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 (33%). Effectiveness evaluation was based on scored clinical signs of normal activity, normal respiration, and 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. 38.9%, 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 Mycoplasma hyopneumoniae in 281 naturally-affected calves. The primarirnal 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 (69.6% vs. 89%, P = 0.0001 and 83.3% vs. 50%, P = 0.0008).

Swine - A safety study was conducted in preruminant calves 13 to 27 days of age receiving 2.5 mg/kg BW or 7.5 mg/kg BW once daily for 7 days. No treatment-related lesions were observed macroscopically or microscopically. A safety study was 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 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 or below 30°C (86°F). Use within 45 days of first puncture and puncture a maximum of 20 times. Consider using automatic injection equipment or a repeater syringe. When using a needle or draw-off spike larger than 16 gauge, do not inject more than 10 mL per injection site.

Table 1. TULISSIN 100 Cattle Dosing Guide

<table>
<thead>
<tr>
<th>Animal Weight (Pounds)</th>
<th>Dose Volume (mL)</th>
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<tr>
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The chemical names of the isomers are [2R,3S,4R,5R,8R,10R,11R,12S,13S,14R]-13-[(3,4,6-trideoxy-3-(dimethylamino)-α-L-ribo-hexopyranosyl]oxy]-2-[(propylamino)methyl]-8-hydroxy-3,6,8,10,12-pentamethyl-9-[3,4,6-trideoxy-3-C-methyl-3-β-D-xylo-hexopyranosyl]oxy]-1-oxa-4-azacyclotridecan-13-one, respectively.

INDICATIONS

Bovine and Non-Lactating Dairy Cattle

TULISSIN 100 Injectable Solution is indicated for the treatment of bovine foot rot (interdigital necrobacillosis) 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 - TULISSIN 100 Injectable Solution is indicated for the treatment of infectious bovine keratoconjunctivitis (IBK) associated with Moraxella bovis.

Sucking Calves, Dairy Calves, and Veal Calves

TULISSIN 100 Injectable Solution is indicated for the treatment of bovine foot rot (interdigital necrobacillosis) associated with Fusobacterium necrophorum and Porphyromonas levii.

Swine

TULISSIN 100 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, Mycoplasma hyopneumoniae in groups of pigs where SRD has been diagnosed.

DOSAGE AND ADMINISTRATION

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

Table 1. TULISSIN 100 Cattle Dosing Guide

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<td>290</td>
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**Table 2. TULISSIN 100 Swine Dosing Guide**

**WARNINGs**

**FOR USE IN ANIMALS ONLY, NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN.**

**NOT FOR USE IN CHICKENS OR TURKEYS.**

**CONTRAINDICATIONS**

The use of TULISSIN® 100 Injectable Solution is contraindicated in animals previously found to be hypersensitive to the drug.

**PRECAUTIONS**

- Cattle
  - The effects of TULISSIN 100 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.
  - In one field study, one out of eight pigs treated with tulathromycin injection at 2.5 mg/kg BW exhibited mild salivation that resolved in less than four hours.

- Swine
  - Swine 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.

**ADVERSE REACTIONS**

Cattle
- In one BRD field study, two calves treated with tulathromycin injection at 2.5 mg/kg BW exhibited transient hyperesthesia. One of these calves also exhibited transient dyspnea, which may have been related to pneumonia.

Swine
- In one field study, one out of eight 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 additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalmed.

**RESIDUE WARNINGS**

- Cattle: The following is a summary of reported drug residues in edible tissues and the limitations of their use.
  - 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.

**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. Markedly higher tiamulin 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.

The relationship between tiamulin and the characteristics of its antimicrobial effects has not been clearly defined. 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 extent. Under these conditions, the time that serum concentrations remain above the MIC becomes the major determinant of antimicrobial effect. Drug concentrations reach 2 to 3 times the minimum inhibitory concentration (MIC) of the targeted pathogen. Under these conditions, the relationship between tulathromycin and the characteristics of its antimicrobial effects has not been clearly defined. 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 extent.

- In untreated calves, serum concentrations of tiamulin typically reach 2 to 3 times the MIC within the first 2 to 3 hours after dosing. Drug concentrations remain above the MIC for 10 to 12 hours after dosing and are maintained for 20 to 24 hours at 25°C.

**MICROBIOLOGY**

- Tiamulin has demonstrated in vitro activity against Mannheimia haemolytica, Pasteurella multocida, Histophilus somni, Actinobacillus pleuropneumoniae, Pasteurella multocida, Haemophilus parasuis, and Mycoplasma hyopneumoniae. The minimum inhibitory concentration (MIC) values for indicated pathogen were determined using methods recommended by the Clinical and Laboratory Standards Institute (CLSI) M100-A16, M1-A and M10-A3.

- Tulathromycin minimum inhibitory concentration (MIC) values were determined using Veterinary Fastidious Medium and were incubated up to 48 hours at 35 to 37°C in a CO₂-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 SRF 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 SRF field study in the U.S. and Canada. The results are shown in Table 4.

**CLINICAL PHARMACOLOGY**

At intramuscular administration to feeder pigs at a dosage of 2.5 mg/kg BW, tulathromycin is rapidly absorbed (Tmax = 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 (CLfree = 187 mL/hr/kg). However, it has a long terminal elimination half-life (50 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.

**ADVERSE EFFECTS**

**Swine**

- In one BRD field study, 314 calves with naturally occurring BRD were treated with tulathromycin injection. 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 categorized as treatment failures. The correlation between in vitro susceptibility data and clinical effectiveness is unknown.

- The MIC for E. coli to encompass 50% and 90% of the most susceptible isolates, respectively.

**Residue Warnings**

- Cattle: The following is a summary of reported drug residues in edible tissues and the limitations of their use.
  - 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.

**CONTRAINDICATIONS**

The use of TULISSIN® 100 Injectable Solution is contraindicated in animals previously found to be hypersensitive to the drug.
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<td>CODE ÉLÉMENT : 84186801</td>
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**ÉLÉMENT : NOTICE**

**LOGICIEL UTILISÉ : INDESIGN CC**

**CORPS DE TEXTE : 9 PTS**

**TRACE FAREVA (L157) - 2PC (FORMAT DOUBLE PLIEE)**

**DIMENSION A PLAT: 157MM X 315MM**

**DIMENSION A PLIÉE: 157 X 40 MM (8 VOLETS)**

**COMMENTAIRE(S) : NC le 31/08/2020 : Changement de paramètres techniques**

**STUDIO GRAPHIQUE CREA**

**NOM DE PRODUIT : TULISSIN 100 250 ML / 500 ML**

**FICHIER, FAIT PAR : NC**

**VERSION LE : v1 - 20/05/2019**

**MAQ. DEPOT**

**MAQ. LANCEMENT**

**MAQ. MODIF**

**FICHIER, FAIT PAR : NC**

**VERSION LE : v1 - 12/02/2020**

**CORRIGÉ PAR : NC**

**VERSION LE : v1 - 17/02/2020**

**FICHIER, FAIT PAR : NC**

**VERSION LE : v2 - 30/03/2020**

**CORRIGÉ PAR : NC**

**VERSION LE : v3 - 18/05/2020**

**CORRIGÉ PAR : NC**

**VERSION LE : v4 - 03/06/2020**

**CORRIGÉ PAR : NC**

**VERSION LE : v5 - 27/08/2020**

**CORRIGÉ PAR : NC**

**VERSION LE : v6 - 28/08/2020**

**CORRIGÉ PAR : NC**

**VERSION LE : v7 - 31/08/2020**

**CORRIGÉ PAR : NC**

**VERSION LE : v8 - 01/09/2020**

**CORRIGÉ PAR : NC**

**VERSION LE : v9 - 02/09/2020**

**CORRIGÉ PAR : NC**

**VERSION LE : v10 - 10/09/2020**

**CORRIGÉ PAR : NC**

**VERSION LE : v11 - 08/10/2020**

**FICHIER, FAIT PAR : NC**

**VERSION LE : v2 - 30/03/2020**

**FICHIER, FAIT PAR : NC**

**VERSION LE : v3 - 18/05/2020**

**FICHIER, FAIT PAR : NC**

**VERSION LE : v4 - 03/06/2020**

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**VERSION LE : v5 - 27/08/2020**

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**FICHIER, FAIT PAR : NC**

**VERSION LE : v9 - 02/09/2020**

**FICHIER, FAIT PAR : NC**

**VERSION LE : v10 - 10/09/2020**

**FICHIER, FAIT PAR : NC**

**VERSION LE : v11 - 08/10/2020**

**VALIDATION PAR : Filiale US**

**LE :**

**13/10/2020**

**29/04/2021**

**26/05/2021**

**28/09/2021**

**01/10/2021**

**LE :**

**DAR/US/2021**