and edema of injection site tissues and corresponding histopathologic changes were seen in animals at all dosages and
restlessness and excessive vocalization. Tremors occurred briefly in one animal receiving 7.5 mg/kg BW. Discoloration
lesions were observed macroscopically or microscopically.

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 15 mg/kg BW.

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 15 mg/kg BW. A total of 166 calves were inoculated intratracheally with a field strain of
M. haemolytica, P. multocida, H. somni, and M. 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%, \( P < 0.001 \) and 15.0% vs. 30.7%, \( P < 0.001 \)).

IBK – Two field studies were conducted evaluating tulathromycin injection for the treatment of IBK associated with
Mycoplasma bovis. A total of 208 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 (\( P < 0.001 \)) 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%/75% vs. 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 (46.4%). 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
lesion was statistically significantly lower (\( P < 0.001 \)) in tulathromycin injection-treated pigs than for saline-treated pigs in both studies (52.52% vs. 53.62% and 11.31% vs. 26.42%).

The effectiveness of tulathromycin injection for the control of SRD was evaluated in a multi-location natural infection
study. When at least 15% of the study candidates showed clinical signs of SRD, all pigs were enroled 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 (55.2% vs. 41.2%).

ANIMAL SAFETY

Cattle - In two 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 15 mg/kg BW.

A safety study was conducted in preclinical 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
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.

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,
discard any remaining product immediately after use.

HOW SUPPLIED: TULISSIN 100 Injectable Solution is available in the following package sizes:
50 mL vial; 100 mL vial; 250 mL vial; 500 mL vial
Manufactured for: Virbac AH, Inc. – P.O. Box 162059, Fort Worth, TX 76161 - Made in France
Approved by FDA under ANDA # 200-669
To report suspected adverse drug events, for technical assistance, or to obtain a copy of the Safety Data Sheet (SDS),
contact Virbac AH, Inc. at 1-800-338-3659 or us.virbac.com. For additional information about adverse drug experience
reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/animaldrugs.

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Following intramuscular administration to feeder pigs at a dosage of 2.5 mg/kg BW, tulathromycin is completely and rapidly absorbed (T<sub>max</sub> = 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<sub>u,v</sub> = 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.

**MICROBIOLOGY**

**Cattle**

Tulathromycin has demonstrated in vitro activity against Mannheimia haemolytica, Pasteurella multocida, Histophilus somni, Porphyromonas levii, and Actinobacillus pleuropneumoniae. Four pathogens associated with BRD, against Mannheimia haemolytica 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). All MICs 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 injection were determined for Mannheimia haemolytica isolates obtained from calves enrolled in IBK field studies in the U.S. in 2004. Isolates were obtained from pre-treatment nasopharyngeal 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 injection were determined for Fusobacterium necrophorum and Porphyromonas levii isolates obtained from cattle enrolled in foot rot field studies in the U.S. and Canada in 2007. Isolates were obtained from pre-treatment digital swabs and biopsies of cattle with clinical signs of foot rot enrolled in the tulathromycin injection and saline-treated groups. The results are shown in Table 3.

**ADVERSE REACTIONS**

Cattle

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

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.

Swine

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.

Intramuscular injection can cause a transient local tissue reaction that may result in trim loss of edible tissue at slaughter.

In cattle, 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. 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 concentration) 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 casted male versus female calves.

In cattle, 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. 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 casted male versus female calves.

In cattle, 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. 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 casted male versus female calves.