxytetracycline Hydrochloride in conjunction with Penicillin.

As with other antibiotics, use of this drug may result in over-growth of nonsusceptible organisms. If any unusual symptoms occur or in the absence of a favorable response following treatment, discontinue use immediately and call a veterinarian.

ADVERSE REACTIONS: Reports of adverse reactions associated with oxytetracycline administration include injection site swelling, restlessness, ataxia, trembling, swelling of eyelids, ears, muzzle, anus and vulva (or scrotum and sheath in males), respiratory abnormalities (labored breathing), frothing at the mouth, collapse and possibly death. Some of these reactions may be attributed either to anaphylaxis (an allergic reaction) or to cardiovascular collapse of unknown cause.

GENERAL INDICATIONS FOR USE

A great many of the pathogens involved in cattle diseases are known to be susceptible to Oxytetracycline Hydrochloride therapy. Many strains of organisms, however, have shown resistance to Oxytetracycline. In the case of certain coliforms,

streptococci and staphylococci, it may be advisable to conduct culture and sensitivity testing to determine susceptibility of the infecting organism to Oxytetracycline. In this manner, the likelihood of successful treatment with Tetroxy-300 (Oxytetracycline Hydrochloride Injection) solution can be determined in advance.

DISEASES FOR WHICH Tetroxy-300 (OXYTETRACYCLINE HYDROCHLORIDE INJECTION) IS INDICATED

The use of Tetroxy-300 (Oxytetracycline Hydrochloride Injection) is indicated in beef cattle, beef calves, non-lactating dairy cattle and dairy calves for treatment of the following disease conditions caused by one or more of the Oxytetracycline sensitive pathogens listed as follows:

Disease	Causative Organism(s) Which Show Sensitivity to Tetroxy-300 (Oxytetracycline HCl Injection)
Bacterial Pneumonia and Shipping Fever Complex Associated with ***Pasteurella*** spp.	***Pasteurella*** spp
Bacterial Enteritis (scours)	***Escherichia coli***
Necrotic Pododermatitis (foot-rot)	***Fusobacterium necrophorum***
Calf Diphtheria	***Fusobacterium necrophorum***
Wooden Tongue	***Actinobacillus ligniéresii***
Wound Infections; Acute Metritis; Traumatic Injury	Caused by oxytetracycline-susceptible strains of streptococcal and staphylococcal organisms.

RECOMMENDED DAILY DOSAGES

Treat at the first clinical signs of disease.

The intravenous injection of 3 to 5 mg of Oxytetracycline Hydrochloride per pound of body weight per day (1 to 1.7 mL per 100 lbs body weight) is the recommended dosage.

Severe foot-rot and the severe forms of the indicated diseases should be treated with 5 mg per pound of body weight. Surgical procedures may be indicated in some forms of foot-rot or other conditions.

In disease treatment, the daily dose of Tetroxy-300 (Oxytetracycline Hydrochloride Injection) should be continued 24 to 48 hours following remission of disease symptoms; however, not to exceed a total of 4 consecutive days.

DIRECTIONS FOR MAKING AN INTRAVENOUS INJECTION IN CATTLE

Equipment Recommended

1. Choke rope – a rope or cord about 5 feet long, with a loop in one end, to be used as a tourniquet.
2. Syringe and needles; gravity flow intravenous set. (See Fig. 1).

FIGURE 1

3. Use new, very sharp hypodermic needles, 16-gauge, 1 1/2 to 2 inches long. Dull needles will not work. Extra needles should be available in case the one being used becomes clogged.
4. Scissors or clippers.
5. 50% rubbing alcohol compound or other equally effective antiseptic for disinfecting the skin.
6. The medication to be given.

PREPARATION OF EQUIPMENT

Thoroughly clean the needles, syringe and intravenous set and disinfect them by boiling in water for twenty minutes or by immersing in a suitable chemical disinfectant such as 70% alcohol for a period of not less than 30 minutes. Warm the bottle of medication to approximately body temperature and keep warm until used.

It is recommended that the correct dose be diluted in water for injection, sodium chloride injection or other suitable vehicle immediately prior to administration. Doses up to 50 mL may be diluted in 250 mL. Larger doses may be diluted in 500 mL of one of the diluents. Adverse reactions may be minimized and the drug dose can be better regulated by this method of administration.

Avoid touching the needle with the hands at all times.

In case of the syringe method of administration, disinfect the vial cap by wiping with 70% alcohol or other suitable

antiseptic. Touching a sterile needle only by the hub, attach it to the syringe and push the plunger down the barrel to empty it of air. Puncture the rubber cap of the vial and withdraw the plunger upward in the syringe to draw up a volume of Tetroxy-300 (Oxytetracycline Hydrochloride Injection), 300 mg/mL of about 5 mL more than is needed for injection. Withdraw from the vial and, pointing the needle upward, remove all air bubbles from the syringe by pushing the plunger upward to the volume required. If the injection cannot be made immediately, the tip of the needle may be covered with cotton soaked in 70% alcohol to prevent contamination.

PREPARATION OF THE ANIMAL FOR INJECTION

1. Approximate location of vein. The jugular vein runs in the jugular groove on each side of the neck from the angle of the jaw to just above the brisket and slightly above and to the side of the windpipe. (See Figure 2 and 3).

FIGURE 2

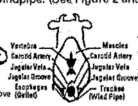


FIGURE 3

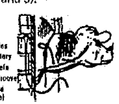


FIGURE 4

2. Method of restraint – A stanchion or chute is ideal for restraining the animal. With a halter, rope or cattle leader (nose tongs), pull the animal's head around the side of the stanchion, cattle chute or post in such a manner to form a bow in the neck, (see Figure 4), then snub the head securely to prevent movement. By forming the bow in the neck, the outside curvature of the bow tends to expose the jugular vein and make it easily accessible. Caution; Avoid a tight rope or halter around the throat or upper neck which might impede blood flow. Animals that are down present no problem so far as restraint is concerned.
3. Clip hair in area where injection is to be made (over the vein in the upper third of the neck). Clean and disinfect the skin with alcohol or other suitable antiseptic.

DOSAGE FOR INJECTION

Refer to the following table for proper dosage according to body weight of the animal.

Weight of Animals, Lbs (Beef Cattle, Beef Calves, Non-Lactating Dairy Cattle, Dairy Calves)	Milligrams of Oxytetracycline Hydrochloride per 100 lbs of Body Weight Per Day	Daily Dosage of Tetroxy-300 (Oxytetracycline Hydrochloride Injection) (mL)
50 lbs	300-500 mg	0.5-0.8 mL
100 lbs	300-500 mg	1.0-1.7 mL
200 lbs	300-500 mg	2.7-3.3 mL
300 lbs	300-500 mg	3.0-3.5 mL
400 lbs	300-500 mg	4.0-6.7 mL
500 lbs	300-500 mg	5.0-8.3 mL
600 lbs	300-500 mg	6.0-10.0 mL
800 lbs	300-500 mg	8.0-13.3 mL
1000 lbs	300-500 mg	10.0-16.7 mL
1200 lbs	300-500 mg	12.7-20.0 mL
1400 lbs	300-500 mg	14.0-23.3 mL

CAUTION: If no improvement is noted within 24 to 48 hours consult a veterinarian.

For intravenous use only.

ENTERING THE VEIN AND MAKING THE INJECTION

1. Raise the vein: this is accomplished by tying the choke rope tight around the neck, close to the shoulder. The rope should be tied in such a way that it will not come loose and so that it can be untied quickly by pulling the loose end. (See Figure 4.) In thick-necked animals, a block of wood placed in the jugular groove between the rope and the hide will help considerably in applying the desired pressure at the right point. The vein is a soft flexible tube through which blood flows back to the heart. Under ordinary conditions it cannot be seen or felt with the fingers. When the flow of blood is blocked at the base of the neck by the choke rope, the vein becomes enlarged and rigid because of the back pressure. If the choke rope is sufficiently tight, the vein stands out and can be easily seen and felt in thick-necked animals. As a further check in identifying the vein,

tap it with the fingers in front of the choke rope. Pulsations that can be seen or felt with the fingers in front of the point being tapped will confirm the fact that the vein is properly distended. It is impossible to put the needle into the vein unless it is distended. Experienced operators are able to raise the vein simply by hand pressure, but the use of a choke rope is more certain.

2. Inserting the needle. This involves three distinct steps. First, insert the needle through the hide. Second, insert the needle into the vein. This may require two or three attempts before the vein is entered. The vein has a tendency to roll away from the point of the needle, especially if the needle is not sharp. The vein can be steadied with the thumb and finger of one hand. With the other hand, the needle point is placed directly over the vein, slanting it so that its direction is along the length of the vein, either toward the head or toward the heart. Properly positioned this way, a quick thrust of the needle will be followed by a spurt of blood through the needle, which indicates that the vein has been entered. Third, once in the vein, the needle should be inserted along the length of the vein all the way to the hub, exercising caution to see that the needle does not penetrate the opposite side of the vein. Continuous steady flow of blood through the needle indicates that the needle is still in the vein. If blood does not flow continuously, the needle is out of the vein (or clogged) and another attempt must be made. If difficulty is encountered, it may be advisable to use the vein on the other side of the neck.
3. While the needle is being placed in proper position in the vein, an assistant should get the medication ready so that the injection can be started without delay after the vein has been entered. Remove the rubber stopper from the bottle of intravenous solution, connect the intravenous tube to the neck of the bottle, invert the bottle and allow some of the solution to run through the tube to eliminate all air bubbles.
4. Making the injection. With needle in proper position as indicated by continuous flow of blood, release the choke rope by a quick pull on the free end. This is essential – the medication cannot flow into the vein while the vein is blocked. Immediately connect the intravenous tube to the

needle, and raise the bottle. The solution will flow by gravity. (See Figure 5.) Rapid injection may occasionally produce shock. Administer slowly. The animal should be observed at all times during the injection in order not to give the solution too fast. This may be determined by watching the respiration of the animal and feeling or listening to the heart beat. If the heart beat and respiration increase markedly, the rate of injection should be immediately stopped by pinching the tube until the animal recovers approximately to

its previous respiration or heart beat rate, when the injection can be resumed at a slower rate. The rate of flow can be controlled by pinching the tube between the thumb and forefinger or by raising and lowering the bottle.

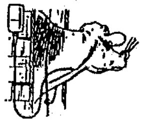


FIGURE 5

Bubbles entering the bottle through the air tube or valve indicate the rate at which the medication is flowing. If the flow should stop, this means the needle has slipped out of the vein (or is clogged) and the operation will have to be repeated. If using the syringe technique, pull back gently on the plunger: if blood flows into the syringe, the needle is in proper position. Depress the plunger slowly. If there is any resistance to the depression of the plunger, stop and repeat insertion procedure. The resistance indicates that either the needle is clogged or it has slipped out of the vein. With either method of administration, syringe or gravity flow, watch for any swelling under the skin near the needle, which would indicate that the medication is not going into the vein. Should this occur, it is best to try the vein on the opposite side of the neck. Sudden movement of the animal,

especially twisting of the neck or raising or lowering the head, may sometimes cause the needle to slip out of the vein. To prevent this, tape the needle hub to the skin of the neck to hold the needle in position. Whenever there is any doubt as to the position of the needle, this should be checked in the following manner: Pinch off the intravenous tube to stop flow, disconnect the tube from the needle and re-apply pressure to the vein. Free flow of blood through the needle indicates that it is in proper position and the injection can then be continued. If using the syringe, gently pull back on the plunger. Blood should flow into the syringe.

5. Removing the needle. When the injection is complete, remove needle with a straight pull. Then apply pressure over area of injection momentarily to control any bleeding through needle puncture, using cotton soaked in alcohol or other suitable antiseptic.

INSTRUCTIONS FOR CARE OF SICK ANIMALS

The use of antibiotics, as with most medications used in the management of diseases, is based on accurate diagnosis and adequate treatment. When properly used in the treatment of diseases caused by oxytetracycline-susceptible organisms, animals usually show a noticeable improvement within 24 to 48 hours. If improvement does not occur within this period of time, the diagnosis and treatment of animal diseases should be carried out by a veterinarian. The use of professional veterinary and laboratory services can reduce treatment costs, time and needless losses. Good management, housing, sanitation and nutrition are essential in the care of animals and in the successful treatment of disease.

PACKAGE INFORMATION

Tetroxy-300® (Oxytetracycline Hydrochloride Injection) is available in 500 mL multidose vials containing 300 mg Oxytetracycline Hydrochloride per mL.

For Use in Animals Only

RESTRICTED DRUG (California) – USE ONLY AS DIRECTED

EACH mL CONTAINS:

Oxytetracycline base (as dihydrate) ..... 300 mg
N-Methyl 2-Pyrrolidone .... 40% w/v
Magnesium Oxide Heavy .... 2.7% w/v
Monoethanolamine .... 11.2 mg/ml
Water for Injection .... q.s. with Sodium Formaldehyde Sulfoxylate, 0.266% w/v as a preservative and Hydrochloric Acid for pH adjustment.

NOTE: Solution may darken on storage but potency remains unaffected.

Storage Temperature 15°C-30°C (59°F-86°F).

Manufactured by:
Phoenix Scientific, Inc.
St. Joseph, MO 64503

Manufactured for:
Bimeda Animal Health, Inc.
Riverside, MO 64150

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