Veterinary Medicine

S4

Solution for Injection

TULAVEN®

Reg. No.: 20/17.1.4/08 (Act 101/1965)

APPROVED
By Annelie de Klerk at 9:31 am, Mar 10, 2022

PROPRIETARY NAME
TULAVEN®

SCHEDULING STATUS
S4

DOSAGE FORM
Solution for Injection

COMPOSITION
Tulathromycin 100 mg per mℓ

Preservatives:	Phenol 0.5 % m/v Sodium formaldehyde sulfoxylate 0.25 % m/v
Excipients:	Monothioglycerol 0.5 % m/v Citric acid 1,92 % m/v Hydrochloric acid, dilute (pH adjustment) Sodium hydroxide (pH adjustment) Propylene glycol 25 % m/v Water for injection to 100 mℓ

PHARMACOLOGICAL CLASSIFICATION
C 17.1.4 Antimicrobials – Macrolides and Lincosamides

PHARMACOLOGICAL ACTION
Pharmacodynamic properties

Tulathromycin is a semi-synthetic macrolide antimicrobial agent, which originates from a fermentation product. It differs from many other macrolides in that it has a long duration of action that is, in part, due to its three amine groups; therefore, it has been given the chemical subclass designation of triamilide.

Macrolides are bacteriostatic acting antibiotics and inhibit essential protein biosynthesis by virtue of their selective binding to bacterial ribosomal RNA. They act by stimulating the dissociation of peptidyl-tRNA from the ribosome during the translocation process.

Tulathromycin possesses in vitro activity against *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni* and *Mycoplasma bovis* in cattle, and *Actinobacillus pleuropneumoniae, Pasteurella multocida, Mycoplasma hyopneumoniae* in swine, *Haemophilus parasuis* and *Bordetella bronchiseptica*, the bacterial pathogens most commonly associated with bovine and swine respiratory disease, respectively.

Tulathromycin also possesses in vitro activity against *Moraxella bovis*, the bacterial pathogen most commonly associated with infectious bovine keratoconjunctivitis (IBK).

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Pharmacokinetic particulars

In cattle, the pharmacokinetic profile of tulathromycin when administered as a single subcutaneous dose of 2.5 mg/kg bodyweight, was characterised by rapid and extensive absorption followed by high distribution and slow elimination. The maximum concentration (Cmax) in plasma was approximately 0.5 µg/ml; this was achieved approximately 30 minutes post-dosing (Tmax). Tulathromycin concentrations in lung homogenate were considerably higher than those in plasma. There is strong evidence of substantial accumulation of tulathromycin in neutrophils and alveolar macrophages. However, the in vivo concentration of tulathromycin at the infection site of the lung is not known. Peak concentrations were followed by a slow decline in systemic exposure with an apparent elimination half-life ($t^{1/2}$) of 90 hours in plasma. Plasma protein binding was low, approximately 40%. The volume of distribution at steady-state (Vss) determined after intravenous administration was 11 l/kg. The bioavailability of tulathromycin after subcutaneous administration in cattle was approximately 90%.

In pigs, the pharmacokinetic profile of tulathromycin when administered as a single intramuscular dose of 2.5 mg/kg bodyweight, was also characterised by rapid and extensive absorption followed by high distribution and slow elimination. The maximum concentration (Cmax) in plasma was approximately 0.6 µg/ml; this was achieved approximately 30 minutes post-dosing (Tmax). Tulathromycin concentrations in lung homogenate were considerably higher than those in plasma. There is strong evidence of substantial accumulation of tulathromycin in neutrophils and alveolar macrophages. However, the in vivo concentration of tulathromycin at the infection site of the lung is not known. Peak concentrations were followed by a slow decline in systemic exposure with an apparent elimination half-life ($t^{1/2}$) of approximately 91 hours in plasma. Plasma protein binding was low, approximately 40 %. The volume of distribution at steady-state (Vss) determined after intravenous administration was 13.2 l/kg. The bioavailability of tulathromycin after intramuscular administration in pigs was approximately 88 %.

INDICATIONS
TULAVEN® is a semi-synthetic macrolide antimicrobial agent, belonging to the chemical subclass triamilides indicated for treatment of respiratory infections associated to strains sensitive to tulathromycin in cattle and pigs.

For Cattle

Treatment and metaphylaxis of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni* and *Mycoplasma bovis* susceptible to tulathromycin. The presence of the disease in the herd should be established before metaphylactic treatment.

Treatment of infectious bovine keratoconjunctivitis (IBK) associated with *Moraxella bovis* susceptible to tulathromycin.

For Swine

Treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida, Mycoplasma hyopneumoniae, Haemophilus parasuis* and *Bordetella bronchiseptica* susceptible to tulathromycin.

CONTRA-INDICATIONS
Do not use in cases of hypersensitivity to macrolide antibiotics or to any of the excipients.

Do not use simultaneously with other macrolides or lincosamides

Do not use in lactating cattle producing milk for human consumption

Do not use in pregnant cows or heifers which are intended to produce milk for human consumption within 2 months of expected parturition.

WARNINGS OR WITHDRAWAL PERIOD IN THE CASE OF FOOD PRODUCING ANIMALS
In the absence of compatibility studies, TULAVEN® must not be mixed with other veterinary medicinal products.

Withdrawal Periods

Cattle (meat and offal) – 40 days

Pigs (meat and offal) – 30 days

Not permitted to use in lactating cattle producing milk for human consumption.

SIDE EFFECTS AND SPECIAL PRECAUTIONS
Side effects

Subcutaneous administration of tulathromycin to cattle causes very commonly transient pain reactions and local swellings at the injection site that can persist for up to 30 days. No such reactions have been observed in pigs after intramuscular administration.

Pathomorphological injection site reactions (including reversible changes of congestion, oedema, fibrosis and haemorrhage) are very common for approximately 30 days after injection in cattle and pig.

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

Use during pregnancy or lactation

The safety of TULAVEN® in cattle and swine has not been established during pregnancy and lactation.

Special precautions for use in animals

Use of TULAVEN® should be based on susceptibility testing of the bacteria isolated from the animal.

Official, national and regional antimicrobial policies should be taken into account when the product is used.

Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to the tulathromycin and may decrease the effectiveness of treatment with other macrolides, due to the potential for cross resistance.

If a hypersensitivity reaction occurs, appropriate treatment should be administered without delay.

Special precautions to be taken by the person administering the product to animals

Tulathromycin is irritating to eyes. In case of accidental eye exposure, flush the eyes immediately with clean water.

Tulathromycin may cause sensitisation by skin contact. In case of accidental spillage onto skin, wash the skin immediately with soap and water.

Wash hands after use.

In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to physician.

Interaction with other medical products

Cross resistance occurs with other macrolides. Do not administer simultaneously with antimicrobials with a similar mode of action such as other macrolides or lincosamides.

KNOWN SIGNS OF OVERDOSE AND PARTICULARS OF ITS TREATMENT

In cattle at dosages of three, five or ten times the recommended dose, transient signs attributed to injection site discomfort were observed and included restlessness, head-shaking, pawing the ground, and brief decrease in feed intake. Mild myocardial degeneration has been observed in cattle receiving 5 to 6 times the recommended dose.

In young pigs weighing approximately 10 kg given three or five times the therapeutic dose transient signs attributed to injection site discomfort were observed and included excessive vocalisation and restlessness. Lameness was also observed when the hind leg was used as the injection site.

QUANTITY AND STRENGTH OF ACTIVE INGREDIENTS PER DOSAGE UNIT

Tulathromycin 100 mg per mℓ

DOSAGE AND DIRECTIONS FOR USE

For Cattle

<u>For subcutaneous use</u>

A single subcutaneous injection of 2.5 mg tulathromycin/kg bodyweight (equivalent to 1 ml/40 kg bodyweight). For treatment of cattle over 300 kg bodyweight, divide the dose so that no more than 7.5 ml are injected at one site.

For Swine

<u>For intramuscular use</u>

A single intramuscular injection of 2.5 mg tulathromycin/kg bodyweight (equivalent to 1 ml/40 kg bodyweight) in the neck.

For treatment of pigs over 80 kg bodyweight, divide the dose so that no more than 2 ml are injected at one site.

For any respiratory disease, it is recommended to treat animals in the early stages of the disease and to evaluate the response to treatment within 48 hours after injection. If clinical signs of respiratory disease persist or increase, or if relapse occurs, treatment should be changed, using another antibiotic, and continued until clinical signs have resolved.

To ensure correct dosage, bodyweight should be determined as accurately as possible to avoid underdosing. For multiple vial entry, an aspirating needle or multi-dose syringe is recommended to avoid excessive broaching of the stopper. The stopper may be punctured up to 20 times.

IDENTIFICATION

A clear colourless to pale brownish yellow solution, free of visible particles.

PRESENTATION

Colourless type I glass vial closed with a bromobutyl rubber stopper and aluminium and plastic flip capsule or Translucent multi-layer (plastic) vial closed with a bromobutyl rubber stopper and aluminium and plastic flip capsule as follows:

Cardboard box containing 1 glass vial of 20 ml
Cardboard box containing 1 plastic vial of 50 ml
Cardboard box containing 1 plastic vial of 100 ml
Cardboard box containing 1 plastic vial of 250 ml
Cardboard box containing 1 plastic vial of 500 ml
Not all pack sizes may be marketed.

STORAGE INSTRUCTIONS

Keep out of reach of children and uninformed persons.
Store at or below 25°C.
Shelf-life after first broaching the vial is 28 days.
The vial may be punctured up to 20 times at most and should be disposed of.
Any unused portion must be discarded according to pharmaceutical waste management.

REGISTRATION NUMBER

20/17.1.4/08

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Ceva Animal Health (Pty) Ltd.
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DATE OF NOTIFICATION OF APPROVAL OF THE SCIENTIFIC IN PACKAGE INSERT

15 February 2022

NOT TULAVEN ZA 400X160/45G/FP 35.5X160 RECTO - VERSO CODE ARTICLE : A4987 BLACK	TULAVEN 100MG/ML 100ML ZA 75052 - 75048 - 75050 CORPS : 10 pts

LOUIS 02/03/21 - 04/03/21