

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Tulaven 25 mg/ml solution for injection for pigs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:

Tulathromycin 25 mg

Excipients:

Qualitative composition of excipients and other constituents	Quantitative composition if that information is essential for proper administration of the veterinary medicinal product
Monothioglycerol	5 mg
Propylene glycol	
Citric acid	
Hydrochloric acid, dilute (for pH adjustment)	
Sodium hydroxide (for pH adjustment)	
Water for injections	

Clear colourless to pale brownish yellow solution.

3. CLINICAL INFORMATION

3.1 Target species

Pigs

3.2 Indications for use for each target species

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

3.3 Contraindications

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

3.4 Special warnings

Cross-resistance has been shown between tulathromycin and other macrolides in the target pathogen(s). Use of the veterinary medicinal product should be carefully considered when susceptibility testing has shown resistance to tulathromycin because its effectiveness may be reduced. Do not administer simultaneously with antimicrobials with a similar mode of action such as other macrolides or lincosamides.

3.5 Special precautions for use

Special precautions for safe use in the target species:

Use of the product should be based on identification and susceptibility testing of the target pathogen(s). If this is not possible, therapy should be based on epidemiological information and knowledge of susceptibility of the target pathogens at farm level, or at local/regional level.

Use of the product should be in accordance with official, national and regional antimicrobial policies.

An antibiotic with a lower risk of antimicrobial resistance selection (lower AMEG category) should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach.

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.

3.6 Adverse events

Pigs:

Very common (>1 animal / 10 animals treated)	Injection site reaction ^{1,2} , Injection site fibrosis ¹ , Injection site haemorrhage ¹ , Injection site oedema ¹
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¹ Can persist for approximately 30 days after injection.

² Reversible changes of congestion.

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.

3.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during pregnancy and lactation.

Use only according to the benefit/risk assessment by the responsible veterinarian.

Laboratory studies in rats and rabbits have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects.

3.8 Interaction with other medicinal products and other forms of interaction

None known.

3.9 Administration routes and dosage

Intramuscular use.

A single intramuscular injection of 2.5 mg tulathromycin/kg body weight (equivalent to 1 ml of the veterinary medicinal product/10 kg body weight) in the neck.

For treatment of pigs over 40 kg body weight, divide the dose so that no more than 4 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 a correct dosage body weight 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.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

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.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

Not applicable

3.12 Withdrawal period

Meat and offal: 13 days.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QJ01FA94.

4.2 Pharmacodynamics

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 *Actinobacillus pleuropneumoniae*, *Bordetella bronchiseptica*, *Haemophilus parasuis*, *Pasteurella multocida* and *Mycoplasma hyopneumoniae*, the bacterial pathogens most commonly associated with swine respiratory disease. Increased minimum inhibitory concentration (MIC) values have been found in some isolates of *Actinobacillus pleuropneumoniae*.

The Clinical and Laboratory Standards Institute CLSI has set the clinical breakpoints for tulathromycin against *P. multocida* and *B. bronchiseptica* of swine respiratory origin, as ≤ 16 mcg/ml susceptible and ≥ 64 mcg/ml resistant. For *A. pleuropneumoniae* of swine respiratory origin the susceptible breakpoint is set at ≤ 64 mcg/ml. CLSI has also published clinical breakpoints for tulathromycin based on a disk diffusion method (CLSI document VET08, 4th ed, 2018). No clinical breakpoints have been set 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 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.

4.3 Pharmacokinetics

In pigs, the pharmacokinetic profile of tulathromycin when administered as a single intramuscular dose of 2.5 mg/kg body weight, 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 mcg/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%.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

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

5.2 Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 3 years.

Shelf-life after first opening the immediate packaging: 28 days.

5.3. Special precautions for storage

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

5.4 Nature and composition of immediate packaging

Translucent multi layer (plastic) vial closed with a bromobutyl rubber stopper coated with fluoropolymer and aluminium and plastic flip capsule.

Pack sizes:

Cardboard box containing one plastic vial of 50 ml.

Cardboard box containing one plastic vial of 100 ml.

Cardboard box containing one plastic vial of 250 ml.

Not all pack sizes may be marketed.

5.5 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 or household waste.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

Ceva Santé Animale

7. MARKETING AUTHORISATION NUMBER(S)

EU/2/20/251/006 (50 ml)

EU/2/20/251/007 (100 ml)

EU/2/20/251/008 (250 ml)

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: 24/04/2020

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (<https://medicines.health.europa.eu/veterinary>).