SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Tulaven 100 mg/ml solution for injection for cattle, pigs and sheep

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:
Active substance:

Tulathromycin	100 mg

Excipients:

Monothioglycerol	5 mg

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for injection.
Clear colourless to pale brownish yellow or slightly pink solution.

4. CLINICAL PARTICULARS

4.1 Target species

Cattle, pigs and sheep.

4.2 Indications for use, specifying the target species

Cattle
Treatment and metaphylaxis of bovine respiratory disease (BRD) associated with*Histophilus somni ,Mannheimia haemolytica*, *Pasteurella multocida* and *Mycoplasma bovis* susceptible to tulathromycin. The presence of the disease in the group must be established before the product is used.
Treatment of infectious bovine keratoconjunctivitis (IBK) associated with *Moraxella bovis* susceptible to tulathromycin.

Pigs
Treatment and metaphylaxis of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Bordetella bronchiseptica, Haemophilus parasuis Pasteurella multocida and Mycoplasma hyopneumoniae* susceptible to tulathromycin. The presence of the disease in the group must be established before the product is used. The veterinary medicinal product should only be used if pigs are expected to develop the disease within 2–3 days.

Sheep
Treatment of the early stages of infectious pododermatitis (foot rot) associated with virulent *Dichelobacter nodosus* requiring systemic treatment.

4.3 Contraindications

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

4.4 Special warnings for each target species

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

Sheep
The efficacy of antimicrobial treatment of foot rot might be reduced by other factors, such as wet environmental conditions, as well as inappropriate farm management. Treatment of foot rot should therefore be undertaken along with other flock management tools, for example providing dry environment.

Antibiotic treatment of benign foot rot is not considered appropriate. Tulathromycin showed limited efficacy in sheep with severe clinical signs or chronic foot rot and should therefore only be given at an early stage of foot rot.

4.5 Special precautions for use

Special precautions for use in animals

Use of the veterinary medicinal product should be based on susceptibility testing of the bacteria isolated from the animal. If this is not possible, therapy should be based on local (regional, farm level) epidemiological information about susceptibility of the target bacteria. Official, national and regional antimicrobial policies should be taken into account when the product is used.

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

Special precautions to be taken by the person administering the veterinary medicinal 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 resulting in e.g. reddening of the skin (erythema) and/or dermatitis. 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 the physician.

If there is suspicion of a hypersensitivity reaction following accidental exposure (recognised by e.g. itching, difficulty in breathing, hives, swelling on the face, nausea, vomiting) appropriate treatment should be administered. Seek medical advice immediately and show the package leaflet or the label to the physician.

Special precautions for the protection of the environment

Not applicable

Other precautions
Not applicable.

4.6 Adverse reactions (frequency and seriousness)

Cattle:

Very common (>1 animal / 10 animals treated)	Injection site swelling[1], Injection site pain[1], Injection site oedema[2], Injection site fibrosis[2], Injection site haemorrhage[2], Injection site haematoma[2]

[1] These signs are observed after subcutaneous administration.
[2] These signs are reversible and can persist for approximately 30 days.

Pigs:

Very common (>1 animal / 10 animals treated)	Injection site oedema, Injection site fibrosis, Injection site haemorrhage, Injection site haematoma

These signs are reversible and can persist for approximately 30 days.

Sheep:

Very common (>1 animal / 10 animals treated)	Discomfort[1]

[1] Head shaking, rubbing injection site, backing away.
These signs appear after intramuscular injection and resolve within a few minutes.
Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

4.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during pregnancy and lactation.
Laboratory studies in rats and rabbits have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects.
Use only according to the benefit/risk assessment by the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interaction

None known.

4.9 Amount(s) to be administered and administration route

Cattle
Subcutaneous use.
A single subcutaneous injection of 2.5 mg tulathromycin/kg bodyweight (equivalent to 1 ml of the veterinary medicinal product/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.

Pigs
Intramuscular use.
A single intramuscular injection of 2.5 mg tulathromycin/kg bodyweight (equivalent to 1 ml of the veterinary medicinal product/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.

Sheep
Intramuscular use.
A single intramuscular injection of 2.5 mg tulathromycin/kg body weight (equivalent to 1 ml of the veterinary medicinal product/40 kg body weight) in the neck.

To ensure correct dosage, bodyweight should be determined as accurately as possible

For multiple vial entry, an aspirating needle or multi-dose syringe is recommended to avoid excessive broaching of the stopper. The stopper may be safely punctured up to 20 times.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

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 five to six 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.
In lambs (approx. 6 weeks old), at dosages of three or five times the recommended dose, transient signs attributed to injection site discomfort were observed, and included walking backwards, head shaking, rubbing the injection site, lying down and getting up, bleating.

4.11 Withdrawal period(s)

Cattle (meat and offal): 22 days.
Pigs (meat and offal): 13 days.
Sheep (meat and offal): 16 days.

Not authorised for use in animals producing milk for human consumption.
Do not use in pregnant animals, which are intended to produce milk for human consumption, within 2 months of expected parturition.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use, macrolides**.**

ATC vet code: QJ01FA94.

5.1 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 *Histophilus somni ,Mannheimia haemolytica*, *Pasteurella multocida, Mycoplasma bovis*, *Actinobacillus pleuropneumoniae Bordetella bronchiseptica, Haemophilus parasuis, and Mycoplasma hyopneumoniae* , the bacterial pathogens most commonly associated with bovine and swine respiratory disease, respectively.
Increased minimum inhibitory concentration (MIC) values have been found in some isolates of *Histophilus somni* and *Actinobacillus pleuropneumoniae. In vitro* activity against *Dichelobacter nodosus (vir)*, the bacterial pathogen most commonly associated with infectious pododermatitis (foot rot) in sheep, has been demonstrated. Tulathromycin also possesses *in vitro* activity against *Moraxella bovis*, the bacterial pathogen most commonly associated with infectious bovine keratoconjunctivitis (IBK).

The Clinical and Laboratory Standards Institute CLSI has set the clinical breakpoints for tulathromycin against *M. haemolytica*, *P. multocida*, and *H. somni* of bovine respiratory origin and *P. multocida* and *B. bronchiseptica* of swine respiratory origin as ≤16 µg/ml susceptible and ≥64 µg/ml resistant. *For A. pleuropneumoniae* of swine respiratory origin the susceptible breakpoint is set at ≤64 µg/ml. CLSI has also published clinical breakpoints for tulathromycin based on a disk diffusion method (CLSI document VET08, 4th ed, 2018). No clinical breakpoints are available for
H. parasuis. Neither EUCAST nor CLSI have developed standard methods for

testing antibacterial agents against veterinary *Mycoplasma* species and thus no interpretative criteria have been set.

Resistance to macrolides can develop by mutations in genes encoding ribosomal RNA (rRNA) or some ribosomal proteins; by enzymatic modification (methylation) of the 23S rRNA target site, generally giving rise to cross-resistance with lincosamides and group B streptogramins (MLS_B resistance); by enzymatic inactivation; or by macrolide efflux. MLS_B resistance may be constitutive or inducible. Resistance may be chromosomal or plasmid-encoded and may be transferable if associated with transposons, plasmids integrative and conjugative elements. Additionally, the genomic plasticity of *Mycoplasma* is enhanced by the horizontal transfer of large chromosomal fragments.

In addition to its antimicrobial properties, tulathromycin demonstrates immune-modulating and anti-inflammatory actions in experimental studies. In both bovine and porcine polymorphonuclear cells (PMNs; neutrophils), tulathromycin promotes apoptosis (programmed cell death) and the clearance of apoptotic cells by macrophages. It lowers the production of the pro-inflammatory mediators leukotriene B4 and CXCL-8 and induces the production of anti-inflammatory and pro-resolving lipid lipoxin A4.

5.2 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 (C_{max}) in plasma was approximately 0.5 µg/ml; this was achieved approximately 30 minutes post-dosing (T_{max}). 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 (V_{SS}) 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 (C_{max}) in plasma was approximately 0.6 µg/ml; this was achieved approximately 30 minutes post-dosing (T_{max}). 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 (V_{SS}) determined after intravenous

administration was 13.2 l/kg. The bioavailability of tulathromycin after intramuscular administration in pigs was approximately 88%.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Monothioglycerol
Propylene glycol
Citric acid
Hydrochloric acid, dilute (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Major incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

6.3 Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 3 years. Shelf-life after first broaching the vial: 28 days.

6.4 Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.

6.5 Nature and composition of immediate packaging

Colourless type I glass vial closed with a bromobutyl rubber stopper coated with fluoropolymer and aluminium and plastic flip capsule.
Translucentmulti layer (plastic) vial closed with a bromobutyl rubber stopper coated with fluoropolymer and aluminium and plastic flip capsule.

Pack sizes:
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

The 500 ml vials must not be used for pigs or sheep.

Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Medicines should not be disposed of via wastewater.

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Ceva Animal Health Ltd
Explorer House
Mercury Park
Wycombe Lane
Wooburn Green
High Wycombe
Buckinghamshire
HP10 0HH
United Kingdom

8. MARKETING AUTHORISATION NUMBER

Vm 15052/5018

9. DATE OF FIRST AUTHORISATION

24 April 2020

10. DATE OF REVISION OF THE TEXT

July 2024

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable

11. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCT

Veterinary medicinal product subject to prescription.
Find more product information by searching for the 'Product Information Database' or 'PID' on www.gov.uk.

Gavin Hall
Approved: 04 February 2025