

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Tuloxxin 25 mg/ml solution for injection for pigs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains

Active substance:

Tulathromycin 25 mg

Excipients:

Monothioglycerol 5 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless to slightly yellow or slightly brown solution.

4. CLINICAL PARTICULARS

4.1 Target species

Pigs.

4.2 Indications for use, specifying the target species

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

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.

4.5 Special precautions for use

Special precautions for use in animals

Use of the 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.

Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to tulathromycin and may decrease the effectiveness of treatment with other macrolides, lincosamides and group B streptogramins, 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 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. In case of accidental spillage onto skin, wash the skin immediately with soap and water.

This product may cause hypersensitivity (allergy) reactions. People with known hypersensitivity to tulathromycin should avoid contact with the product.

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.

4.6 Adverse reactions (frequency and seriousness)

Pathomorphological injection site reactions (including reversible changes of congestion, oedema, fibrosis and haemorrhage) are present for approximately 30 days after injection.

4.7 Use during pregnancy, lactation or lay

Laboratory studies in rats and rabbits have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects. The safety of the veterinary medicinal product has not been established during pregnancy and lactation in pigs. 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 Amounts to be administered and administration route

A single intramuscular injection of 2.5 mg tulathromycin/kg bodyweight (equivalent to 1 ml/10 kg bodyweight) in the neck.

For treatment of pigs over 40 kg bodyweight, 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 correct dosage bodyweight should be determined as accurately as possible to avoid underdosing. The cap may be safely punctured up to 20 times. For multiple vial entry, an aspirating needle or multi-dose syringe is recommended to avoid excessive broaching of the stopper.

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

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.

4.11 Withdrawal period(s)

Meat and offal: 13 days.

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 *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Mycoplasma hyopneumoniae*, *Haemophilus parasuis* and *Bordetella bronchiseptica*, 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 $\mu\text{g/ml}$ susceptible and ≥ 64 $\mu\text{g/ml}$ resistant. For *A. pleuropneumoniae* of swine respiratory origin the susceptible breakpoint is set at ≤ 64 $\mu\text{g/ml}$. 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 (MLSB resistance); by enzymatic inactivation; or by macrolide efflux. MLSB 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 immunomodulating 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.

5.2 Pharmacokinetic particulars

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 $\mu\text{g/ml}$; 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

Propylene glycol
Monothioglycerol
Citric acid
Hydrochloric acid
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: 2 years.
Shelf life after first opening the immediate packaging: 28 days.

6.4 Special precautions for storage

No special temperature storage conditions are required.
Store in the original container.

6.5 Nature and composition of immediate packaging

Cardboard box containing one clear type I glass vial of 50 ml, 100 ml or 250 ml, with a type I chlorobutyl/butyl film laminated rubber stopper and aluminium cap with plastic tear tab (flip-off).
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

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

7. MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

8. MARKETING AUTHORISATION NUMBER

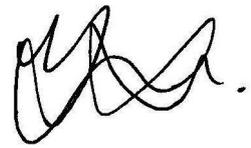
Vm 01656/4189

9. DATE OF FIRST AUTHORISATION

30 September 2020

10. DATE OF REVISION OF THE TEXT

July 2023

A handwritten signature in black ink, consisting of several loops and a trailing flourish.

Approved: 04 July 2023