

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Tulaject 25 mg/ml solution for injection for pigs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 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 colorless to pale yellow colored solution free from visible particles.

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 veterinary medicinal 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 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 target bacteria.

Official, national and regional antimicrobial policies should be taken into account when the veterinary medicinal product is used.

Use of the veterinary medicinal product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to the 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.

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. 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. When treating groups of animals in one run, use a draw-off needle that has been placed in the vial stopper to avoid excess broaching of the stopper. The draw-off needle should be removed after treatment.

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 (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.

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

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

Clear Type I glass vial with fluoropolymer coated chlorobutyl stopper and an aluminum overseal.

Pack sizes:

Cardboard box containing 1 vial of 50 ml
Cardboard box containing 1 vial of 100 ml
Cardboard box containing 1 vial of 250 ml

Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste material derived from 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 AUTHORIZATION HOLDER

Alivira Animal Health Limited
16 Glenoks Close, Glenconner, Clonmel,
Clonmel,
Co Tipperary
Ireland. E91-T8Y6.

8. MARKETING AUTHORIZATION NUMBER (S)

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF AUTHORIZATION

10. DATE OF REVISION OF THE TEXT

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not Applicable

ANNEX II
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 25 mg/ml solution for injection for pigs
tulathromycin



2. STATEMENT OF ACTIVE SUBSTANCES

Tulathromycin 25 mg/ml

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

Intramuscular use.

Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

Withdrawal periods:
Meat and offal: 13 days

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP { month/year }
Once broached use within 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 Limited
16 Glenoaks Close, Glenconner,
Clonmel, Co Tipperary
Ireland. E91T8Y6

16. MARKETING AUTHORISATION NUMBER(S)

17. MANUFACTURER’S BATCH NUMBER

Lot {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

Vials (100 ml/ 250 ml)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Tulaject 25 mg/ml solution for injection for pigs
tulathromycin



2. STATEMENT OF ACTIVE SUBSTANCES

Tulathromycin 25 mg/ml

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

Intramuscular use.

Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

Withdrawal periods:
Meat and offal: 13 days.

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}
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 Limited
16 Glenoaks Close, Glenconner,
Clonmel, Co Tipperary
Ireland. E91T8Y6

16. MARKETING AUTHORISATION NUMBER(S)

17. MANUFACTURER’S BATCH NUMBER

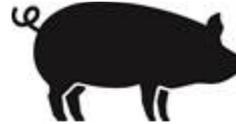
Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial (50 ml)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Tulaject 25 mg/ml solution for injection for pigs
tulathromycin



2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

Tulathromycin 25 mg/ml

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

50 ml

4. ROUTE(S) OF ADMINISTRATION

i.m.

5. WITHDRAWAL PERIOD(S)

Withdrawal periods:
Meat and offal: 13 days.

6. BATCH NUMBER

Lot {number}

7. EXPIRY DATE

EXP {month/year}
Shelf life after first opening the container: 28 days.
Once broached use by

8. THE WORDS “FOR ANIMAL TREATMENT ONLY”

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET:
Tulaject 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:
Alivira Animal Health Limited
16 Glenoaks Close, Glenconner,
Clonmel, Co Tipperary
Ireland. E91T8Y6

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

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Tulaject 25 mg/ml solution for injection for pigs
Tulathromycin

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

Each ml contains:

Active substance:
Tulathromycin 25 mg

Excipients:
Monothioglycerol 5 mg

Clear colourless to pale yellow colored solution for injection free from visible particles.

4. INDICATION(S)

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 veterinary medicinal 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.

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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

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.

The cap may be safely punctured up to 20 times

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)

Meat and offal: 13 days.

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. The expiry date refers to the last day of that month.”

Shelf life after first opening the container: 28 days.

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 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 target bacteria.

Official, national and regional antimicrobial policies should be taken into account when the veterinary medicinal product is used.

Use of the veterinary medicinal product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to the 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.

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 or household waste.
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

15. OTHER INFORMATION

Pack sizes:

Cardboard box containing 1 vial of 50 ml

Cardboard box containing 1 vial of 100 ml

Cardboard box containing 1 vial of 250 ml

Not all pack sizes may be marketed.