ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Box

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Tuloxxin 25 mg/ml solution for injection for pigs
Tulathromycin

2. STATEMENT OF ACTIVE SUBSTANCES

1 ml contains 25 mg tulathromycin.

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

50 ml
100 ml
250 ml

5. TARGET SPECIES

Pigs

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Route of administration: IM

Dose:
1 ml of product/10 kg body weight

8. WITHDRAWAL PERIOD(S)

Withdrawal period:
Meat and offal: 13 days.

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP
Shelf life after first opening the container: 28 days
Once opened use by...

11. SPECIAL STORAGE CONDITIONS

Store in the original package.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Disposal: read package leaflet.

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only. To be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

16. MARKETING AUTHORISATION NUMBER(S)

Vm 01656/4189

17. MANUFACTURER'S BATCH NUMBER

Lot

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

Label

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Tuloxxin 25 mg/ml solution for injection for pigs
Tulathromycin

2. STATEMENT OF ACTIVE SUBSTANCES

1 ml contains 25 mg tulathromycin.

3. PHARMACEUTICAL FORM

Solution for injection

4. PACKAGE SIZE

100 ml
250 ml

5. TARGET SPECIES

Pigs

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Route of administration: IM

8. WITHDRAWAL PERIOD(S)

Withdrawal period:
Meat and offal): 13 days.

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP
Shelf life after first opening the container: 28 days
Once opened use by...

11. SPECIAL STORAGE CONDITIONS

Store in the original package.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only. To be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

16. MARKETING AUTHORISATION NUMBER(S)

Vm 01656/4189

17. MANUFACTURER'S BATCH NUMBER

Lot

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Tuloxxin 25 mg/ml solution for injection for pigs
Tulathromycin

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

25 mg/ml

3. CONTENTS BY WEIGHT, BY VOLUME OR BY NUMBER OF DOSES

50 ml

4. ROUTE(S) OF ADMINISTRATION

IM

5. WITHDRAWAL PERIOD(S)

Withdrawal period (meat and offal): 13 days.

6. BATCH NUMBER

Lot

7. EXPIRY DATE

EXP
Shelf life after first opening the container: 28 days
Once opened use by...

8. THE WORDS “FOR ANIMAL TREATMENT ONLY”

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET:
Tuloxxin 25 mg/ml solution for injection for pigs

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder:
KRKA d.d, Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

Manufacturer responsible for batch release:
KRKA d.d, Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia
TAD Pharma GmbH, Heinz-Lohmann-Straße 5, 27472 Cuxhaven, Germany

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Tuloxxin 25 mg/ml solution for injection for pigs
Tulathromycin

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

1 ml contains

Active substance:
Tulathromycin 25 mg

Excipients:
Monothioglycerol 5 mg

Clear, colourless to slightly yellow or slightly brown solution.

4. INDICATION(S)

Treatment and metaphylaxis of swine respiratory disease 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.

5. CONTRAINDICATIONS

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

6. ADVERSE REACTIONS

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

If you notice any side effects, even those not already listed in this package leaflet or you think that the medicine has not worked, please inform your veterinary surgeon.

Alternatively you can report via your national reporting system {national system details}.

7. TARGET SPECIES

Pigs.

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

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.

9. ADVICE ON CORRECT ADMINISTRATION

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.

10. WITHDRAWAL PERIOD(S)

Meat and offal: 13 days.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.

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

Shelf life after first opening the container: 28 days.
Do not use this veterinary medicinal product after the expiry date which is stated on the package after EXP. The expiry date refers to the last day of that month.

12. SPECIAL WARNING(S)

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.

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 leaflet 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.

Pregnancy and lactation:
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. Use only according to the benefit/risk assessment by the responsible veterinarian.

Interaction with other medicinal products and other forms of interaction:
None known.

Overdose (symptoms, emergency procedures, 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.

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

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Medicines should not be disposed of via wastewater.
Ask your veterinary surgeon or pharmacist how to dispose of medicines no longer required. These measures should help to protect the environment.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

September 2021

15. OTHER INFORMATION

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 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 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.

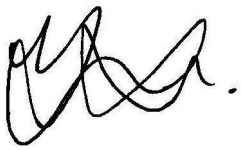
Resistance to macrolides can develop by mutations in genes encoding ribosomal RNA (rRNA) or some ribosomal proteins; by enzymatic modification (methylation) of the 23S rRNA target site, generally giving rise to cross-resistance with lincosamides and group B streptogramins (MLSB resistance); by enzymatic 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 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.

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 (t1/2) 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%.

Pack sizes:
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.

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.



Approved: 04 July 2023