ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Cardboard box (50 ml/ 100 ml/ 250 ml)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCES

Tulathromycin 100 mg/ml

3. PHARMACEUTICAL FORM

Solution for Injection

4. PACKAGE SIZE

50 ml
100 ml
250 ml

5. TARGET SPECIES

Cattle, pigs and sheep

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Cattle: For subcutaneous use.
Pigs and sheep: For intramuscular use.

Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

Withdrawal periods:
Meat and offal:
Cattle: 22 days.
Pigs: 13 days.
Sheep: 16 days.

Not authorised for use in lactating 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.

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.

11. SPECIAL STORAGE CONDITIONS

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

Alivira Animal Health UK Ltd.
Hygeia Building, Rear Ground Floor
66-68 College Road
Harrow
Middlesex
HA1 1BE
United Kingdom

16. MARKETING AUTHORISATION NUMBER(S)

Vm 54375/4000

17. MANUFACTURER'S BATCH NUMBER

Lot

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

Vials (100 ml/ 250 ml)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCES

Tulathromycin 100 mg/ml

3. PHARMACEUTICAL FORM

Solution for Injection

4. PACKAGE SIZE

100 ml
250 ml

5. TARGET SPECIES

Cattle, pigs and sheep

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Cattle: SC.
Pigs and sheep: IM.

Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

Withdrawal periods:
Meat and offal:
Cattle: 22 days.
Pigs: 13 days.

Sheep: 16 days.

Not authorised for use in lactating 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.

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 broached, use by

11. SPECIAL STORAGE CONDITIONS

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

Alivira Animal Health UK Ltd.
Hygeia Building, Rear Ground Floor
66-68 College Road
Harrow
Middlesex
HA1 1BE
United Kingdom

16. MARKETING AUTHORISATION NUMBER(S)

Vm 54375/4000

17. MANUFACTURER'S BATCH NUMBER

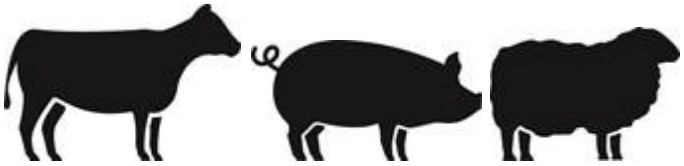
Lot

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial (50 ml)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

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



2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

Tulathromycin 100 mg/ml

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

50 ml

4. ROUTE(S) OF ADMINISTRATION

Cattle: SC.
Pigs and sheep: IM.

5. WITHDRAWAL PERIOD(S)

Withdrawal periods:
Meat and offal:
Cattle: 22 days.
Pigs: 13 days.
Sheep: 16 days.

Not authorised for use in lactating animals producing milk for human consumption.

6. BATCH NUMBER

Lot

7. EXPIRY DATE

EXP

Once broached use by

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET:
Tulaject 100 mg/ml solution for injection for cattle, pigs and sheep

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

Marketing authorisation holder:
Alivira Animal Health UK Ltd.
Hygeia Building, Rear Ground Floor
66-68 College Road
Harrow
Middlesex
HA1 1BE
United Kingdom

Manufacturer responsible for batch release:
Bremer Pharma GmbH
Werkstrasse 42
34414 Warburg GERMANY

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

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

Tulathromycin	100 mg/ml
Monothioglycerol	5 mg/ml

Clear colourless to pale yellow coloured solution for injection.

4. INDICATION(S)

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 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 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.

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

5. CONTRAINDICATIONS

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

6. ADVERSE REACTIONS

Subcutaneous administration of the veterinary medicinal product 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 and sheep 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 pigs.

In sheep, transient signs of discomfort (head shaking, rubbing injection site, backing away) are very common after intramuscular injection. These signs resolve within a few minutes.

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).

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.

7. TARGET SPECIES

Cattle, pigs and sheep

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

Cattle
2.5 mg tulathromycin/kg bodyweight (equivalent to 1 ml/40 kg bodyweight).

A single subcutaneous injection. 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
2.5 mg tulathromycin/kg bodyweight (equivalent to 1 ml/40 kg bodyweight).

A single intramuscular injectionin 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
2.5 mg tulathromycin/kg body weight (equivalent to 1 ml/40 kg body weight)

A single intramuscular injection in the neck.

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. For multiple vial entry, an aspirating needle or multi-dose syringe is recommended to avoid excessive broaching of the stopper.

10. 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.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.

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

Do not use this veterinary medicinal product after the expiry date which is stated on the label after EXP.

Shelf life after first opening the container: 28 days.

When the container is broached for the first time, using the in-use shelf-life which is specified on this package leaflet, the date on which any product remaining in the container should be discarded should be worked out. This discard date should be written in the space provided on the vial.

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.

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 showedlimited efficacy in sheep with severe clinical signs or chronic foot rot, and should therefore only be given at an early stage of foot rot.

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 sensitization 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 macrolides, such as 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 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.

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.

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

November 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 proteinbiosynthesis 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*, and *Actinobacillus pleuropneumoniae*, *Pasteurella multocida, Mycoplasma hyopneumoniae,*

Haemophilus parasuis and *Bordetella bronchiseptica*, 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 (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 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.

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 (t1/2) 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 (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%.

In sheep, the pharmacokinetic profile of tulathromycin, when administered as a single intramuscular dose of 2.5 mg/kg bodyweight, achieved a maximum plasma concentration (Cmax) of 1.19 µg/ml in approximately 15 minutes (Tmax) post-dosing and had an elimination half-life (t1/2) of 69.7 hours.Plasma protein binding was approximately 60-75%. Following intravenous dosing the volume of distribution at steady-state (Vss) was 31.7 l/kg. The bioavailability of tulathromycin after intramuscular administration in sheep was 100%.

Type I clear glass bottles of 50 ml, 100 ml or 250 ml with fluoropolymer coated chlorobutyl rubber stopper and aluminium overseal.
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 19 November 2021