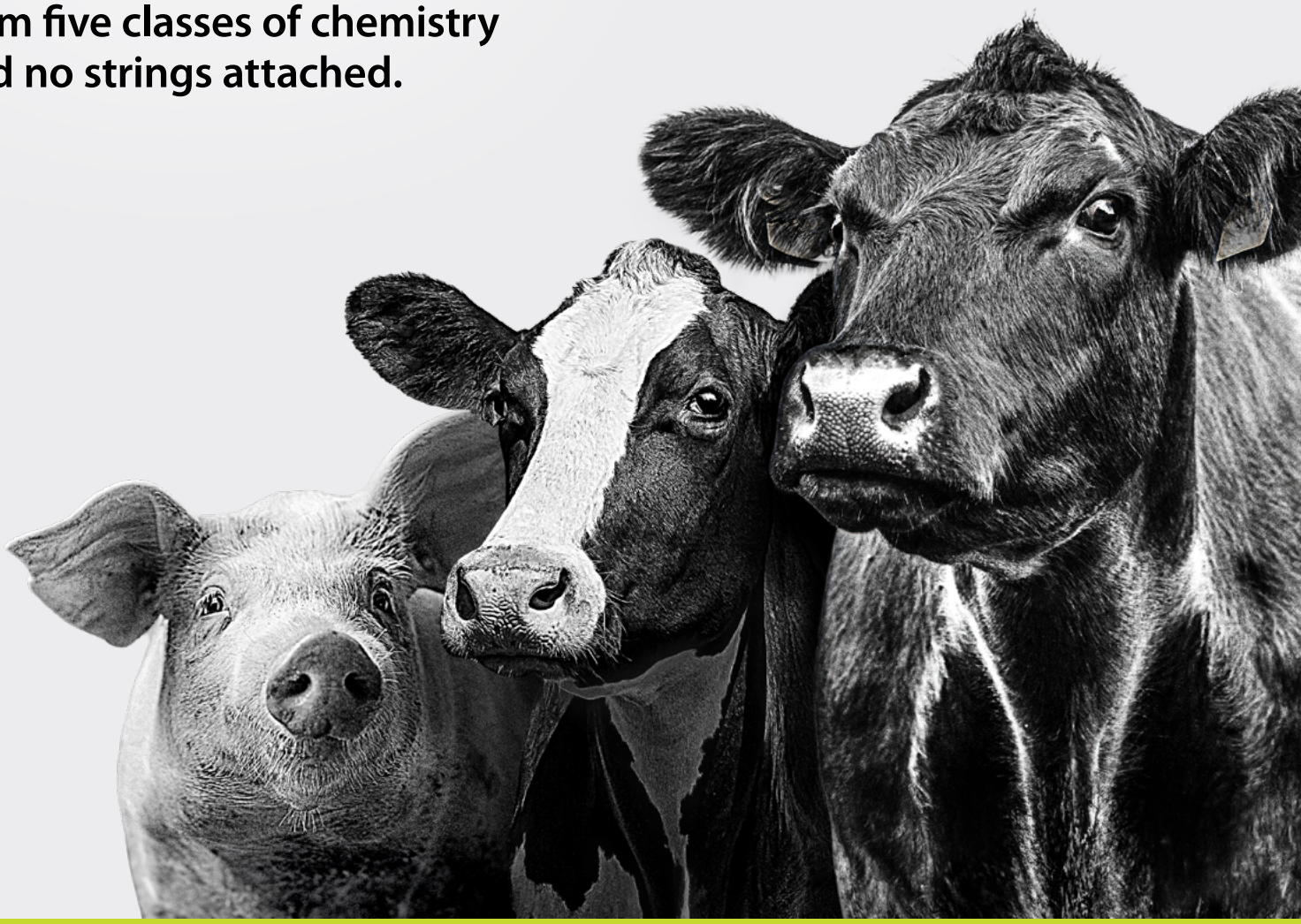
Norbrook®

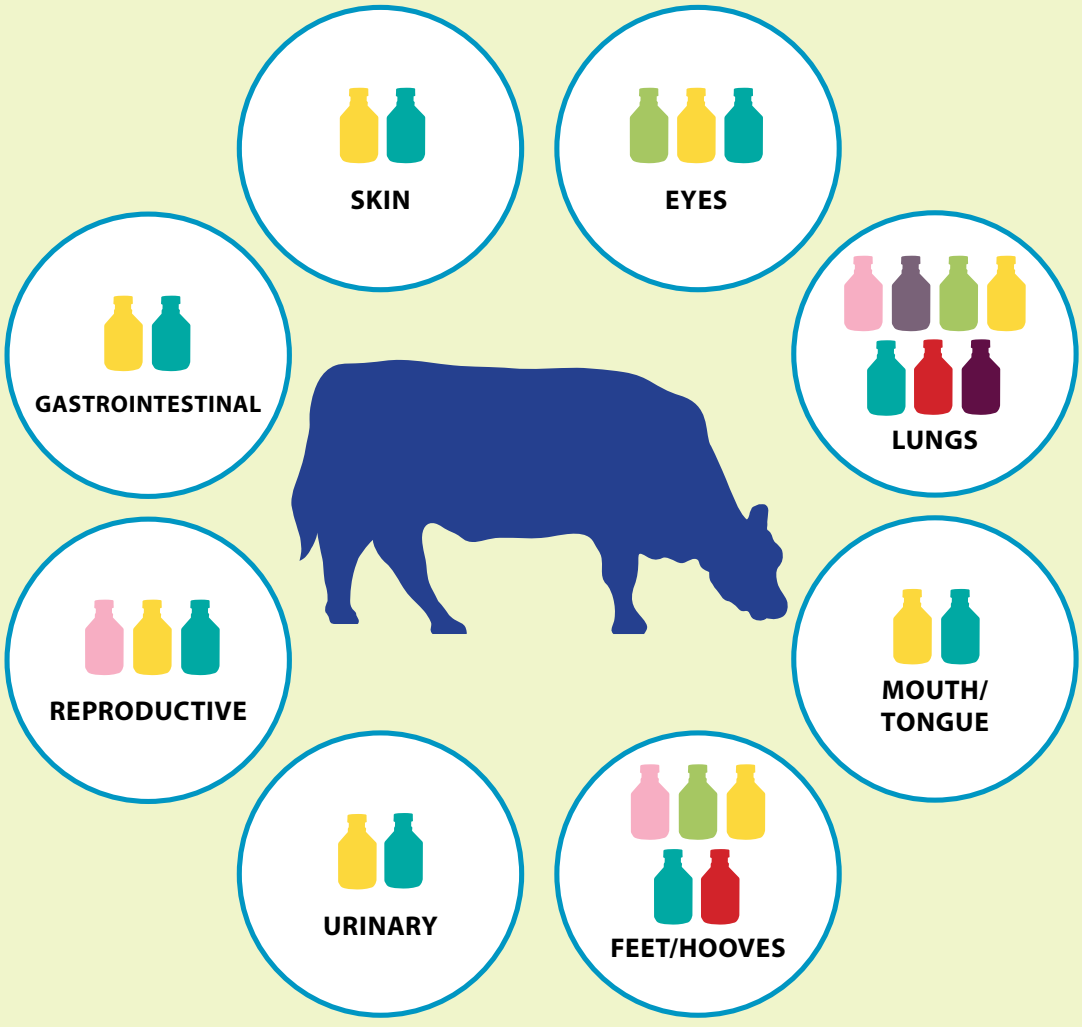
# GET THE ANTIBIOTICS YOU WANT

**without the bundles you don't, with multiple treatment options from five classes of chemistry and no strings attached.**



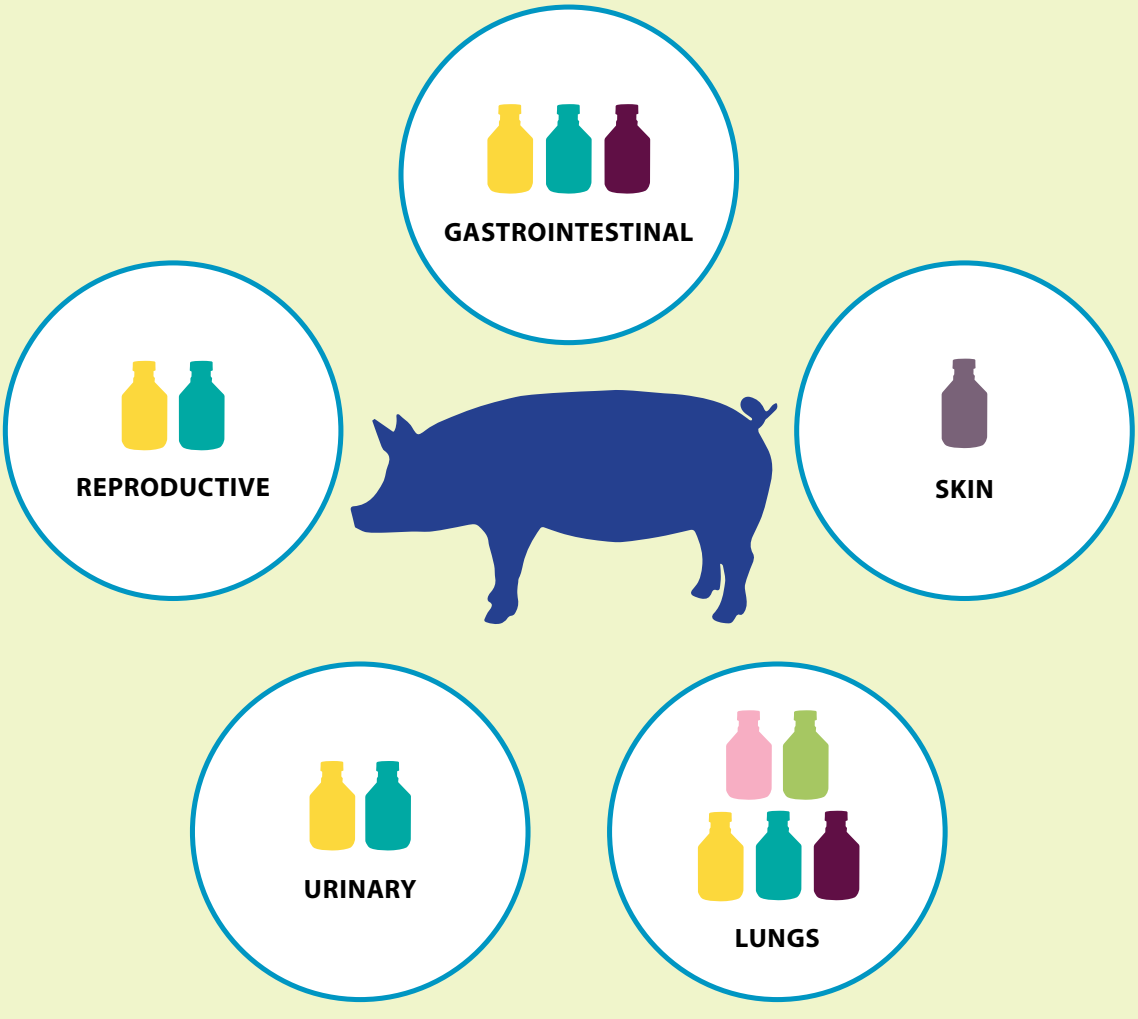
# CATTLE

| Target | Cell Wall | | Protein Synthesis | | | | DNA Synthesis |
|---|---|---|---|---|---|---|---|
| Class | Beta Lactam | | Macrolide | Tetracycline | | Phenicol | Quinolone |
| Antibiotic | Cefenil® RTU | Norocillin® | Tulieve® | Noromycin® 300 LA | Oxytetracycline 200 | Norfenicol® | Enroflox® 100 |
| Pioneer | Excenel® | Norbrook® | Draxxin® | Norbrook® | LA 200® | Nuflor® | Baytril® |
| Eyes | | | ✓ | ✓ | ✓ | | |
| Skin | | | | ✓ | ✓ | | |
| Gastrointestinal | | | | ✓ | ✓ | | |
| Reproductive | ✓ | | | ✓ | ✓ | | |
| Urinary | | | | ✓ | ✓ | | |
| Feet/Hooves | ✓ | | ✓ | ✓ | ✓ | ✓ | |
| Lungs | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Mouth/Tongue | | | | ✓ | ✓ | | |



# SWINE

| Target | Cell Wall | | Protein Synthesis | | | DNA Synthesis |
|---|---|---|---|---|---|---|
| Class | Beta Lactam | | Macrolide | Tetracycline | | Quinolone |
| Antibiotic | Cefenil® RTU | Norocillin® | Tulieve® | Noromycin® 300 LA | Oxytetracycline 200 | Enroflox® 100 |
| Pioneer | Excenel® | Norbrook® | Draxxin® | Norbrook® | LA 200® | Baytril® |
| Skin | | ✓ | | | | |
| Gastrointestinal | | | | ✓ | ✓ | ✓ |
| Reproductive | | | | ✓ | ✓ | |
| Urinary | | | | ✓ | ✓ | |
| Lungs | ✓ | | ✓ | ✓ | ✓ | ✓ |



**See product labeling for full product information.**

**Tulieve® (tulathromycin) Injectable Solution**
IMPORTANT SAFETY INFORMATION FOR CATTLE
Do not use in female dairy cattle 20 months of age or older, including dry dairy cows. Effects on reproductive performance, pregnancy and lactation have not been determined. Tulieve has a pre-slaughter withdrawal time of 18 days. Tulieve should not be used in animals known to be hypersensitive to the product.

IMPORTANT SAFETY INFORMATION FOR SWINE. Tulieve has a pre-slaughter withdrawal time of 5 days. Tulieve should not be used in animals known to be hypersensitive to the product.

**Norfenicol® (florfenicol) Injectable Solution**
Observe label direction and withdrawal times. Federal law restricts this drug to use by or on the order of a licensed veterinarian. For use in beef and non-lactating dairy cattle only. Not approved for use in female dairy cattle 20 months of age or older, including dry dairy cows. Animals intended for human consumption must not be slaughtered within 28 days of the last intramuscular treatment or within 33 days of subcutaneous treatment. Do not use in calves to be processed for veal. Intramuscular injection may result in local tissue reaction which may result in trim loss at slaughter. See product labeling for full product information, including adverse reactions.

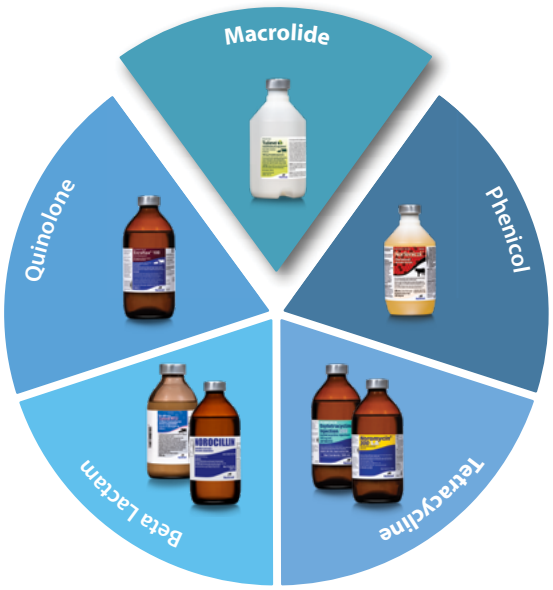
**Enroflox® 100 (enrofloxacin) Injectable Solution**
For use by or on the order of a licensed veterinarian. Federal law prohibits the extra-label use of this drug in food producing animals. Cattle intended for human consumption must not be slaughtered within 28 days from the last treatment. This product is not approved for female dairy cattle 20 months of age or older, including dry dairy cows. Use in these cattle may cause drug residues in milk and/or calves born to these cows. A withdrawal period has not been established in pre-ruminating calves. Do not use in calves to be processed for veal. To assure responsible antimicrobial drug use, enrofloxacin should only be used as a second-line drug for colibacillosis in swine following consideration of other therapeutic options. Swine intended for human consumption must not be slaughtered within 5 days of receiving a single-injection dose. Use with caution in animals with known or suspected CNS disorders. Observe label directions and withdrawal times. See product labeling for full product information.

**Cefenil® RTU (ceftiofur hydrochloride sterile suspension)**
Observe label directions and withdrawal times. Not for use in calves to be processed for veal. As with all drugs, the use of Cefenil® RTU (ceftiofur hydrochloride sterile suspension) is contraindicated in animals previously found to be hypersensitive to the drug. See product labeling for full product information.

**Norocillin® (penicillin G procaine injectable suspension)**
Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.
Observe label directions and withdrawal times. Do not use in calves to be processed for veal. Allergic or anaphylactic reactions, sometimes fatal, have been known to occur in animals hypersensitive to penicillin and procaine. Therefore, animals administered should be kept under close observation for at least one-half hour following injection. See product labeling for full product information.

**Noromycin® 300 LA (oxytetracycline injection)**
Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.
Observe label directions and withdrawal times. Not for use in lactating dairy animals. Adverse reactions, including injection site swelling, restlessness, ataxia, trembling, respiratory abnormalities (labored breathing), collapse and possibly death have been reported. See product labeling for full product information.

**Oxytetracycline Injection 200 (oxytetracycline injection)**
Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.
Observe label directions and withdrawal times. Adverse reactions, including injection site swelling, restlessness, ataxia, trembling, respiratory abnormalities (labored breathing), collapse and possibly death have been reported. See product labeling for full product information.




**SCAN THIS CODE TO FIND SPECIFIC PRODUCT INFORMATION AND DOSING INSTRUCTIONS.**



007-25-072

# Cefenil® RTU

**(ceftiofur hydrochloride sterile suspension)**

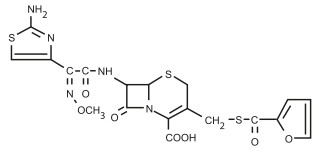
**For intramuscular and subcutaneous use in cattle and intramuscular use in swine. This product may be used in lactating dairy cattle. Not for use in calves to be processed for veal.**

**CAUTION:** Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian. Federal law prohibits extra-label use of this drug in cattle and swine for disease prevention purposes; at unapproved doses, frequencies, durations, or routes of administration; and in unapproved major food producing species/production classes.

## DESCRIPTION

CEFENIL® RTU (ceftiofur hydrochloride sterile suspension) is a ready to use formulation that contains the hydrochloride salt of ceftiofur, which is a broad spectrum cephalosporin antibiotic. Each mL of this ready-to-use sterile suspension contains ceftiofur hydrochloride equivalent to 50 mg ceftiofur, 5.73 mg aluminum monostearate, 1.03 mg sorbitan monooleate and medium chain triglycerides.

Structure:



• HCl

Figure 1

Chemical Name of Ceftiofur Hydrochloride: 5-Thia-1-azabicyclo[4,2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)(methoxyimino) -acetyl]amio]-3-[[(2-furanylcarbonyl) thio]methyl]-8-oxo-, hydrochloride salt [6R-[6α,7β(Z)]]-

## INDICATIONS

**Swine:** CEFENIL RTU is indicated for treatment/control of swine bacterial respiratory disease (swine bacterial pneumonia) associated with *Actinobacillus (Haemophilus) pleuropneumoniae, Pasteurella multocida, Salmonella choleraesuis* and *Streptococcus suis.*

**Cattle:** CEFENIL RTU is indicated for treatment of the following bacterial diseases:

- Bovine respiratory disease (BRD, shipping fever, pneumonia) associated with *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni.*
- Acute bovine interdigital necrobacillosis (foot rot, pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus.*
- Acute metritis (0 to 14 days post-partum) associated with bacterial organisms susceptible to ceftiofur.

## DOSAGE AND ADMINISTRATION

**Shake for 90 seconds to ensure complete resuspension before using.**

**Swine:** Administer intramuscularly at a dosage of 1.36 to 2.27 mg ceftiofur equivalents/lb (3.0 to 5.0 mg/kg) BW (1 mL of sterile suspension per 22 to 37 lb BW). Treatment should be repeated at 24 h intervals for a total of three consecutive days.

**Cattle:** - For bovine respiratory disease and acute bovine interdigital necrobacillosis: administer by intramuscular or subcutaneous administration at the dosage of 0.5 to 1.0 mg ceftiofur equivalents/lb (1.1 to 2.2 mg/kg) BW (1 to 2 mL sterile suspension per 100 lb BW). Administer daily at 24 h intervals for a total of three consecutive days. Additional treatments may be administered on Days 4 and 5 for animals which do not show a satisfactory response (not recovered) after the initial three treatments. In addition, for BRD only, administer intramuscularly or subcutaneously 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW every other day on Days 1 and 3 (48 h interval). Do not inject more than 15 mL per injection site.

Selection of dosage level (0.5 to 1.0 mg/lb) and regimen/duration (daily or every other day for BRD only) should be based on an assessment of the severity of disease, pathogen susceptibility and clinical response.

- For acute post-partum metritis: administer by intramuscular or subcutaneous administration at the dosage of 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW (2 mL sterile suspension per 100 lb BW). Administer at 24 h intervals for five consecutive days. Do not inject more than 15 mL per injection site.

## CONTRAINDICATIONS

As with all drugs, the use of CEFENIL RTU is contraindicated in animals previously found to be hypersensitive to the drug.

## WARNINGS

**NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN.**

Penicillins and cephalosporins can cause allergic reactions in sensitized individuals. Topical exposures to such antimicrobials, including ceftiofur, may elicit mild to severe allergic reactions in some individuals. Repeated or prolonged exposure may lead to sensitization. Avoid direct contact of the product with the skin, eyes, mouth, and clothing. Persons with a known hypersensitivity to penicillin or cephalosporins should avoid exposure to this product. In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. If allergic reaction occurs (e.g., skin rash, hives, difficult breathing), seek medical attention. The safety data sheet contains more detailed occupational safety information. To report suspected adverse drug events, for technical assistance or to obtain a copy of the safety data sheet (SDS), contact Norbrook at 1-866-591-5777. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at www.fda.gov/reportanimalae.

**RESIDUE WARNINGS:**

**Swine:** When used according to label indications, dosage, and route of administration, treated swine must not be slaughtered for 4 days following the last treatment.

Use of dosages in excess of those indicated or by unapproved routes of administration may result in illegal residues in edible tissues.

**Cattle:** When used according to label indications, dosage and route of administration, treated cattle must not be slaughtered for 3 days following the last treatment. When used according to label indications, dosage and route of administration, a milk discard time is not required. Uses of dosages in excess of those indicated or by unapproved routes of administration, such as intramammary, may result in illegal residues in edible tissues and/or milk. A withdrawal period has not been established in pre-ruminating calves. Do not use in calves to be processed for veal.

## PRECAUTIONS

The effects of ceftiofur on cattle and swine reproductive performance, pregnancy, and lactation have not been determined.

**Swine:** Areas of discoloration associated with the injection site at time periods of 11 days or less may result in trim-out of edible tissues at slaughter. The safety of ceftiofur has not been demonstrated for pregnant swine or swine intended for breeding.

**Cattle:** Following intramuscular or subcutaneous administration in the neck, areas of discoloration at the site may persist beyond 11 days resulting in trim loss of edible tissues at slaughter. Following intramuscular administration in the rear leg, areas of discoloration at the injection site may persist beyond 28 days resulting in trim loss of edible tissues at slaughter.

## CLINICAL PHARMACOLOGY

**Swine**: Ceftiofur administered as either ceftiofur sodium or ceftiofur hydrochloride is metabolized rapidly to desfuroylceftiofur, the primary metabolite. Administration of ceftiofur to swine as either the sodium or hydrochloride salt provides effective concentrations of ceftiofur and desfuroylceftiofur metabolites in plasma above the $MIC_{90}$ for the labeled pathogens: *Actinobacillus pleuropneumoniae, Pasteurella multocida, Streptococcus suis* and *Salmonella choleraesuis* for the 24 hour (h) period between the dosing intervals. The $MIC_{90}$ for *Salmonella choleraesuis* (1.0 µg/mL) is higher than the other three pathogens and plasma concentrations exceed this value for the entire dosing interval only after the 2.27 mg/lb (5.0 mg/kg) body weight (BW) dose.

**Comparative Bioavailability Summary**

Comparable plasma concentrations of ceftiofur administered as ceftiofur hydrochloride sterile suspension or ceftiofur sodium sterile solution were demonstrated after intramuscular administration of 2.27 mg ceftiofur equivalents/lb (5.0 mg/kg) BW. See Table 1 and Figure 2.

Table 1. Swine plasma concentrations and related parameters * of ceftiofur and desfuroylceftiofur metabolites after ceftiofur hydrochloride sterile suspension, 50 mg/mL, or ceftiofur sodium sterile powder, 50 mg/mL, administered at 2.27 mg/lb ceftiofur equivalents /lb (5.0 mg/kg) BW IM.

| | Ceftiofur hydrochloride | Ceftiofur sodium |
|---|---|---|
| $C_{max}$ µg/mL: | 26.1 ± 5.02 | 29.2 ± 5.01 |
| $t_{max}$ h: | 0.66 – 2.0 (range) | 0.33 – 2.0 (range) |
| $AUC_{0\text{-}LOQ}$ µg·h/mL: | 321 ± 50.2 | 314 ± 55.1 |
| $t_{1/2}$ h: | 16.2 ± 1.55 | 14.0 ± 1.23 |
| $C_{24\,h}$ µg/mL: | 3.45 ± 0.431 | 3.53 ± 0.791 |
| $C_{72\,h}$ µg/mL: | 0.518 ± 0.126 | 0.407 ± 0.0675 |
| $t_{>0.2}$ h: | 93.8 ± 7.98 | 85.0 ± 7.71 |

Definitions:

$C_{max}$ - maximum plasma concentration in µg/mL.

$t_{max}$ - the time after initial injection to when Cmax occurs, measured in hours.

$AUC_{0\text{-}LOQ}$ -the area under the plasma concentration vs. time curve from time of injection to the limit of quantitation of the assay (0.15 µg/mL).

$t_{1/2}$ - the plasma half life of the drug in hours.

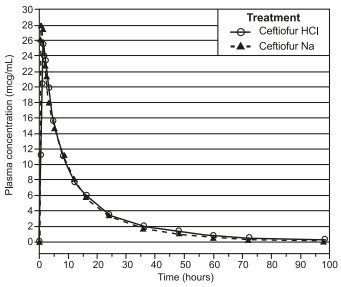
$C_{24\,h}$ - the concentration of drug at 24 h after administration.

$C_{72\,h}$ - the concentration of drug at 72 h after administration.

$t_{>0.2}$ - the time (in hours) plasma concentrations remain above 0.2 µg/mL.

*Due to significant period effect and significant sequence effect in this study, data from period 1 only were used to evaluate these parameters.

Figure 2. Swine plasma concentrations of ceftiofur and desfuroylceftiofur metabolites after ceftiofur hydrochloride sterile suspension, 50 mg/mL, or ceftiofur sodium sterile powder, 50 mg/mL, were administered intramuscularly at 2.27 mg ceftiofur equivalents/lb (5.0 mg/kg) BW.




Concentrations of total ceftiofur in the lungs of pigs administered radiolabeled ceftiofur at 2.27 or 3.41 mg ceftiofur equivalents/lb (5.0 or 7.5 mg/kg) BW 12 h after the last of three daily intramuscular injections at 24 h intervals averaged 3.66 and 5.63 µg/g.

**Cattle:** Ceftiofur administered as either ceftiofur sodium or ceftiofur hydrochloride is metabolized rapidly to desfuroylceftiofur, the primary metabolite. Administration of ceftiofur to cattle as either the sodium or hydrochloride salt provides effective concentrations of ceftiofur and desfuroylceftiofur metabolites in plasma above the $MIC_{90}$ for the bovine respiratory disease (BRD) label pathogens *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni* for at least 48 h. The relationship between plasma concentrations of ceftiofur and desfuroylceftiofur metabolites above the $MIC_{90}$ in plasma and efficacy has not been established for the treatment of bovine interdigital necrobacillosis (foot rot) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus.*

**Comparative Bioavailability Summary**

The comparability of plasma concentrations of ceftiofur following administration of ceftiofur hydrochloride sterile suspension or ceftiofur sodium sterile solution was demonstrated after intramuscular or subcutaneous administration of ceftiofur hydrochloride and intramuscular administration of ceftiofur sodium at 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW. See Table 2 and Figure 3.

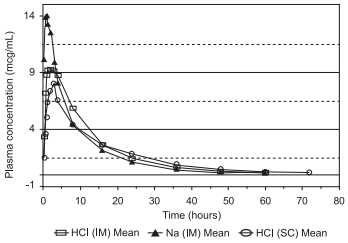
Table 2. Cattle plasma concentrations and related parameters of ceftiofur and desfuroylceftiofur metabolites after ceftiofur hydrochloride sterile suspension, 50 mg/mL, administered intramuscularly or subcutaneously at 1.0 mg ceftiofur equivalents /lb (2.2 mg/kg) BW and ceftiofur sodium sterile powder, 50 mg/mL, administered intramuscularly at 1.0 mg ceftiofur equivalents /lb (2.2 mg/kg) BW.

| | Ceftiofur hydrochloride | | Ceftiofur sodium |
|---|---|---|---|
| | IM | SC | IM* |
| $C_{max}$ µg/mL | 11.0 ± 1.69 | 8.56 ± 1.89 | 14.4–16.5 |
| $t_{max}$ h | 1–4 (range) | 1-5 (range) | 0.33–3.0 |
| $t_{>0.2}$ h | 60.5 ± 6.27 | 51.0 ± 6.53 | 50.7–50.9 |
| $AUC_{0\text{-}LOQ}$ µg·h/mL | 160 ± 30.7 | 95.4 ± 17.8 | 115–142 |
| $t_{1/2}$ h | 12.0 ± 2.63 | 11.5 ± 2.57 | 9.50–11.1 |
| $C_{24\,h}$ µg/mL | 1.47 ± 0.380 | 0.926 ± 0.257 | 0.86–1.16 |
| $C_{48\,h}$ µg/mL | 0.340 ± 0.110 | 0.271 ± 0.086 | 0.250–0.268 |

Definitions:

$C_{max}$ - maximum concentration of drug in plasma in µg/mL. $t_{max}$ - the time after initial injection to when $C_{max}$ occurs, measured in hours. $t_{>0.2}$ - the time (in hours) plasma drug concentrations remain above 0.2 µg/mL. $AUC_{0\text{-}LOQ}$ -the area under the plasma drug concentrations vs. time curve from time of injection to the limit of quantitation of the assay (0.15 µg/mL). $t_{1/2}$ - the drug half life in plasma expressed in hours. $C_{24\,h}$ - the plasma drug concentration 24 h after administration. $C_{48\,h}$ - the plasma drug concentration 48 h after administration. * Values represent the separate means from each study.

Figure 3. Cattle plasma concentrations of ceftiofur and desfuroylceftiofur metabolites after ceftiofur hydrochloride sterile suspension, 50 mg/mL, was administered either intramuscularly or subcutaneously or ceftiofur sodium sterile powder, 50 mg/mL, was administered intramuscularly at 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW.




Total residues of ceftiofur were measured in the lungs of cattle administered radiolabeled ceftiofur at 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW at 24 h intervals for five consecutive days. Twelve h after the fifth injection of ceftiofur hydrochloride, total ceftiofur concentrations in the lung averaged 1.15 µg/g, while total ceftiofur concentrations in the lung 8 h after the fifth ceftiofur sodium injection averaged 1.18 µg/g.

## CLINICAL MICROBIOLOGY

CEFENIL RTU is a ready to use formulation that contains the hydrochloride salt of ceftiofur, which is a broad spectrum cephalosporin antibiotic active against gram-positive and gram-negative bacteria including β-lactamase-producing strains. Like other cephalosporins, ceftiofur is bacteriocidal, *in vitro*, resulting in inhibition of cell wall synthesis.

**Swine**: Studies with ceftiofur have demonstrated *in vitro* and *in vivo* activity against gram-negative pathogens, including *Actinobacillus (Haemophilus) pleuropneumoniae, Pasteurella multocida, Salmonella choleraesuis*, and the gram-positive pathogen *Streptococcus suis*, all of which can be associated with swine bacterial respiratory disease – SRD (swine bacterial pneumonia). A summary of the minimum inhibitory concentration (MIC) values from SRD pathogens isolated from clinical field effectiveness studies is found in Table 3. Historic diagnostic laboratory MIC values for SRD pathogens from the US and Canada are found in Table 4.

**Cattle:** Studies with ceftiofur have demonstrated *in vitro* and *in vivo* activity against *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni*, the three major pathogenic bacteria associated with bovine respiratory disease (BRD, pneumonia, shipping fever), and against *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*, two of the major pathogenic anaerobic bacteria associated with acute bovine interdigital necrobacillosis (foot rot, pododermatitis). A summary of the MIC values for BRD and foot rot pathogens isolated from clinical field effectiveness studies is found in Table 3. Historic diagnostic MIC values for BRD and foot rot pathogens from the US and Canada are found in Table 4.

**Antimicrobial Susceptibility**

Summaries of MIC data are presented in Tables 3 and 4. Testing followed Clinical and Laboratory Standards Institute (CLSI) Guidelines.

**Table 3. Ceftiofur MIC Values of Bacterial Isolates from Clinical Field Studies in the USA**

| Animal | Organism | Number Tested | Date Tested | $MIC_{90}$* (µg/mL) | MIC Range (µg/mL) |
|---|---|---|---|---|---|
| **Bovine** | *Mannheimia haemolytica* | 461 | 1988 -1992 | 0.06 | ≤0.03-0.13 |
| | *Mannheimia haemolytica* | 42 | 1993 | 0.015 | ≤0.003-0.03 |
| | *Pasteurella multocida* | 318 | 1988 -1992 | 0.06 | ≤0.03-0.25 |
| | *Pasteurella multocida* | 48 | 1993 | ≤0.003 | ≤0.003-0.015 |
| | *Histophilus somni* | 109 | 1988 -1992 | 0.06 | ≤0.03-0.13 |
| | *Histophilus somni* | 59 | 1993 | ≤0.0019 | no range |
| | *Fusobacterium necrophorum* | 17 | 1994 | ≤0.06 | no range |
| **Swine** | *Actinobacillus pleuropn.* | 83 | 1993 | ≤0.03 | ≤0.03-0.06 |
| | *Pasteurella multocida* | 74 | 1993 | ≤0.03 | ≤0.03-0.06 |
| | *Streptococcus suis* | 94 | 1993 | 0.25 | ≤0.03-1.0 |
| | *Salmonella choleraesuis* | 50 | 1993 | 1.0 | 1.0-2.0 |
| | beta–hemolytic *Streptococcus* spp. | 24 | 1993 | ≤0.03 | ≤0.03-0.06 |
| | *Actinobacillus suis* | 77 | 1998 | 0.0078 | 0.0019-0.0078 |
| | *Haemophilus parasuis* | 76 | 1998 | 0.06 | 0.0039-0.25 |

*Minimum inhibitory concentration (MIC) for 90% of the isolates

**Table 4. Ceftiofur MIC Values of Bacterial Isolates from Diagnostic Laboratories* in the USA and Canada**

| Animal | Organism | Number Tested | Date Tested | $MIC_{90}$** (µg/mL) | MIC Range (µg/mL) |
|---|---|---|---|---|---|
| **Bovine** | *Mannheimia haemolytica* | 110 | 1997-1998 | 0.06 | ≤0.03-0.25 |
| | *Mannheimia haemolytica* | 139 | 1998-1999 | ≤0.03 | ≤0.03-0.5 |
| | *Mannheimia haemolytica* | 209 | 1999-2000 | ≤0.03 | ≤0.03-0.12 |
| | *Mannheimia haemolytica* | 189 | 2000-2001 | ≤0.03 | ≤0.03-0.12 |
| | *Pasteurella multocida* | 107 | 1997-1998 | ≤0.03 | ≤0.03-0.25 |
| | *Pasteurella multocida* | 181 | 1998-1999 | ≤0.03 | ≤0.03-0.5 |
| | *Pasteurella multocida* | 208 | 1999-2000 | ≤0.03 | ≤0.03-0.12 |
| | *Pasteurella multocida* | 259 | 2000-2001 | ≤0.03 | ≤0.03-0.12 |
| | *Histophilus somni* | 48 | 1997-1998 | ≤0.03 | ≤0.03-0.25 |
| | *Histophilus somni* | 87 | 1998-1999 | ≤0.03 | ≤0.03-0.125 |
| | *Histophilus somni* | 77 | 1999-2000 | ≤0.03 | ≤0.03-0.06 |
| | *Histophilus somni* | 129 | 2000-2001 | ≤0.03 | ≤0.03-0.12 |
| | *Bacteroides fragilis* group | 29 | 1994 | 16.0 | ≤0.06->16.0 |
| | *Bacteroides* spp., non-*fragilis* group | 12 | 1994 | 16.0 | 0.13->16.0 |
| | *Peptostreptococcus anaerobius* | 12 | 1994 | 2.0 | 0.13-2.0 |
| **Swine** | *Actinobacillus pleuropn.* | 97 | 1997-1998 | ≤0.03 | no range |
| | *Actinobacillus pleuropn.* | 111 | 1998-1999 | ≤0.03 | ≤0.03-0.25 |
| | *Actinobacillus pleuropn.* | 126 | 1999-2000 | ≤0.03 | ≤0.03-0.06 |
| | *Actinobacillus pleuropn.* | 89 | 2000-2001 | ≤0.03 | ≤0.03-0.06 |
| | *Pasteurella multocida* | 114 | 1997-1998 | ≤0.03 | ≤0.03-1.0 |
| | *Pasteurella multocida* | 147 | 1998-1999 | ≤0.03 | ≤0.03-0.5 |
| | *Pasteurella multocida* | 173 | 1999-2000 | ≤0.03 | ≤0.03-0.06 |
| | *Pasteurella multocida* | 186 | 2000-2001 | ≤0.03 | ≤0.03-0.12 |
| | *Streptococcus suis* | 106 | 1997-1998 | 0.5 | ≤0.03-4.0 |
| | *Streptococcus suis* | 142 | 1998-1999 | 0.25 | ≤0.03-1.0 |
| | *Streptococcus suis* | 146 | 1999-2000 | 0.06 | ≤0.03-4.0 |
| | *Streptococcus suis* | 167 | 2000-2001 | 0.06 | ≤0.03-4.0 |
| | *Salmonella choleraesuis* | 96 | 1999-2000 | 1.0 | 0.03->4.0 |
| | *Salmonella choleraesuis* | 101 | 2000-2001 | 1.0 | 0.5-2.0 |

*The following *in vitro* data are available but their clinical significance is unknown.
**Minimum inhibitory concentration (MIC) for 90% of the isolates.

Based on the pharmacokinetic studies of ceftiofur in swine and cattle after a single intramuscular injection of 1.36 to 2.27 mg ceftiofur equivalents/lb (3.0 to 5.0 mg/kg) BW (swine) or 0.5 to 1.0 mg ceftiofur equivalents/lb (1.1 to 2.2 mg/kg) BW (cattle) and the MIC and disk (30 µg) diffusion data, the following breakpoints are recommended by CLSI.

| Zone Diameter (mm) | MIC (µg/mL) | Interpretation |
|---|---|---|
| ≥ 21 | ≤ 2.0 | (S) Susceptible |
| 18-20 | 4.0 | (I) Intermediate |
| ≤ 17 | ≥ 8.0 | (R) Resistant |

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Intermediate" is a technical buffer zone and isolates falling into this category should be retested. Alternatively the organism may be successfully treated if the infection is in a body site where drug is physiologically concentrated. A report of "Resistant" indicates that the achievable drug concentrations are unlikely to be inhibitory and other therapy should be selected. Standardized procedures[1] require the use of laboratory control organisms for both standardized diffusion techniques and standardized dilution techniques. The 30 µg ceftiofur sodium disk should give the following zone diameters and the ceftiofur sodium standard reference powder (or disk) should provide the following MIC values for the reference strain. Ceftiofur sodium disks or powder reference standard is appropriate for both ceftiofur salts.

**Table 5. Acceptable quality control ranges for ceftiofur against Clinical and Laboratory Standards Institute recommended American type Culture Collection (ATCC) reference strains**

| Organism name (ATCC No.) | Zone diameter* (mm) | MIC range (µg/mL) |
|---|---|---|
| *Escherichia coli* (25922) | 26-31 | 0.25-1.0 |
| *Staphylococcus aureus* (29213) | - | 0.25-1.0 |
| *Staphylococcus aureus* (25923) | 27-31 | - |
| *Pseudomonas aeruginosa* (27853) | 14-18 | 16.0-64.0 |
| *Actinobacillus pleuropneumoniae* (27090) | 34-42** | 0.004-0.015*** |
| *Histophilus somni* (700025) | 36-46** | 0.0005-0.004*** |

*All testing performed using a 30 µg disk.
**Quality control ranges are applicable only to tests performed by disk diffusion test using a chocolate Mueller-Hinton agar, incubated in 5-7% $CO_2$ for 20-24 hours.
***MIC quality control ranges are applicable only to tests performed by broth microdilution procedures using veterinary fastidious medium (VFM).

## CLINICAL EFFICACY

**Cattle:** In addition to demonstrating comparable plasma concentrations, the following clinical efficacy data are provided.

A clinical study was conducted to evaluate the efficacy of ceftiofur hydrochloride administered subcutaneously for the treatment of the bacterial component of BRD under natural field conditions. When uniform clinical signs of BRD were present, 60 cattle (111 to 207 kg) were randomly assigned to one of the following treatment groups: negative control or ceftiofur hydrochloride at 0.5 or 1.0 ceftiofur equivalents/lb (1.1 or 2.2 mg/kg) BW. Treatments were administered daily for three consecutive days. Cattle were evaluated daily and animals that died or were euthanatized were necropsied and the lung lesions scored. On Day 15, all surviving animals were euthanatized and necropsied and the lung lesions scored. Mortality rates were 65%, 10% and 5% for negative controls, 0.5 mg ceftiofur equivalents/lb and 1.0 mg ceftiofur equivalents/lb, (1.1 or 2.2 mg/kg) BW, respectively. Mortality rates for both ceftiofur hydrochloride treatment groups were lower than for negative controls ($P < 0.0001$). Rectal temperatures 24 h after third treatment were 104.0°F, 103.1°F and 102.8°F for negative controls, 0.5 mg/lb and 1.0 mg/lb (1.1 or 2.2 mg/kg) BW, respectively. The temperatures for both ceftiofur hydrochloride treatment groups were lower than the negative controls ($P \leq 0.05$). Ceftiofur hydrochloride administered subcutaneously for three consecutive days at 0.5 or 1.0 mg ceftiofur equivalents/lb (1.1 or 2.2 mg/kg) BW is an effective treatment for the bacterial component of BRD. A three-location clinical field study was conducted to evaluate the efficacy of ceftiofur hydrochloride administered intramuscularly daily for three days or every other day (Days 1 and 3) for the treatment of the bacterial component of naturally occurring BRD. When uniform signs of BRD were present, 360 beef crossbred cattle were randomly assigned to one of the following treatment groups: negative control, ceftiofur sodium at 0.5 mg ceftiofur equivalents/lb (1.1 mg/kg) BW daily for three days, ceftiofur hydrochloride at 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW daily for three days, or ceftiofur hydrochloride at 1.0 mg ceftiofur equivalents/lb BW on Days 1 and 3 (every other day). All treatments were administered intramuscularly. All ceftiofur treatment groups (hydrochloride and sodium) and treatment regimens (every day and every other day) significantly ($P<0.05$) reduced Day 4 rectal temperature as compared to the negative control. Clinical success on Days 10 and 28 and mortality to Day 28 were not different for the ceftiofur groups (hydrochloride and sodium) and treatment regimens (every day and every other day). The results of this study demonstrate that daily and every other day (Days 1 and 3) intramuscular administration of ceftiofur hydrochloride are effective treatment regimens for the bacterial component of BRD. An eight location study was conducted under natural field conditions to evaluate the efficacy of ceftiofur hydrochloride for the treatment of acute post-partum metritis (0 to 14 days post-partum). When clinical signs of acute post-partum metritis (rectal temperature ≥103°F and fetid vaginal discharge) were observed, 361 lactating dairy cows were assigned randomly to treatment or negative control. Cattle were dosed either subcutaneously or intramuscularly, daily for five consecutive days. On days 1, 5 and 9 after the last day of dose administration, cows were evaluated for clinical signs of acute post-partum metritis. A cure was defined as rectal temperature <103°F and lack of fetid discharge. Cure rate for the 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW dose group was significantly improved relative to cure rate of the negative control on day 9. The results of this study demonstrate that ceftiofur hydrochloride administered daily for five consecutive days at a dose of 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW is an effective treatment for acute post-partum metritis.

## ANIMAL SAFETY

**Swine:** Results from a five-day tolerance study in normal feeder pigs indicated that ceftiofur sodium was well tolerated when administered at 57 mg ceftiofur equivalents/lb (125 mg/kg) (more than 25 times the highest recommended daily dosage of 2.27 mg/lb (5.0 mg/kg)) BW for five consecutive days. Ceftiofur administered intramuscularly to pigs produced no overt adverse signs of toxicity.

To determine the safety margin in swine, a safety/toxicity study was conducted. Five barrows and five gilts per group were administered ceftiofur sodium intramuscularly at 0, 2.27, 6.81 and 11.36 mg ceftiofur equivalents/lb (0, 5, 15, 25 mg/kg) BW for 15 days. This is 0, 1, 3 and 5 times the highest recommended dose of 2.27 mg/lb (5.0 mg/kg) BW/day and 5 times the recommended treatment length of 3 days. There were no adverse systemic effects observed, indicating that ceftiofur has a wide margin of safety when injected intramuscularly into feeder pigs at the highest recommended dose of 2.27 mg ceftiofur equivalents/lb (5.0 mg/kg) BW daily for 3 days or at levels up to 5 times the highest recommended dose for 5 times the recommended length of treatment.

A separate study evaluated the injection site tissue tolerance of ceftiofur hydrochloride in swine when administered intramuscularly in the neck at 1.36 and 2.27 mg ceftiofur equivalents/lb (3.0 to 5.0 mg/kg) BW. Animals were necropsied at intervals to permit evaluations at 12 h, and 3, 5, 7, 9, 11, 15, 20, and 25 days after last injection. Injection sites were evaluated grossly at necropsy. No apparent changes (swelling or inflammation) were observed clinically after 12 h post-injection. Areas of discoloration associated with the injection site were observed at time periods less than 11 days after last injection.

**Cattle:** Results from a five-day tolerance study in feeder calves indicated that ceftiofur sodium was well tolerated at 25 times (25 mg ceftiofur equivalents/lb {55 mg/kg} BW) the highest recommended dose of 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW for five consecutive days. Ceftiofur administered intramuscularly had no adverse systemic effects. In a 15-day safety/toxicity study, five steer and five heifer calves per group were administered ceftiofur sodium intramuscularly at 0 (vehicle control), 1, 3, 5 and 10 times the highest recommended dose of 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW to determine the safety factor. There were no adverse systemic effects indicating that ceftiofur sodium has a wide margin of safety when injected intramuscularly into the feeder calves at 10 times (10 mg ceftiofur equivalents/lb {22 mg/kg} BW) the recommended dose for three times (15 days) the recommended length of treatment of three to five days. Local tissue tolerance to intramuscular injection of ceftiofur hydrochloride was evaluated in the following study. Results from a tissue tolerance study indicated that ceftiofur hydrochloride was well tolerated and produced no systemic toxicity in cattle when administered intramuscularly in the neck and rear leg at a dose of 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW at each injection site. This represents a total dose per animal of 2.0 mg ceftiofur equivalents/lb (4.4 mg/kg) BW. Clinically noted changes (local swelling) at injection sites in the neck were very infrequent (2/48 sites) whereas noted changes in rear leg sites were more frequent (21/48 sites). These changes in the rear leg injection sites were generally evident on the day following injection and lasted from 1 to 11 days. At necropsy, injection sites were recognized by discoloration of the subcutaneous tissues and muscle that resolved in approximately 7 to 15 days in the neck and 19 to 28 days in the rear leg.

Results from another tissue tolerance study indicated that ceftiofur hydrochloride was well tolerated and produced no systemic toxicity to cattle when administered subcutaneously at 0.5 or 1.0 mg ceftiofur equivalents/lb (1.1 or 2.2 mg/kg) BW at 24 h intervals for 5 days. Mild and usually transient, clinically visible or palpable reactions (local swelling) were localized at the injection site. At necropsy, injection sites were routinely recognized by edema, limited increase in thickness and color changes of the subcutaneous tissue and/or fascial surface of underlying muscle. The fascial surface of the muscle was visibly affected in most cases through 9.5 days after injection. Underlying muscle mass was not involved. There were no apparent differences in tissue response to administration of ceftiofur hydrochloride at 0.5 or 1.0 mg ceftiofur equivalents/lb (1.1 or 2.2 mg/kg) BW.

## TISSUE RESIDUE DEPLETION

**Swine:** A pivotal tissue residue decline study was conducted in swine. In this study, pigs received 2.27 mg of ceftiofur per lb body weight (5 mg of ceftiofur per kg body weight) per day for three consecutive days. Ceftiofur residues in tissues were less than the tolerances for ceftiofur residues in tissues such as kidney, liver and muscle by 4 days after dosing. These data collectively support a 4-day pre-slaughter withdrawal period in swine when used according to label directions.

**Cattle:** Two pivotal tissue residue decline studies were conducted in cattle. In the first study, cattle received an intramuscular injection of 1.0 mg of ceftiofur per lb body weight (2.2 mg of ceftiofur per kg body weight) for five consecutive days. Ceftiofur residues in tissues were less than the tolerances for ceftiofur residues in tissues such as kidney, liver and muscle by 3 days after dosing. In the second study, cattle received a subcutaneous injection of 1.0 mg of ceftiofur per lb body weight (2.2 mg of ceftiofur per kg body weight) for five consecutive days. Ceftiofur residues in tissues were less than the tolerances for ceftiofur residues in tissues such as kidney, liver and muscle by 3 days after dosing. These data collectively support a 3-day pre-slaughter withdrawal period in cattle when used according to label directions. In addition, two blood-level bioequivalence studies were conducted in cattle (one using subcutaneous administration and one using intramuscular administration). Blood concentrations of ceftiofur (measured as ceftiofur free acid equivalents) were greater than the analytical method's limit of quantification through 12 hours after administration, and these data demonstrated bioequivalence between Cefenil® RTU and the referenced listed new animal drug. These data support a zero-day milk discard time in lactating dairy cows.

## STORAGE CONDITIONS

Do not store above 30ºC (86ºF). Shake well before using. Protect from freezing. Contents should be used within 42 days after the first dose is removed.

## HOW SUPPLIED

CEFENIL RTU is available in 100 mL and 250 mL vials.

[1] Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated from Animals; Approved Standard – Second Edition. NCCLS document M31-A2. CLSI, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898, 2002.

**Approved by FDA under ANADA # 200-616**

**Made in the UK**
Manufactured by: Norbrook Laboratories Limited,
Newry, Co. Down, BT35 6PU, Northern Ireland



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Approved by FDA under ANADA # 200-495

# Enroflox® 100

(enrofloxacin)

**100 mg/mL Antimicrobial Injectable Solution**

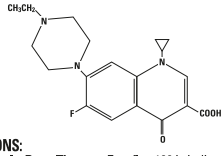
For Subcutaneous Use in Beef Cattle And Non-Lactating Dairy Cattle
For Intramuscular or Subcutaneous Use In Swine
Not for Use in Female Dairy Cattle 20 Months of Age Or Older Or In Calves To Be Processed For Veal

**CAUTION:**
Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.
Federal (U.S.A.) law prohibits the extra-label use of this drug in food-producing animals.

To assure responsible antimicrobial drug use, enrofloxacin should only be used as a second-line drug for colibacillosis in swine following consideration of other therapeutic options.

**PRODUCT DESCRIPTION:**
Enroflox® 100 is a sterile, ready-to-use injectable antimicrobial solution that contains enrofloxacin, a broad-spectrum fluoroquinolone antimicrobial agent. Each mL of Enroflox 100 contains 100 mg of enrofloxacin. Excipients are L-arginine base 200 mg, n-butyl alcohol 30 mg, benzyl alcohol (as a preservative) 20 mg and water for injection q.s.

**CHEMICAL NOMENCLATURE AND STRUCTURE:**
1-cyclopropyl-7-(4-ethyl-1-piperazinyl)-6-fluoro-1, 4-dihydro-4-oxo-3-quinolinecarboxylic acid.




**INDICATIONS:**
**Cattle - Single-Dose Therapy:** Enroflox 100 is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni* and *Mycoplasma bovis* in beef and non-lactating dairy cattle; and for the control of BRD in beef and non-lactating dairy cattle at high risk of developing BRD associated with *M. haemolytica, P. multocida, H. somni* and *M. bovis*.

**Cattle - Multiple-Day Therapy:** Enroflox 100 is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni* in beef and non-lactating dairy cattle.

**Swine:** Enroflox 100 is indicated for the treatment and control of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida, Haemophilus parasuis, Streptococcus suis, Bordetella bronchiseptica* and *Mycoplasma hyopneumoniae*. Enroflox 100 is indicated for the control of colibacillosis in groups or pens of weaned pigs where colibacillosis associated with *Escherichia coli* has been diagnosed.

**DOSAGE AND ADMINISTRATION:**
Enroflox 100 provides flexible dosages and durations of therapy.
Enroflox 100 may be administered as a single dose for one day for treatment and control of BRD (cattle), for treatment and control of SRD or for control of colibacillosis (swine), or for multiple days for BRD treatment (cattle). Selection of the appropriate dose and duration of therapy for BRD treatment in cattle should be based on an assessment of the severity of the disease, pathogen susceptibility and clinical response.

**Cattle:**
**Single-Dose Therapy (BRD Treatment):** Administer, by subcutaneous injection, a single dose of 7.5-12.5 mg/kg of body weight (3.4-5.7 mL/100 lb).

**Multiple-Day Therapy (BRD Treatment):** Administer daily, a subcutaneous dose of 2.5-5 mg/kg of body weight (1.1-2.3 mL/100 lb). Treatment should be repeated at 24-hour intervals for three days. Additional treatments may be given on Days 4 and 5 to animals that have shown clinical improvement but not total recovery.
**Single-Dose Therapy (BRD Control):** Administer, by subcutaneous injection, a single dose of 7.5 mg/kg of body weight (3.4 mL/100 lb). Examples of conditions that may contribute to calves being at high risk for developing BRD include, but are not limited to, the following:
- Transportation with animals from two or more farm origins.
- An extended transport time with few to no rest stops.
- An environmental temperature change of ≥30°F during transportation.
- A ≥30°F range in temperature fluctuation within a 24-hour period.
- Exposure to wet or cold weather conditions.
- Excessive shrink (more than would be expected with a normal load of cattle).
- Stressful arrival processing procedures (e.g., castration or dehorning).
- Exposure within the prior 72 hours to animals showing clinical signs of BRD.

Administered dose volume should not exceed 20 mL per injection site.

**Table 1 – Enroflox 100 Dose and Treatment Schedule for Cattle***

| | Treatment | | Control |
|---|---|---|---|
| Weight (lb) | Single-Dose Therapy 7.5 - 12.5 mg/kg Dose Volume (mL) | Multiple-Day Therapy 2.5 - 5.0 mg/kg Dose Volume (mL) | Single-Dose Therapy 7.5 mg/kg Dose Volume (mL) |
| 100 | 3.5 - 5.5 | 1.5 - 2.0 | 3.5 |
| 200 | 7.0 - 11.0 | 2.5 - 4.5 | 7.0 |
| 300 | 10.5 - 17.0 | 3.5 - 6.5 | 10.5 |
| 400 | 14.0 - 22.5 | 4.5 - 9.0 | 14.0 |
| 500 | 17.0 - 28.5 | 5.5 - 11.5 | 17.0 |
| 600 | 20.5 - 34.0 | 7.0 - 13.5 | 20.5 |
| 700 | 24.0 - 39.5 | 8.0 - 16.0 | 24.0 |
| 800 | 27.5 - 45.5 | 9.0 - 18.0 | 27.5 |
| 900 | 31.0 - 51.0 | 10.0 - 20.5 | 31.0 |
| 1000 | 34.0 - 57.0 | 11.0 - 23.0 | 34.0 |
| 1100 | 37.5 - 62.5 | 12.5 - 25.0 | 37.5 |

*Dose volumes have been rounded to the nearest 0.5 mL within the dose range.

**Swine:**
Administer, either by intramuscular or subcutaneous (behind the ear) injection, a single dose of 7.5 mg/kg of body weight (3.4 mL/100 lb). Administered dose volume should not exceed 5 mL per injection site.

For the control of colibacillosis, administration should be initiated within the first 60 days post-weaning when clinical signs are present in at least 2% of the animals in the group. If no improvement is noted within 48 hours, the diagnosis should be reevaluated.

**Table 2 – Enroflox 100 Dose Schedule for Swine**

| Weight (lb) | Dose Volume (mL) |
|---|---|
| 15 | 0.5 |
| 30 | 1.0 |
| 50 | 1.7 |
| 100 | 3.4 |
| 150 | 5.1 |
| 200 | 6.8 |
| 250 | 8.5 |

**Dilution of Enroflox 100:** Enroflox 100 may be diluted with sterile water prior to injection. The diluted product should be used within 24 hours. Store diluted solution in amber glass bottles between 4-40°C (36-104°F).

**Table 3 - Dilution Schedule***

| Swine Weight | mL of Enroflox 100 | mL of sterile water | Number of doses |
|---|---|---|---|
| 10 lb | 34 mL | 66 mL | 100 |
| 15 lb | 51 mL | 49 mL | 100 |
| 20 lb | 68 mL | 32 mL | 100 |
| 25 lb | 85 mL | 15 mL | 100 |

*For 1 mL dose volume from diluted solution

For the **100 mL vial**: Use within 30 days of first puncture and puncture a maximum of 36 times. When using a needle or draw-off spike larger than 16 gauge, discard any remaining product immediately after use.
For the **250 mL and 500 mL vials**: Use within 30 days of first puncture. Puncture a maximum of 36 times with a needle or dosage delivery device 16 gauge or smaller, or 4 times with a draw-off spike 5 mm or smaller. When using a needle larger than 16 gauge, or a draw-off spike larger than 5 mm, discard any remaining product immediately after use.

**RESIDUE WARNINGS:**
**Cattle:** Animals intended for human consumption must not be slaughtered within 28 days from the last treatment. This product is not approved for female dairy cattle 20 months of age or older, including dry dairy cows. Use in these cattle may cause drug residues in milk and/or in calves born to these cows. A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal.
**Swine:** Animals intended for human consumption must not be slaughtered within 5 days of receiving a single-injection dose.

**HUMAN WARNINGS:**
**Not for use in humans. Keep out of reach of children.**
Avoid contact with eyes. In case of contact, immediately flush eyes with copious amounts of water for 15 minutes. In case of dermal contact, wash skin with soap and water. Consult a physician if irritation persists following ocular or dermal exposures. Individuals with a history of hypersensitivity to quinolones should avoid this product. In humans, there is a risk of user photosensitization within a few hours after excessive exposure to quinolones. If excessive accidental exposure occurs, avoid direct sunlight. For customer service, to obtain a copy of the Safety Data Sheet (SDS) or to report adverse reactions, call Norbrook at 1-866-591-5777.

**PRECAUTIONS:**
The effects of enrofloxacin on cattle or swine reproductive performance, pregnancy and lactation have not been adequately determined.
The long-term effects on articular joint cartilage have not been determined in pigs above market weight.
Subcutaneous injection in cattle or swine, or intramuscular injection in swine, can cause a transient local tissue reaction that may result in trim loss of edible tissue at slaughter.
Enroflox 100 contains different excipients than other enrofloxacin products. The safety and efficacy of this formulation in species other than cattle and swine have not been determined.
Quinolone-class drugs should be used with caution in animals with known or suspected Central Nervous System (CNS) disorders. In such animals, quinolones have, in rare instances, been associated with CNS stimulation which may lead to convulsive seizures. Quinolone-class drugs have been shown to produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. See Animal Safety section for additional information.

**ADVERSE REACTIONS:**
No adverse reactions were observed during clinical trials.
To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Norbrook at 1-866-591-5777. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at www.fda.gov/reportanimalae.

**MICROBIOLOGY:**
Enrofloxacin is bactericidal and exerts its antibacterial effect by inhibiting bacterial DNA gyrase (a type II topoisomerase) thereby preventing DNA supercoiling and replication which leads to cell death.[1] Enrofloxacin is active against Gram-negative and Gram-positive bacteria.

**EFFECTIVENESS:**
**Cattle:** A total of 845 calves with naturally-occurring BRD were treated with enrofloxacin injection in eight field trials located in five cattle-feeding states. Response to treatment was compared to non-treated controls. Single-dose and multiple-day therapy regimens were evaluated. BRD and mortality were significantly reduced in enrofloxacin-treated calves. No adverse reactions were reported in treated animals.
The effectiveness of enrofloxacin injection for the control of respiratory disease in cattle at high risk of developing BRD was evaluated in a six-location study in the U.S. and Canada. A total of 1,150 crossbred beef calves at high risk of developing BRD were enrolled in the study. Enrofloxacin injection (7.5 mg/kg BW) or an equivalent volume of sterile saline was administered as a single subcutaneous injection within two days after arrival. Cattle were observed daily for clinical signs of BRD and were evaluated for success on Day 14 post-treatment. Treatment success in the enrofloxacin injection group (497/573, 87.83%) was significantly higher (P = 0.0013) than success in the saline control group (455/571, 80.92%). In addition, there were more treatment successes (n=13) than failures (n=3) in the group of animals positive for *M. bovis* on Day 0 that were treated with enrofloxacin injection. No product-related adverse reactions were reported.

**Swine:** A total of 590 pigs were treated with enrofloxacin injection or saline in two separate natural infection SRD field trials. For the treatment of SRD, the success rate of enrofloxacin-treated pigs that were defined as "sick and febrile" (increased respiratory rate, labored or dyspneic breathing, depressed attitude and a rectal temperature ≥104.0°F) was statistically significantly greater than the success rate of saline-treated "sick and febrile" pigs. For the control of SRD, mean rectal temperature, mortality (one trial) and morbidity were statistically significantly lower for enrofloxacin-treated pigs in pens containing a percentage of "sick and febrile" pigs compared to saline-treated pigs.

The effectiveness of enrofloxacin injection administered as a single SC dose of 7.5 mg/kg BW for the treatment and control of SRD associated with *M. hyopneumoniae* was demonstrated using an induced infection model study and three single-site natural infection field studies. In the model study, 72 healthy pigs were challenged with a representative *M. hyopneumoniae* isolate and treated with enrofloxacin injection or saline. A statistically significant (P<0.0001) decrease in the mean total lung lesion score was observed in the enrofloxacin injection-treated group (4%) compared with the saline-treated group (27%) at 10 days post-treatment. In two field studies evaluating effectiveness for treatment of SRD, a total of 300 pigs with clinical signs of SRD (moderate depression, moderately increased respiratory rate, and a rectal temperature of ≥ 104°F) were enrolled and treated with enrofloxacin injection or saline. At 7 days post-treatment, the cure rate was statistically significantly higher at each site (P < 0.0001) in the enrofloxacin injection-treated groups (61.3% and 92%) compared with the saline-treated groups (26.7% and 33.3%). In one field study evaluating effectiveness for control of SRD, a group of 400 pigs in which > 15% had clinical signs of SRD (moderate depression score, moderately increased respiratory rate, and a rectal temperature of ≥ 104°F) was enrolled and treated with enrofloxacin injection or saline. At 7 days post-treatment, the cure rate was statistically significantly higher (P < 0.0002) in the enrofloxacin injection-treated group (70.0%) compared with the saline-treated group (48.5%). In addition to *M. hyopneumoniae, B. bronchiseptica* was also isolated in sufficient numbers from these field studies to be included in the SRD treatment and control indications.

The effectiveness of enrofloxacin injection for the control of colibacillosis associated with *E. coli* was evaluated in a multi-site natural infection field study. At each site, when at least 5% of the pigs were defined as "clinically affected" (presence of diarrhea and either depression or gauntness), all pigs were administered enrofloxacin injection as a single IM dose of 7.5 mg/kg BW or an equivalent dose volume of saline. At 7 days post-treatment, the success rate was statistically significantly higher (P = 0.0350) in the enrofloxacin injection-treated group (61.5%) compared with the saline-treated group (44.7%).

The effectiveness of enrofloxacin injection administered as a single IM dose of 7.5 mg/kg BW for the treatment and control of SRD or as a single SC dose of 7.5 mg/kg BW for the control of colibacillosis was confirmed by demonstrating comparable serum enrofloxacin concentrations following IM or SC injection into the neck of healthy male and female pigs.

**TOXICOLOGY:**
The oral LD50 for laboratory rats was greater than 5000 mg/kg of body weight. Ninety-day feeding studies in dogs and rats revealed no observable adverse effects at treatment rates of 3 and 40 mg/kg respectively. Chronic studies in rats and mice revealed no observable adverse effects at 5.3 and 323 mg/kg respectively. There was no evidence of carcinogenic effect in laboratory animal models. A two-generation rat reproduction study revealed no effect with 10 mg/kg treatments. No teratogenic effects were observed in rabbits at doses of 25 mg/kg or in rats at 50 mg/kg.

**ANIMAL SAFETY:**
**Cattle:** Safety studies were conducted in feeder calves using single doses of 5, 15, and 25 mg/kg for 15 consecutive days and 50 mg/kg for 5 consecutive days. No clinical signs of toxicity were observed when a dose of 5 mg/kg was administered for 15 days. Clinical signs of depression, incoordination, and muscle fasciculation were observed in calves when doses of 15 or 25 mg/kg were administered for 10 to 15 days. Clinical signs of depression, inappetence and incoordination were observed when a dose of 50 mg/kg was administered for 3 days.
No drug-related abnormalities in clinical pathology parameters were identified. No articular cartilage lesions were observed after examination of stifle joints from animals administered 25 mg/kg for 15 days.

A safety study was conducted in 23-day-old calves using doses of 5, 15, and 25 mg/kg for 15 consecutive days. No clinical signs of toxicity or changes in clinical pathology parameters were observed. No articular cartilage lesions were observed in the stifle joints at any dose level at 2 days and 9 days following 15 days of drug administration.

An injection site study conducted in feeder calves demonstrated that the formulation may induce a transient reaction in the subcutaneous tissue and underlying muscle. No painful responses to administration were observed.

**Swine: Subcutaneous Safety:** A safety study was conducted in 32 pigs weighing approximately 57 kg (125 lb) using single doses of 5, 15, or 25 mg/kg daily for 15 consecutive days. Incidental lameness of short duration was observed in all groups, including the saline-treated controls. Musculoskeletal stiffness was observed following the 15 and 25 mg/kg treatments with clinical signs appearing during the second week of treatment. Clinical signs of lameness improved after treatment ceased and most animals were clinically normal at necropsy.

A second study was conducted in two pigs weighing approximately 23 kg (50 lb), treated with 50 mg/kg for 5 consecutive days. There were no clinical signs of toxicity or pathological changes.

An injection site study conducted in pigs demonstrated that the formulation may induce a transient reaction in the subcutaneous tissue. No painful responses to administration were observed.

**Intramuscular Safety:** A safety study was conducted in 48 weaned, 20- to 22-day-old pigs. Pigs were administered enrofloxacin injection at 7.5, 22.5 and 37.5 mg/kg BW by IM injection into the neck once weekly for 3 consecutive weeks. All pigs remained clinically normal throughout the study. Transient decreases in feed and water consumption were observed after each treatment. Mild, transient, post-treatment injection site swellings were observed in pigs receiving the 37.5 mg/kg BW dose. Injection site inflammation was found on post-mortem examination in all enrofloxacin-treated groups.

**STORAGE CONDITIONS:**
Protect from direct sunlight. Do not refrigerate or freeze. Store below 77°F (25°C). Precipitation may occur due to cold temperature. To redissolve, warm and then shake the vial.

**HOW SUPPLIED:**
Enroflox 100:

| | |
|---|---|
| 100 mg/mL | 100 mL Bottle |
| 100 mg/mL | 250 mL Bottle |
| 100 mg/mL | 500 mL Bottle |

**REFERENCES:**
1. Hooper, D. C., Wolfson, J. S., *Quinolone Antimicrobial Agents*, 2nd ed, 59 - 75,1993.

For customer service, to obtain a copy of the Safety Data Sheet (SDS) or to report adverse reactions, call Norbrook at 1-866-591-5777.

**Restricted Drug - California. Use Only as Directed.**

**Made in the UK.**



Norbrook Laboratories Limited
Newry, BT35 6PU, Co. Down,
Northern Ireland

June 2021

353670103

Norbrook®

Approved by FDA under
ANADA # 200-591

**PRODUCT INFORMATION**

# Norfenicol®

## (florfenicol)

Injectable Solution

300 mg/mL

**For intramuscular and subcutaneous use in beef and non-lactating dairy cattle only.**

**Not for use in female dairy cattle 20 months of age or older or in calves to be processed for veal.**

**CAUTION:** Federal law restricts this drug to use by or on the order of a licensed veterinarian.

**DESCRIPTION:** Norfenicol® Injectable Solution is a solution of the synthetic antibiotic florfenicol. Each milliliter of sterile Norfenicol Injectable Solution contains 300 mg of florfenicol, 250 mg 2-pyrrolidone, and glycerol formal qs.
The chemical name for florfenicol is *2,2-Dichloro-N-[1-(_uoromethyl)-2-hydroxy-2-[4-(methylsulfonyl)phenyl]ethyl]acetamide*.

**INDICATIONS:** Norfenicol Injectable Solution is indicated for treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida,* and *Histophilus somni,* and for the treatment of bovine interdigital phlegmon (foot rot, acute interdigital necrobacillosis, infectious pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*. Also, it is indicated for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia haemolytica, Pasteurella multocida,* and *Histophilus somni.*

**DOSAGE AND ADMINISTRATION:** For treatment of bovine respiratory disease (BRD) and bovine interdigital phlegmon (foot rot): Norfenicol Injectable Solution should be administered by intramuscular injection to cattle at a dose rate of 20 mg/kg body weight (3 mL/100 lbs). A second dose should be administered 48 hours later. Alternatively, Norfenicol Injectable Solution can be administered by a single subcutaneous (SC) injection to cattle at a dose rate of 40 mg/kg body weight (6 mL/100 lbs). Do not administer more than 10 mL at each site. The injection should be given only in the neck.
NOTE: Intramuscular injection may result in local tissue reaction which persists beyond 28 days. This may result in trim loss of edible tissue at slaughter. Tissue reaction at injection sites other than the neck is likely to be more severe.

**For control of respiratory disease in cattle at high-risk of developing BRD:** Norfenicol Injectable Solution should be administered by a single subcutaneous injection to cattle at a dose rate of 40 mg/kg body weight (6 mL/100lbs). Do not administer more than 10 mL at each site. The injection should be given only in the neck.

NORFENICOL INJECTABLE SOLUTION
DOSAGE GUIDE

| ANIMAL WEIGHT (lbs) | IM DOSAGE 3.0 mL/100 lb Body Weight (mL) | SC DOSAGE 6.0 mL/100 lb Body Weight (mL) |
|---|---|---|
| 100 | 3.0 | 6.0 |
| 200 | 6.0 | 12.0 |
| 300 | 9.0 | 18.0 |
| 400 | 12.0 | 24.0 |
| 500 | 15.0 | 30.0 |
| 600 | 18.0 | 36.0 |
| 700 | 21.0 | 42.0 |
| 800 | 24.0 | 48.0 |
| 900 | 27.0 | 54.0 |
| 1000 | 30.0 | 60.0 |

**Recommended Injection Location**

Do not inject more than 10 mL per injection site.

Clinical improvement should be evident in most treated subjects within 24 hours of initiation of treatment. If a positive response is not noted within 72 hours of initiation of treatment, the diagnosis should be re-evaluated.

**CONTRAINDICATIONS:** Do not use in animals that have shown hypersensitivity to florfenicol.

**WARNINGS: NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN.** This product contains materials that can be irritating to skin and eyes. Avoid direct contact with skin, eyes, and clothing. In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. Consult a physician if irritation persists. Accidental injection of this product may cause local irritation. Consult a physician immediately. The Safety Data Sheet (SDS) contains more detailed occupational safety information.
To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Norbrook at 1-866-591-5777.

**PRECAUTIONS:** Not for use in animals intended for breeding purposes. The effects of florfenicol on bovine reproductive performance, pregnancy, and lactation have not been determined. Toxicity studies in dogs, rats, and mice have associated the use of florfenicol with testicular degeneration and atrophy. Intramuscular injection may result in local tissue reaction which persists beyond 28 days. This may result in trim loss of edible tissue at slaughter. Tissue reaction at injection sites other than the neck is likely to be more severe.

**RESIDUE WARNINGS:** Animals intended for human consumption must not be slaughtered within 28 days of the last intramuscular treatment. Animals intended for human consumption must not be slaughtered within 33 days of subcutaneous treatment. This product is not approved for use in female dairy cattle 20 months of age or older, including dry dairy cows. Use in these cattle may cause drug residues in milk and/or in calves born to these cows. A withdrawal period has not been established in pre-ruminating calves. Do not use in calves to be processed for veal.

**ADVERSE REACTIONS:** Inappetence, decreased water consumption, or diarrhea may occur transiently following treatment.

**CLINICAL PHARMACOLOGY:** The pharmacokinetic disposition of florfenicol injectable solution was evaluated in feeder calves following single intramuscular (IM) administration at the recommended dose of 20 mg/kg body weight. Florfenicol injectable solution was also administered intravenously (IV) to the same cattle in order to calculate the volume of distribution, clearance, and percent bioavailability[1] (Table 1).

**TABLE 1.** Pharmacokinetic Parameter Values for Florfenicol Following IM Administration of 20 mg/kg Body Weight to Feeder Calves (n=10).

| Parameter | Median | Range |
|---|---|---|
| $C_{max}$ (µg/mL) | 3.07* | 1.43 - 5.60 |
| $T_{max}$ (hr) | 3.33 | 0.75 - 8.00 |
| T ½ (hr) | 18.3** | 8.30 - 44.0 |
| AUC (µg·min/mL) | 4242 | 3200 - 6250 |
| Bioavailability (%) | 78.5 | 59.3 - 106 |
| $Vd_{SS}$ (L/kg)*** | 0.77 | 0.68 - 0.85 |
| $Cl_t$ (mL/min/kg)*** | 3.75 | 3.17 - 4.31 |

* harmonic mean
** mean value
*** following IV administration

$C_{max}$ Maximum serum concentration
$T_{max}$ Time at which $C_{max}$ is observed
T ½ Biological half-life
AUC Area under the curve
$Vd_{ss}$ Volume of distribution at steady state
$Cl_t$ Total body clearance

Florfenicol was detectible in the serum of most animals through 60 hours after intramuscular administration with a mean concentration of 0.19 µg/mL. The protein binding of florfenicol was 12.7%, 13.2%, and 18.3% at serum concentrations of 0.5, 3.0, and 16.0 µg/mL, respectively.

**MICROBIOLOGY:** Florfenicol is a synthetic, broad-spectrum antibiotic active against many Gram-negative and Gram-positive bacteria isolated from domestic animals. It acts by binding to the 50S ribosomal subunit and inhibiting bacterial protein synthesis. Florfenicol is generally considered a bacteriostatic drug, but exhibits bactericidal activity against certain bacterial species. *In vitro* studies demonstrate that florfenicol is active against the bovine respiratory disease (BRD) pathogens *Mannheimia haemolytica, Pasteurella multocida,* and *Histophilus somni,* and that florfenicol exhibits bactericidal activity against strains of *M. haemolytica* and *H. somni*. Clinical studies confirm the efficacy of florfenicol against BRD as well as against commonly isolated bacterial pathogens in bovine interdigital phlegmon including *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*.
The minimum inhibitory concentrations (MICs) of florfenicol for BRD organisms were determined using isolates obtained from natural infections from 1990 to 1993. The MICs for interdigital phlegmon organisms were determined using isolates obtained from natural infections from 1973 to 1997 (Table 2).

**TABLE 2.** Florfenicol Minimum Inhibitory Concentration (MIC) Values*of Indicated Pathogens Isolated from Natural Infections of Cattle.

| Indicated Pathogens | Year of Isolation | Number of isolates | $MIC_{50}$** (µg/mL) | $MIC_{90}$** (µg/mL) |
|---|---|---|---|---|
| *Mannheimia haemolytica* | 1990 to 1993 | 398 | 0.5 | 1 |
| *Pasteurella multocida* | 1990 to 1993 | 350 | 0.5 | 0.5 |
| *Histophilus somni* | 1990 to 1993 | 66 | 0.25 | 0.5 |
| *Fusobacterium necrophorum* | 1973 to 1997 | 33 | 0.25 | 0.25 |
| *Bacteroides melaninogenicus* | 1973 to 1997 | 20 | 0.25 | 0.25 |

* The correlation between the *in vitro* susceptibility data and clinical effectiveness is unknown.
** The lowest MIC to encompass 50% to 90% of the most susceptible isolates, respectively.

**ANIMAL SAFETY:** A 10X safety study was conducted in feeder calves. Two intramuscular injections of 200 mg/kg were administered at a 48-hour interval. The calves were monitored for 14 days after the second dose. Marked anorexia, decreased water consumption, decreased body weight, and increased serum enzymes were observed following dose administration. These effects resolved by the end of the study.
A 1X, 3X, and 5X (20, 60, and 100 mg/kg) safety study was conducted in feeder calves for 3X the duration of treatment (6 injections at 48-hour intervals). Slight decrease in feed and water consumption was observed in the 1X dose group. Decreased feed and water consumption, body weight, urine pH, and increased serum enzymes, were observed in the 3X and 5X dose groups. Depression, soft stool consistency, and dehydration were also observed in some animals (most frequently at the 3X and 5X dose levels), primarily near the end of dosing.
A 43-day controlled study was conducted in healthy cattle to evaluate effects of florfenicol injectable solution administered at the recommended dose on feed consumption. Although a transient decrease in feed consumption was observed, florfenicol injectable solution administration had no long-term effect on body weight, rate of gain, or feed consumption.

**STORAGE INFORMATION: Store at or below 77°F (25°C).** Refrigeration is not required. Excursions permitted up to 86°F (30°C). Brief exposure to temperature up to 104°F (40°C) may be tolerated provided the mean kinetic temperature does not exceed 77°F (25°C); however, such exposure should be minimized. The solution is light yellow to straw colored. Color does not affect potency. Use within 28 days of first vial puncture.

**HOW SUPPLIED:** Norfenicol Injectable Solution is packaged in 100 mL, 250 mL, and 500 mL sterile multiple-dose vials.

**REFERENCE:** [1] Lobell RD, Varma KJ, et al. Pharmacokinetics of florfenicol following intravenous and intramuscular doses to cattle. J Vet Pharmacol Therap. 1994; 17: 253-258.

**Restricted Drug – California. Use Only as Directed.**
Made in the UK.
Manufactured by: Norbrook Laboratories Limited, Newry, BT35 6PU, Co. Down, Northern Ireland.



162670I02 November 2020

Norbrook®

**Approved by FDA under NADA # 065-010**

# NOROCILLIN

**(penicillin G procaine injectable suspension)**

**For use in Cattle, Sheep, Swine and Horses.**

**ANTIBIOTIC**

**Caution:** Federal law restricts this drug to use by or on the order of a licensed veterinarian.

**READ ENTIRE BROCHURE CAREFULLY BEFORE USING THIS PRODUCT**

**Description:**
Norocillin is a suspension of penicillin G procaine in 100, 250, and 500 mL multiple dose vials. Each mL is designed to provide 300,000 units of penicillin G as procaine in a stable suspension. Penicillin G procaine is an antibacterial agent which has activity against a variety of pathogenic organisms, mainly in the Gram-positive category.

**Indications:**
Norocillin is indicated for treatment of bacterial pneumonia (shipping fever) caused by *Pasteurella multocida* in cattle and sheep, erysipelas caused by *Erysipelothrix rhusiopathiae* in swine, and strangles caused by *Streptococcus equi* in horses.

**Directions for Use:**
A thoroughly cleaned, sterile needle and syringe should be used for each injection (needles and syringes may be sterilized in boiling water for 15 minutes). Before withdrawing the solution from the bottle, disinfect the rubber cap top with 70% alcohol. The injection site should be similarly disinfected with alcohol. Needles of 16 to 18 gauge and 1 to 1.5 inches long are adequate for intramuscular injections.

In livestock intramuscular injections should be made by directing the needle of suitable gauge and length into the fleshy part of a thick muscle, such as rump, hip, or thigh region; avoid blood vessels and major nerves. Before injecting the solution, pull back gently on the plunger. If blood appears in the syringe, a blood vessel has been entered; withdraw the needle and select a different site.

**Dosage:**
Norocillin is administered by the intramuscular route. The product is ready for injection after warming the vial to room temperature and shaking to ensure a uniform suspension.

The daily dose of penicillin is 3,000 units per pound of body weight (1 mL per 100 lbs body weight). Continue daily treatment until recovery is apparent and for at least one day after symptoms disappear, usually in two to three days.

Treatment should not exceed four consecutive days.

No more than 10 mL should be injected at any one site. Rotate injection sites for each succeeding treatment.

**Care of Sick Animals:**
The use of antibiotics in the management of diseases is based on an accurate diagnosis and an adequate course of treatment. When properly used in the treatment of diseases caused by penicillin-susceptible organisms, most animals treated with Norocillin show a noticeable improvement within 24 to 48 hours. If improvement does not occur within this period of time, the diagnosis and course of treatment should be re-evaluated. It is recommended that the diagnosis and treatment of animal diseases be carried out by a veterinarian.

Since many diseases look alike but require different types of treatment, the use of professional veterinary and laboratory services can reduce treatment time, costs and needless losses. Good housing, sanitation and nutrition are important in the maintenance of healthy animals and are essential in the treatment of disease.

**Residue Warnings:**
Exceeding the daily dosage of 3,000 units per pound of body weight, administering for more than four consecutive days, or exceeding the maximum injection site volume per injection site may result in antibiotic residues beyond the withdrawal time. Milk taken from treated dairy animals within 48 hours after the last treatment must not be used for food. Discontinue use of this drug for the following time period before treated animals are slaughtered for food:

Cattle – 14 days, Sheep – 9 days,
Swine – 7 days.

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

**Warning:**
Do not use in horses intended for human consumption. Not for use in humans.
Keep out of reach of children.

**Precautions:**
Intramuscular injection in cattle, sheep, and swine may result in a local tissue reaction which persists beyond the withdrawal period of 14 days (cattle), 9 days (sheep), or 7 days (swine). This may result in trim loss of edible tissue at slaughter.

Allergic or anaphylactic reactions, sometimes fatal, have been known to occur in animals hypersensitive to penicillin and procaine. Such reactions can occur unpredictably with varying intensity. Animals administered penicillin G procaine should be kept under close observation for at least one half hour. Should allergic or anaphylactic reactions occur, discontinue use of the product and call a veterinarian. If respiratory distress is severe, immediate injection of epinephrine or antihistamine following manufacturer's recommendations may be necessary.

As with all antibiotic preparations, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. A lack of response by the treated animal, or the development of new signs or symptoms suggest that an overgrowth of nonsusceptible organisms has occurred. In such instances, consult your veterinarian.

It is advisable to avoid giving penicillin in conjunction with bacteriostatic drugs such as tetracyclines.

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Norbrook at 1-866-591-5777. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at www.fda.gov/reportanimalae.

**Storage Conditions:**
Norocillin should be stored between 2 to 8°C (36 to 46°F). Use within 60 days of first puncture and puncture a maximum of 100 times. 250 and 500 mL vials: If using a needle or draw-off spike larger than 16 gauge, discard any remaining product immediately after use.

**Made in the UK.**

Norbrook Laboratories Limited
Newry, BT35 6QQ,
Co. Down, Northern Ireland

January 2024
112670I02

Norbrook®

Approved by FDA under NADA # 141-143

# Noromycin® 300 LA

**(oxytetracycline injection)**
**ANTIBIOTIC**

Each mL contains 300 mg of oxytetracycline base (equivalent to 323.5 mg of oxytetracycline dihydrate).

**For Use in Beef Cattle, Non-lactating Dairy Cattle, Calves, Including Pre-ruminating (Veal) Calves and Swine.**

**READ ENTIRE BROCHURE CAREFULLY BEFORE USING THIS PRODUCT.**

**Caution:** Federal law restricts this drug to use by or on the order of a licensed veterinarian.

## INTRODUCTION:

Noromycin 300 LA (oxytetracycline injection) is a sterile, ready to use solution of the broad-spectrum antibiotic oxytetracycline dihydrate. Oxytetracycline is an antimicrobial agent that is effective in treatment of a wide range of diseases caused by susceptible gram-positive and gram-negative bacteria. The antibiotic activity of oxytetracyline is not appreciably diminished in the presence of body fluids, serum or exudates.

## INGREDIENTS:

Noromycin 300 LA (oxytetracycline injection) is a sterile, pre-constituted solution of the broad-spectrum antibiotic oxytetracycline dihydrate. Each mL contains 300 mg of oxytetracycline base (equivalent to 323.5 mg of oxytetracycline dihydrate), 40% (v/v) glycerol formal, 10% (v/v) polyethylene glycol 200, 2.7% (w/v) magnesium oxide, 0.4% (w/v) sodium formaldehyde sulphoxylate (as a preservative) and monoethanolamine (as required to adjust pH).

## INDICATIONS:

Noromycin 300 LA is intended for use in treatment for the following diseases when due to oxytetracycline - susceptible organisms:

*Beef cattle, non-lactating dairy cattle, calves, including pre-ruminating (veal) calves:*
Noromycin 300 LA is indicated in the treatment of pneumonia and shipping fever complex associated with *Pasteurella* spp., and *Histophilus* spp. Noromycin 300 LA is indicated for the treatment of infectious bovine keratoconjunctivitis (pink eye) caused by *Moraxella bovis,* foot-rot and diphtheria caused by *Fusobacterium necrophorum;* bacterial enteritis (scours) caused by *Escherichia coli;* wooden tongue caused by *Actinobacillus lignieresii;* leptospirosis caused by *Leptospira pomona;* and wound infections and acute metritis caused by strains of staphylococcal and streptococcal organisms sensitive to oxytetracycline. Also, it is indicated for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia (Pasteurella) haemolytica.*

*Swine:*
Noromycin 300 LA is indicated in the treatment of bacterial enteritis (scours, colibacillosis) caused by *Escherichia coli;* pneumonia caused by *Pasteurella multocida;* and leptospirosis caused by *Leptospira pomona.*

In sows Noromycin 300 LA is indicated as an aid in control of infectious enteritis (baby pig scours, colibacillosis) in suckling pigs caused by *Escherichia coli.*

## PHARMACOLOGY:

Oxytetracycline is derived from the metabolic activity of the actinomycete, *Streptomyces rimosus.* Oxytetracycline is an antimicrobial agent that is effective in the treatment of a wide range of diseases caused by susceptible gram-positive and gram-negative bacteria.

The antibiotic activity of oxytetracycline is not appreciably diminished in the presence of body fluids, serum or exudates.

Studies have shown that the half-life of oxytetracycline in blood following intramuscular treatment with Noromycin 300 LA at 5 mg per pound of bodyweight is approximately 23 hours in cattle and 18 hours in swine.

Studies have shown when Noromycin 300 LA is administered once intramuscularly to cattle or swine at 9 mg per pound of bodyweight, blood oxytetracycline concentration of greater than 0.2 mcg/mL have been observed for 3 to 4 days.

Studies have shown when Noromycin 300 LA is administered once intramuscularly or subcutaneously to cattle at 13.6 mg per pound of bodyweight, blood oxytetracycline concentration of greater than 0.2 mcg/mL have been observed for at least 7 to 8 days.

## DOSAGE AND ADMINISTRATION:

*Beef cattle, non-lactating dairy cattle, calves, including pre-ruminating (veal) calves:*
A single intramuscular or subcutaneous dosage of 13.6 mg of oxytetracycline per pound of bodyweight, Noromycin 300 LA is recommended for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia (Pasteurella) haemolytica.*

At a single intramuscular or subcutaneous dose range of 9 to 13.6 mg of oxytetracycline per pound of bodyweight, Noromycin 300 LA is recommended in the treatment of the following conditions:

(1) Bacterial pneumonia caused by *Pasteurella* spp (shipping fever) in calves and yearlings where retreatment is impractical due to husbandry conditions, such as cattle on range, or where their repeated restraint is inadvisable.

(2) Infectious bovine kertaconjunctivitis (pink eye) caused by *Moraxella bovis.*

For other indications Noromycin 300 LA is to be administered intramuscularly, subcutaneously or intravenously at a level of 3 to 5 mg of oxytetracycline per pound of bodyweight per day. In treatment of foot-rot and advanced cases of other indicated diseases, a dosage level of 5 mg per pound of bodyweight per day is recommended. Treatment should be continued 24 to 48 hours following remission of disease signs, however, not to exceed a total of four (4) consecutive days. If improvement is not noted within 24 to 48 hours of the beginning of treatment, diagnosis and therapy should be re-evaluated.

Do not administer intramuscularly in the neck of small calves due to lack of sufficient muscle mass.

Use extreme care when administering this product by intravenous injection. Perivascular injection or leakage from an intravenous injection may cause severe swelling at the injection site.

*Swine:*
A single dosage of 9 mg of oxytetracycline per pound of bodyweight administered intramuscularly is recommended in the treatment of bacterial pneumonia caused by *Pasteurella multocida* in swine, where retreatment is impractical due to husbandry conditions or where repeated restraint is inadvisable.

For the treatment of bacterial enteritis, pneumonia, and leptospirosis, administer 3 to 5 mg of oxytetracycline per pound of bodyweight per day by intramuscular injection. Treatment should be continued 24 to 48 hours following remission of disease signs; however, not to exceed a total of four (4) consecutive days. If improvement is not noted within 24 to 48 hours of the beginning of treatment, diagnosis and therapy should be re-evaluated.

For sows, administer once intramuscularly 3 mg of oxytetracycline per pound of bodyweight approximately eight (8) hours before farrowing or immediately after completion of farrowing as an aid in the control of infectious enteritis in baby pigs.

For swine weighing 25 lbs of bodyweight and under, Noromycin 300 LA should be administered undiluted for treatment at 9 mg/lb but should be administered diluted for treatment at 3 or 5 mg/lb.

| | 9 mg dosage of undiluted Noromycin 300 LA | 3 or 5 mg/lb volume of diluted Noromycin 300 LA | | |
|---|---|---|---|---|
| **Bodyweight** | **9 mg/lb** | **3 mg/lb** | **Dilution*** | **5 mg/lb** |
| 5 lb | 0.15 mL | 0.4 mL | 37.5 mg/mL | 0.7 mL |
| 10 lb | 0.30 mL | 0.6 mL | 50 mg/mL | 1.0 mL |
| 25 lb | 0.75 mL | 1.0 mL | 75 mg/mL | 1.7 mL |

*** To prepare dilutions, add one part of Noromycin 300 LA to three (3), five (5) or seven (7) parts of the sterile water, or 5% dextrose solution as indicated; the diluted product should be used immediately.**

## PRECAUTIONS:

Exceeding the highest recommended level of drug per pound of bodyweight per day, administering more than the recommended number of treatments, and/or exceeding 10 mL intramuscularly or subcutaneously per injection site in adult beef cattle and non-lactating dairy cattle and 5 mL intramuscularly per injection site in adult swine, may result in antibiotic residues beyond the withdrawal period.

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 the product and seek the advice of your veterinarian. Some of the reactions may be attributable either to anaphylaxis (an allergic reaction) or to cardiovascular collapse of unknown cause.

Shortly after injection treated animals may have transient hemoglobinuria resulting in darkened urine.

As with all antibiotic preparations, use of this drug may result in overgrowth of non-susceptible organisms, including fungi. The absence of a favourable response following treatment, or the development of new signs or symptoms may suggest an overgrowth of non-susceptible organisms. If superinfections occur, the use of this product should be discontinued and appropriate specific therapy should be instituted.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving Noromycin 300 LA in conjunction with penicillin.

## STORAGE CONDITIONS:

Store at controlled room temperature 20-25°C (68-77°F); excursions permitted 15-30°C (59-86°F). Protect from freezing. For 100 mL size: Use within 60 days of first puncture and puncture a maximum of 24 times. For 250 mL and 500 mL sizes: Use within 60 days of first puncture and puncture a maximum of 36 times. If using a needle or draw-off spike larger than 16 gauge, discard any remaining product immediately after use.

## WARNINGS:

**WARNINGS:** Discontinue treatment at least 28 days prior to slaughter of cattle and swine. Not for use in lactating dairy animals. Rapid intravenous administration may result in animal collapse. Oxytetracycline should be administered intravenously slowly over a period of at least 5 minutes.

The Safety Data Sheet (SDS) contains more detailed occupational safety information. To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Norbrook at 1-866-591-5777.

## CAUTION:

Intramuscular or subcutaneous injection may result in local tissue reactions which persists beyond the slaughter withdrawal period. This may result in trim loss of edible tissue at slaughter.

Intramuscular injection in the rump area may cause mild temporary lameness associated with swelling at the injection site. Subcutaneous injection in the neck area may cause swelling at the injection site.

## 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. To report a suspected adverse reaction call 1-866-591-5777.

## PRESENTATION:

Noromycin 300 LA is available in 100 mL, 250 mL and 500 mL vials.

**Livestock Drug - Not for Human Use.**

**Manufactured by:**
Norbrook Laboratories Limited,
Newry, BT35 6QQ, Co. Down, Northern Ireland.

**MADE IN THE UK**

U.S. Patent No. 6,110,905
U.S. Patent No. 6,310,053

014670I01

March 2023

Norbrook®

# OXYTETRACYCLINE INJECTION 200

**(oxytetracycline injection)**

**200 mg/mL**

**ANTIBIOTIC**

**Each mL contains 200 mg of oxytetracycline**

**For the treatment of disease in beef cattle; dairy cattle; calves, including preruminating (veal) calves; and swine.**

**Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.**

**For animal use only.**

**Read Entire Package Insert Carefully Before Using This Product.**

Oxytetracycline Injection 200 (oxytetracycline injection) is a sterile, ready-to-use solution for the administration of the broad-spectrum antibiotic oxytetracycline by injection.

Oxytetracycline Injection 200 does not require refrigeration; however, it is recommended that it be stored at controlled room temperature 20-25°C (68-77°F); excursions permitted 15-30°C (59-86°F). The antibiotic activity of oxytetracycline is not appreciably diminished in the presence of body fluids, serum, or exudates.

**CAUTION:** When administered to cattle, muscle discoloration may necessitate trimming of the injection site(s) and surrounding tissues during the dressing procedure.

**WARNINGS:**
Discontinue treatment at least 28 days prior to slaughter of cattle and swine. Milk taken from animals during treatment and for 96 hours after the last treatment must not be used for food. Rapid intravenous administration may result in animal collapse. Oxytetracycline should be administered intravenously slowly over a period of at least 5 minutes.

**PRECAUTIONS:**
Exceeding the highest recommended dosage level of drug per lb of body weight per day, administering more than the recommended number of treatments, and/or exceeding 10 mL intramuscularly or subcutaneously per injection site in adult beef and dairy cattle, and 5 mL intramuscularly per injection site in adult swine, may result in antibiotic residues beyond the withdrawal period.

At the first sign of any adverse reaction, discontinue use of the 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.

Shortly after injection, treated animals may have transient hemoglobinuria resulting in darkened urine.

As with all antibiotic preparations, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. A lack of response by the treated animal, or the development of new signs, may suggest that an overgrowth of nonsusceptible organisms has occurred. If any of these conditions occur, consult your veterinarian.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving Oxytetracycline Injection 200 in conjunction with penicillin.

**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 to anaphylaxis (an allergic reaction) or to cardiovascular collapse of unknown cause. To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Norbrook at 1-866-591-5777. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at www.fda.gov/reportanimalae.

**STORAGE CONDITIONS:** Store at controlled room temperature 20-25°C (68-77°F); excursions permitted 15-30°C (59-86°F). Protect from freezing. For 100 mL size: Use within 60 days of first puncture and puncture a maximum of 36 times. For 250 mL and 500 mL sizes: Use within 60 days of first puncture and puncture a maximum of 36 times. If using a needle or draw-off spike larger than 16 gauge, discard any remaining product immediately after use.

**CARE OF SICK ANIMALS:** The use of antibiotics in the management of diseases is based on an accurate diagnosis and an adequate course of treatment. When properly used in the treatment of diseases caused by oxytetracycline-susceptible organisms, most animals that have been treated with Oxytetracycline Injection 200 show a noticeable improvement within 24-48 hours.

**INDICATIONS:**
Oxytetracycline Injection 200 is intended for use in the treatment of the following diseases in beef cattle; dairy cattle; calves, including preruminating (veal) calves; and swine when due to oxytetracycline-susceptible organisms:

**Cattle:** Oxytetracycline Injection 200 is indicated in the treatment of pneumonia and shipping fever complex associated with *Pasteurella* spp. and *Haemophilus* spp.; infectious bovine keratoconjunctivitis (pink eye) caused by *Moraxella bovis;* foot rot and diphtheria caused by *Fusobacterium necrophorum;* bacterial enteritis (scours) caused by *Escherichia coli;* wooden tongue caused by *Actinobacillus lignieresii;* leptospirosis caused by *Leptospira pomona;* and wound infections and acute metritis caused by strains of staphylococci and streptococci organisms sensitive to oxytetracycline.

**Swine:** Oxytetracycline Injection 200 is indicated in the treatment of bacterial enteritis (scours, colibacillosis) caused by *Escherichia coli;* pneumonia caused by *Pasteurella multocida;* and leptospirosis caused by *Leptospira pomona.*

In sows, Oxytetracycline Injection 200 is indicated as an aid in the control of infectious enteritis (baby pig scours, colibacillosis) in suckling pigs caused by *Escherichia coli.*

**DOSAGE:**
**Cattle:** Oxytetracycline Injection 200 is to be administered by intramuscular, subcutaneous, or intravenous injection. Intramuscular administration is not recommended according to Beef Quality Assurance Guidelines.

A single dosage of 9 mg of Oxytetracycline Injection 200 per lb of body weight administered intramuscularly or subcutaneously is recommended in the treatment of the following conditions:

(1) bacterial pneumonia caused by *Pasteurella* spp. (shipping fever) in calves and yearlings, where retreatment is impractical due to husbandry conditions, such as cattle on range, or where repeated restraint is inadvisable.

(2) infectious bovine keratoconjunctivitis (pink eye) caused by *Moraxella bovis.*

Oxytetracycline Injection 200 can also be administered by intravenous, subcutaneous, or intramuscular injection at a level of 3-5 mg of oxytetracycline per lb of body weight per day. In the treatment of severe foot rot and advanced cases of other indicated diseases, a dosage level of 5 mg/lb of body weight per day is recommended. Treatment should be continued 24-48 hours following remission of disease signs; however, not to exceed a total of 4 consecutive days. Consult your veterinarian if improvement is not noted within 24-48 hours of the beginning of treatment.

**Swine:** A single dosage of 9 mg of Oxytetracycline Injection 200 per lb of body weight administered *intramuscularly* in the neck region is recommended in the treatment of bacterial pneumonia caused by *Pasteurella multocida* in swine, where re-treatment is impractical due to husbandry conditions or where repeated restraint is inadvisable.

Oxytetracycline Injection 200 can also be administered by intramuscular injection at a level of 3-5 mg of oxytetracycline per lb of body weight per day. Treatment should be continued 24-48 hours following remission of disease signs; however, not to exceed a total of 4 consecutive days. Consult your veterinarian if improvement is not noted within 24-48 hours of the beginning of treatment.

For sows, administer once intramuscularly in the neck region 3 mg of oxytetracycline per lb of body weight approximately 8 hours before farrowing or immediately after completion of farrowing.

*For swine weighing 25 lb of body weight and under,* Oxytetracycline Injection 200 should be administered *undiluted* for treatment at 9 mg/lb but should be administered *diluted* for treatment at 3 or 5 mg/lb.

| | 9 mg/lb Dosage Volume of Undiluted Oxytetracycline Injection 200 | 3 or 5 mg/lb Dosage Volume of Diluted Oxytetracycline Injection 200 | | |
|---|---|---|---|---|
| **Body weight** | **9 mg/lb** | **3 mg/lb** | **Dilution*** | **5 mg/lb** |
| 5 lb | 0.2 mL | 0.6 mL | 1:7 | 1.0 mL |
| 10 lb | 0.5 mL | 0.9 mL | 1:5 | 1.5 mL |
| 25 lb | 1.1 mL | 1.5 mL | 1:3 | 2.5 mL |

* To prepare dilutions, add one part of Oxytetracycline Injection 200 to 3, 5, or 7 parts of sterile water, or 5% dextrose solution as indicated; the diluted product should be used immediately.

**DIRECTIONS FOR USE:**
Oxytetracycline Injection 200 is intended for use in the treatment of disease due to oxytetracycline-susceptible organisms in beef cattle; dairy cattle; calves, including preruminating (veal) calves; and swine. A thoroughly cleaned, sterile needle and syringe should be used for each injection (needles and syringes may be sterilized by boiling in water for 15 minutes). In cold weather, Oxytetracycline Injection 200 should be warmed to room temperature before administration to animals. Before withdrawing the solution from the bottle, disinfect the rubber cap on the bottle with suitable disinfectant, such as 70% alcohol. The injection site should be similarly cleaned with the disinfectant. Needles of 16-18 gauge and 1-1½ inches long are adequate for intramuscular and subcutaneous injections. Needles 2-3 inches are recommended for intravenous use.

**Intramuscular Administration:**
Intramuscular injections should be made by directing the needle of suitable gauge and length into the fleshy part of a thick muscle in the neck region; avoid blood vessels and major nerves. Before injecting the solution, pull back gently on the plunger. If blood appears in the syringe, a blood vessel has been entered; withdraw the needle and select a different site. In cattle, intramuscular administration is not recommended according to Beef Quality Assurance Guidelines. No more than 10 mL should be injected intramuscularly at any one site in adult beef and dairy cattle, and not more than 5 mL per site in adult swine; rotate injection sites for each succeeding treatment. The volume administered per injection site should be reduced according to age and body size so that 1-2 mL per site is injected in small calves.

**Subcutaneous Administration:**
Subcutaneous injections in beef cattle, dairy cattle, and calves, including preruminating (veal) calves, should be made by directing the needle of suitable gauge and length through the loose folds of the neck skin in front of the shoulder. Care should be taken to ensure that the tip of the needle has penetrated the skin but is not lodged in muscle. Before injecting the solution, pull back gently on the plunger. If blood appears in the syringe, a blood vessel has been entered; withdraw the needle and select a different site. The solution should be injected slowly into the area between the skin and muscles. No more than 10 mL should be injected subcutaneously at any one site in adult beef and dairy cattle; rotate injection sites for each succeeding treatment. The volume administered per injection site should be reduced according to age and body size so that 1-2 mL per site is injected in small calves.

**Intravenous Administration:**
Oxytetracycline Injection 200 may be administered intravenously to beef and dairy cattle. As with all highly concentrated materials, Oxytetracycline Injection 200 should be administered slowly by the intravenous route.

**Preparation of the Animal for Injection:**
1. Approximate the 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 Fig. I).

2. 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 Fig. II), 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 restraining the animal with 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.

Figure I


Figure II

**Entering the Vein and Making the Injection:**
1. Raise the vein. This is accomplished by tying the choke rope tightly 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 Fig. II). 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 thin-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 3 distinct steps. First, insert the needle through the hide. Second, insert the needle into the vein. This may require 2 or 3 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.

4. Making the injection. With the needle in 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 it is blocked. Immediately connect the syringe containing Oxytetracycline Injection 200 to the needle and slowly depress the plunger. If there is resistance to depression of the plunger, this indicates that the needle has slipped out of the vein (or is clogged) and the procedure will have to be repeated. 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.

5. Removing the needle. When injection is complete, remove needle with 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.

**Not for Human Use.**

**MADE IN THE UK**

Approved by FDA under ANADA # 200-306

**Manufactured by:**
Norbrook Laboratories Limited,
Newry, BT35 6QQ, Co. Down,
Northern Ireland.

118670I01
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Norbrook®

# Tulieve®
## (tulathromycin injection)

Injectable Solution

**Antibiotic**

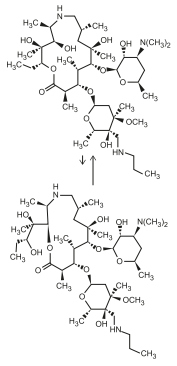
**100 mg of tulathromycin/mL**

For use in beef cattle (including suckling calves), non-lactating dairy cattle (including dairy calves), veal calves, and swine. Not for use in female dairy cattle 20 months of age or older.

**CAUTION:** Federal (USA) law restricts this drug use by or on the order of a licensed veterinarian.

**DESCRIPTION:**
Tulieve® Injectable Solution is a ready-to-use sterile parenteral preparation containing tulathromycin, a semi-synthetic macrolide antibiotic of the subclass triamilide. Each mL of Tulieve contains 100 mg of tulathromycin, 500 mg propylene glycol, 19.2 mg citric acid and 5 mg monothioglycerol. Sodium hydroxide or hydrochloric acid may be added to adjust pH.
Tulieve consists of an equilibrated mixture of two isomeric forms of tulathromycin in a 9:1 ratio. Structures of the isomers are shown below.

Figure 1.



The chemical names of the isomers are (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-13-[[2,6-dideoxy-3-C-methyl-3-O-methyl-4-C-[(propylamino)methyl]-α-L-ribo-hexopyrano-syl]oxy]-2-ethyl-3,4,10-trihydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]-oxy]-1-oxa-6-azacyclopentadecan-15-one and (2R,3R,6R,8R,9R,10S,11S,12R)-11-[[2,6-dideoxy-3-C-methyl-3-O-methyl-4-C-[(propylamino)methyl]-α-L-ribo-hexopyrano-syl]oxy]-2-[(1R,2R)-1,2-dihydroxy-1-methylbutyl]-8-hydroxy-3,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-1-oxa-4- azacyclotridecan-13-one, respectively.

**INDICATIONS**
**Beef and Non-Lactating Dairy Cattle**
**BRD**-Tulieve Injectable Solution is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, and *Mycoplasma bovis*; and for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, and *Mycoplasma bovis*.
**IBK**-Tulieve Injectable Solution is indicated for the treatment of infectious bovine keratoconjunctivitis (IBK) associated with *Moraxella bovis*.
**Foot Rot**-Tulieve Injectable Solution is indicated for the treatment of bovine foot rot (interdigital necrobacillosis) associated with *Fusobacterium necrophorum* and *Porphyromonas levii*.
**Suckling Calves, Dairy Calves, and Veal Calves**
**BRD**-Tulieve Injectable Solution is indicated for the treatment of BRD associated with *M. haemolytica*, *P. multocida*, *H. somni*, and *M. bovis*.
**Swine**
Tulieve Injectable Solution is indicated for the treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Bordetella bronchiseptica*, *Haemophilus parasuis*, and *Mycoplasma hyopneumoniae*; and for the control of SRD associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, and *Mycoplasma hyopneumoniae* in groups of pigs where SRD has been diagnosed.

**DOSAGE AND ADMINISTRATION**
**Cattle**
Inject subcutaneously as a single dose in the neck at a dosage of 2.5 mg/kg (1.1 mL/100 lb) bodyweight (BW). Do not inject more than 10 mL per injection site.

**Table 1**. Tulieve Cattle Dosing Guide

| Animal Weight (Pounds) | Dose Volume (mL) |
|---|---|
| 100 | 1.1 |
| 200 | 2.3 |
| 300 | 3.4 |
| 400 | 4.5 |
| 500 | 5.7 |
| 600 | 6.8 |
| 700 | 8.0 |
| 800 | 9.1 |
| 900 | 10.2 |
| 1000 | 11.4 |

**Swine**
Inject intramuscularly as a single dose in the neck at a dosage of 2.5 mg/kg (0.25 mL/22 lb) BW. Do not inject more than 2.5 mL per injection site.

**Table 2**. Tulieve Swine Dosing Guide

| Animal Weight (Pounds) | Dose Volume (mL) |
|---|---|
| 15 | 0.2 |
| 30 | 0.3 |
| 50 | 0.6 |
| 70 | 0.8 |
| 90 | 1.0 |
| 110 | 1.3 |
| 130 | 1.5 |
| 150 | 1.7 |
| 170 | 1.9 |
| 190 | 2.2 |
| 210 | 2.4 |
| 230 | 2.6 |
| 250 | 2.8 |
| 270 | 3.1 |
| 290 | 3.3 |

**CONTRAINDICATIONS**
The use of Tulieve Injectable Solution is contraindicated in animals previously found to be hypersensitive to the drug.

**WARNINGS**
**FOR USE IN ANIMALS ONLY.**
**NOT FOR HUMAN USE.**
**KEEP OUT OF REACH OF CHILDREN.**
**NOT FOR USE IN CHICKENS OR TURKEYS.**

**RESIDUE WARNINGS**
**Cattle**
Cattle intended for human consumption must not be slaughtered within 18 days from the last treatment. This drug is not approved for use in female dairy cattle 20 months of age or older, including dry dairy cows. Use in these cattle may cause drug residues in milk and/or in calves born to these cows.
**Swine**
Swine intended for human consumption must not be slaughtered within 5 days from the last treatment.

**PRECAUTIONS**
**Cattle**
The effects of tulathromycin injection on bovine reproductive performance, pregnancy, and lactation have not been determined. Subcutaneous injection can cause a transient local tissue reaction that may result in trim loss of edible tissue at slaughter.
**Swine**
The effects of tulathromycin injection on porcine reproductive performance, pregnancy, and lactation have not been determined. Intramuscular injection can cause a transient local tissue reaction that may result in trim loss of edible tissue at slaughter.

**ADVERSE REACTIONS**
**Cattle**
In one BRD field study, two calves treated with tulathromycin injection at 2.5 mg/kg BW exhibited transient hypersalivation. One of these calves also exhibited transient dyspnea, which may have been related to pneumonia.
**Swine**
In one field study, one out of 40 pigs treated with tulathromycin injection at 2.5 mg/kg BW exhibited mild salivation that resolved in less than four hours.
**POST APPROVAL EXPERIENCE**
The following adverse events are based on post approval adverse drug experience reporting. Not all adverse events are reported to the FDA CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data. The following adverse events are listed in decreasing order of reporting frequency in cattle: Injection site reactions and anaphylaxis/anaphylactoid reactions. For a complete listing of adverse reactions for tulathromycin injection reported to the CVM see: www.fda.gov/reportanimalae.

**CLINICAL PHARMACOLOGY**
At physiological pH, tulathromycin (a weak base) is approximately 50 times more soluble in hydrophilic than hydrophobic media. This solubility profile is consistent with the extracellular pathogen activity typically associated with the macrolides.[1] Markedly higher tulathromycin concentrations are observed in the lungs as compared to the plasma. The extent to which lung concentrations represent free (active) drug was not examined. Therefore, the clinical relevance of these elevated lung concentrations is undetermined.
Although the relationship between tulathromycin and the characteristics of its antimicrobial effects has not been characterized, as a class, macrolides tend to be primarily bacteriostatic, but may be bactericidal against some pathogens.[2] They also tend to exhibit concentration independent killing; the rate of bacterial eradication does not change once serum drug concentrations reach 2 to 3 times the minimum inhibitory concentration (MIC) of the targeted pathogen. Under these conditions, the time that serum concentrations remain above the MIC becomes the major determinant of antimicrobial activity.
Macrolides also exhibit a post-antibiotic effect (PAE), the duration of which tends to be both drug and pathogen dependent. In general, by increasing the macrolide concentration and the exposure time, the PAE will increase to some maximal duration. Of the two variables, concentration and exposure time, drug concentration tends to be the most powerful determinant of the duration of PAE.
Tulathromycin is eliminated from the body primarily unchanged via biliary excretion.
[1] Carbon, C. 1998. *Pharmacodynamics of Macrolides, Azalides, and Streptogramins: Effect on Extracellular Pathogens. Clin. Infect. Dis.*, **27**:28-32.
[2] Nightingale, C.J. 1997. *Pharmacokinetics and Pharmacodynamics of Newer Macrolides. Pediatr. Infect. Dis. J.*, **16**:438-443.
**Cattle** Following subcutaneous administration into the neck of feeder calves at a dosage of 2.5 mg/kg BW, tulathromycin is rapidly and nearly completely absorbed. Peak plasma concentrations generally occur within 15 minutes after dosing and product relative bioavailability exceeds 90%. Total systemic clearance is approximately 170 mL/hr/kg. Tulathromycin distributes extensively into body tissues, as evidenced by volume of distribution values of approximately 11 L/kg in healthy ruminating calves.[3] This extensive volume of distribution is largely responsible for the long elimination half-life of this compound [approximately 2.75 days in the plasma (based on quantifiable terminal plasma drug concentrations) versus 8.75 days for total lung concentrations (based on data from healthy animals)]. Linear pharmacokinetics are observed with subcutaneous doses ranging from 1.27 mg/kg BW to 5.0 mg/kg BW. No pharmacokinetic differences are observed in castrated male versus female calves.
[3] *Clearance and volume estimates are based on intersubject comparisons of 2.5 mg/ kg BW administered by either subcutaneous or intravenous injection.*
**Swine** Following intramuscular administration to feeder pigs at a dosage of 2.5 mg/kg BW, tulathromycin is completely and rapidly absorbed ($T_{max}$ ~0.25 hour). Subsequently, the drug rapidly distributes into body tissues, achieving a volume of distribution exceeding 15 L/kg. The free drug is rapidly cleared from the systemic circulation ($CL_{systemic}$ = 187 mL/hr/kg). However, it has a long terminal elimination half-life (60 to 90 hours) owing to its extensive volume of distribution. Although pulmonary tulathromycin concentrations are substantially higher than concentrations observed in the plasma, the clinical significance of these findings is undetermined. There are no gender differences in swine tulathromycin pharmacokinetics.

**MICROBIOLOGY**
**Cattle** Tulathromycin has demonstrated *in vitro* activity against *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, and *Mycoplasma bovis*, four pathogens associated with BRD; against *Moraxella bovis* associated with IBK; and against *Fusobacterium necrophorum* and *Porphyromonas levii* associated with bovine foot rot.
The MICs of tulathromycin against indicated BRD and IBK pathogens were determined using methods recommended by the Clinical and Laboratory Standards Institute (CLSI, M31-A2). The MICs against foot rot pathogens were also determined using methods recommended by the CLSI (M11-A6). All MIC values were determined using the 9:1 isomer ratio of this compound.
**BRD** -The MICs of tulathromycin were determined for BRD isolates obtained from calves enrolled in therapeutic and at-risk field studies in the U.S. in 1999. In the therapeutic studies, isolates were obtained from pre-treatment nasopharyngeal swabs from all study calves, and from lung swabs or lung tissue of saline-treated calves that died. In the at-risk studies, isolates were obtained from nasopharyngeal swabs of saline-treated non-responders, and from lung swabs or lung tissue of saline-treated calves that died. The results are shown in Table 3.
**IBK** -The MICs of tulathromycin were determined for *Moraxella bovis* isolates obtained from calves enrolled in IBK field studies in the U.S. in 2004. Isolates were obtained from pre-treatment conjunctival swabs of calves with clinical signs of IBK enrolled in the tulathromycin injection and saline-treated groups. The results are shown in Table 3.
**Foot Rot** -The MICs of tulathromycin were determined for *Fusobacterium necrophorum* and *Porphyromonas levii* obtained from cattle enrolled in foot rot field studies in the U.S. and Canada in 2007. Isolates were obtained from pretreatment interdigital biopsies and swabs of cattle with clinical signs of foot rot enrolled in the tulathromycin injection and saline-treated groups. The results are shown in Table 3.

**Table 3**. Tulathromycin minimum inhibitory concentration (MIC) values* for indicated pathogens isolated from field studies evaluating BRD and IBK in the U.S. and from foot rot field studies in the U.S. and Canada.

| Indicated pathogen | Date Isolated | No. of isolates | $MIC_{50}$** (µg/mL) | $MIC_{90}$** (µg/mL) | MIC range (µg/mL) |
|---|---|---|---|---|---|
| *Mannheimia haemolytica* | 1999 | 642 | 2 | 2 | 0.5 to 64 |
| *Pasteurella multocida* | 1999 | 221 | 0.5 | 1 | 0.25 to 64 |
| *Histophilus somni* | 1999 | 36 | 4 | 4 | 1 to 4 |
| *Mycoplasma bovis* | 1999 | 43 | 0.125 | 1 | ≤ 0.063 to > 64 |
| *Moraxella bovis* | 2004 | 55 | 0.5 | 0.5 | 0.25 to 1 |
| *Fusobacterium necrophorum* | 2007 | 116 | 2 | 64 | ≤ 0.25 to >128 |
| *Porphyromonas levii* | 2007 | 103 | 8 | 128 | ≤ 0.25 to >128 |

*The correlation between in vitro susceptibility data and clinical effectiveness is unknown.
** The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.

**Swine** In vitro activity of tulathromycin has been demonstrated against *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Bordetella bronchiseptica*, *Haemophilus parasuis*, and *Mycoplasma hyopneumoniae*.
The MICs of tulathromycin against indicated SRD pathogens were determined using methods recommended by the Clinical and Laboratory Standards Institute (CLSI, M31-A and M31-A3). MICs for *Haemophilus parasuis* were determined using Veterinary Fastidious Medium and were incubated up to 48 hours at 35 to 37°C in a $CO_2$-enriched atmosphere. All MIC values were determined using the 9:1 isomer ratio of this compound. Isolates obtained in 2000 and 2002 were from lung samples from saline-treated pigs and non-treated sentinel pigs enrolled in Treatment of SRD field studies in the U.S. and Canada. Isolates obtained in 2007 and 2008 were from lung samples from saline-treated and tulathromycin injection-treated pigs enrolled in the Control of SRD field study in the U.S. and Canada. The results are shown in Table 4.

**Table 4**. Tulathromycin minimum inhibitory concentration (MIC) values* for indicated pathogens isolated from field studies evaluating SRD in the U.S. and Canada.

| Indicated pathogen | Date Isolated | No. of isolates | $MIC_{50}$** (µg/mL) | $MIC_{90}$** (µg/mL) | MIC range (µg/mL) |
|---|---|---|---|---|---|
| *Actinobacillus pleuropneumoniae* | 2000-2002 | 135 | 16 | 32 | 16 to 32 |
| | 2007-2008 | 88 | 16 | 16 | 4 to 32 |
| *Haemophilus parasuis* | 2000-2002 | 31 | 1 | 2 | 0.25 to >64 |
| *Pasteurella multocida* | 2000-2002 | 55 | 1 | 2 | 0.5 to >64 |
| | 2007-2008 | 40 | 1 | 2 | ≤0.03 to 2 |
| *Bordetella bronchiseptica* | 2000-2002 | 42 | 4 | 8 | 2 to 8 |

*The correlation between in vitro susceptibility data and clinical effectiveness is unknown.
** The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.

**EFFECTIVENESS**
**Cattle**
**BRD**-In a multi-location field study, 314 calves with naturally occurring BRD were treated with tulathromycin injection. Responses to treatment were compared to saline-treated controls. A cure was defined as a calf with normal attitude/activity, normal respiration, and a rectal temperature of ≤104°F on Day 14. The cure rate was significantly higher (P ≤0.05) in tulathromycin injection-treated calves (78%) compared to saline treated calves (24%). There were two BRD-related deaths in the tulathromycin injection -treated calves compared to nine BRD-related deaths in the saline-treated calves.
Fifty-two tulathromycin injection -treated calves and 27 saline-treated calves from the multi-location field BRD treatment study had *Mycoplasma bovis* identified in cultures from pre-treatment nasopharyngeal swabs. Of the 52 tulathromycin injection -treated calves, 37 (71.2%) calves were categorized as cures and 15 (28.8%) calves were categorized as treatment failures. Of the 27 saline-treated calves, 4 (14.8%) calves were categorized as cures and 23 (85.2%) calves were treatment failures.
A Bayesian meta-analysis was conducted to compare the BRD treatment success rate in young calves (calves weighing 250 lbs or less and fed primarily a milk-based diet) treated with tulathromycin injection to the success rate in older calves (calves weighing more than 250 lbs and fed primarily a roughage and grain-based diet) treated with tulathromycin injection. The analysis included data from four BRD treatment effectiveness studies conducted for the approval of tulathromycin injection in the U.S. and nine contemporaneous studies conducted in Europe. The analysis showed that the BRD treatment success rate in young calves was at least as good as the BRD treatment success rate in older calves. As a result, tulathromycin injection is considered effective for the treatment of BRD associated with *M. haemolytica*, *P. multocida*, *H. somni*, and *M. bovis* in suckling calves, dairy calves, and veal calves.
In another multi-location field study with 399 calves at high risk of developing BRD, administration of tulathromycin injection resulted in a significantly reduced incidence of BRD (11 %) compared to saline-treated calves (59%). Effectiveness evaluation was based on scored clinical signs of normal attitude/activity, normal respiration, and a rectal temperature of ≤104°F on Day 14. There were no BRD-related deaths in the tulathromycin injection -treated calves compared to two BRD-related deaths in the saline-treated calves. Fifty saline-treated calves classified as non-responders in this study had *Mycoplasma bovis* identified in cultures of post-treatment nasopharyngeal swabs or lung tissue. Two induced infection model studies were conducted to confirm the effectiveness of tulathromycin injection against *Mycoplasma bovis*. A total of 166 calves were inoculated intratracheally with field strains of *Mycoplasma bovis*. When calves became pyrexic and had abnormal respiration scores, they were treated with either tulathromycin injection (2.5 mg/kg BW) subcutaneously or an equivalent volume of saline. Calves were observed for signs of BRD for 14 days post-treatment, then were euthanized and necropsied. In both studies, mean lung lesion percentages were statistically significantly lower in the tulathromycin injection -treated calves compared with saline-treated calves (11.3% vs. 28.9%, P = 0.0001 and 15.0% vs. 30.7%, P < 0.0001 ).
**IBK**-Two field studies were conducted evaluating tulathromycin injection for the treatment of IBK associated with *Moraxella bovis* in 200 naturally-infected calves. The primary clinical endpoint of these studies was cure rate, defined as a calf with no clinical signs of IBK and no corneal ulcer, assessed on Days 5, 9, 13, 17, and 21. Time to improvement, defined as the first day on which a calf had no clinical signs of IBK in both eyes, provided that those scores were maintained at the next day of observation, was assessed as a secondary variable. At all time points, in both studies, the cure rate was significantly higher (P < 0.05) for tulathromycin injection -treated calves compared to saline-treated calves. Additionally, time to improvement was significantly less (P < 0.0001) in both studies for tulathromycin injection -treated calves compared to saline-treated calves.
**Foot Rot**-The effectiveness of tulathromycin injection for the treatment of bovine foot rot was evaluated in 170 cattle in two field studies. Cattle diagnosed with bovine foot rot were enrolled and treated with a single subcutaneous dose of tulathromycin injection (2.5 mg/kg BW) or an equivalent volume of saline. Cattle were clinically evaluated 7 days after treatment for treatment success, which was based on defined decreases in lesion, swelling, and lameness scores. In both studies, the treatment success percentage was statistically significantly higher in tulathromycin injection -treated calves compared with saline-treated calves (60% vs. 8%, P < 0.0001 and 83.3% vs. 50%, P = 0.0088).
**Swine**
In a multi-location field study to evaluate the treatment of naturally occurring SRD, 266 pigs were treated with tulathromycin injection. Responses to treatment were compared to saline-treated controls. Success was defined as a pig with normal attitude, normal respiration, and rectal temperature of < 104°F on Day 7. The treatment success rate was significantly greater (P ≤ 0.05) in tulathromycin injection -treated pigs (70.5%) compared to saline-treated pigs (46.1%).
*M. hyopneumoniae* was isolated from 106 saline-treated and non-treated sentinel pigs in this study. Two induced infection model studies were conducted to confirm the effectiveness of tulathromycin injection against *M. hyopneumoniae*. Ten days after inoculation intranasally and intratracheally with a field strain of *M. hyopneumoniae*, 144 pigs were treated with either tulathromycin injection (2.5 mg/kg BW) intramuscularly or an equivalent volume of saline. Pigs were euthanized and necropsied 10 days post-treatment. The mean percentage of gross pneumonic lung lesions was statistically significantly lower (P < 0.0001) for tulathromycin injection -treated pigs than for saline-treated pigs in both studies (8.52% vs. 23.62% and 11.31% vs. 26.42%).
The effectiveness of tulathromycin injection for the control of SRD was evaluated in a multi-location natural infection field study. When at least 15% of the study candidates showed clinical signs of SRD, all pigs were enrolled and treated with tulathromycin injection (226 pigs) or saline (227 pigs). Responses to treatment were evaluated on Day 7. Success was defined as a pig with normal attitude, normal respiration, and rectal temperature of < 104°F. The treatment success rate was significantly greater (P < 0.05) in tulathromycin injection -treated pigs compared to saline-treated pigs (59.2% vs. 41.2%).

**ANIMAL SAFETY**
**Cattle**
Safety studies were conducted in feeder calves receiving a single subcutaneous dose of 25 mg/kg BW, or 3 weekly subcutaneous doses of 2.5, 7.5, or 12.5 mg/kg BW. In all groups, transient indications of pain after injection were seen, including head shaking and pawing at the ground. Injection site swelling, discoloration of the subcutaneous tissues at the injection site and corresponding histopathologic changes were seen in animals in all dosage groups. These lesions showed signs of resolving over time. No other drug-related lesions were observed macroscopically or microscopically.
An exploratory study was conducted in feeder calves receiving a single subcutaneous dose of 10, 12.5, or 15 mg/kg BW. Macroscopically, no lesions were observed. Microscopically, minimal to mild myocardial degeneration was seen in one of six calves administered 12.5 mg/kg BW and two of six calves administered 15mg/kg BW. A safety study was conducted in pre ruminant calves 13 to 27 days of age receiving 2.5 mg/kg BW or 7.5 mg/kg BW once subcutaneously. With the exception of minimal to mild injection site reactions, no drug-related clinical signs or other lesions were observed macroscopically or microscopically.
**Swine**
Safety studies were conducted in pigs receiving a single intramuscular dose of 25 mg/kg BW, or 3 weekly intramuscular doses of 2.5, 7.5, or 12.5 mg/kg BW. In all groups, transient indications of pain after injection were seen, including restlessness and excessive vocalization. Tremors occurred briefly in one animal receiving 7.5 mg/kg BW. Discoloration and edema of injection site tissues and corresponding histopathologic changes were seen in animals at all dosages and resolved over time. No other drug-related lesions were observed macroscopically or microscopically.

**STORAGE CONDITIONS**
Store at 59° to 86°F (15° to 30°C). Exposure to temperature up to 104°F (40°C) may be tolerated provided the mean kinetic temperature does not exceed 77°F (25°C); however, such exposure should be minimized. Exposure to temperatures down to 36°F (2°C) may be tolerated. For 50 & 100 mL vials: Use within 60 days of the first puncture and puncture a maximum of 52 times. For 250, 500 & 1000 mL vials: Use within 60 days of the first puncture and puncture a maximum of 80 times. If using a needle or draw-off spike larger than 16 gauge discard any remaining product immediately after use.

**HOW SUPPLIED**
Tulieve Injectable Solution is available in the following package sizes:
50 mL vial, 100 mL vial, 250 mL vial, 500 mL vial, 1000 mL vial

Approved by FDA under ANADA # 200-723

Tulieve® is a registered trademark of Norbrook Laboratories Limited
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Manufactured by:
Norbrook Laboratories Limited, Newry, BT35 6PU, Co. Down, Northern Ireland

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Norbrook at 1-866-591-5777. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

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