ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:
Tulathromycin 100 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

Cattle, pigs and sheep

4.2. Indications for use, specifying the target species

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 (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.

Sheep
Treatment of the early stages of infectious pododermatitis (foot rot) associated with

virulent *Dichelobacter nodosus* requiring systemic treatment.

4.3. Contraindications

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

Do not use simultaneously with other macrolides or lincosamides (see section 4.8).

4.4. Special warnings < for each target species>

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

4.5. Special precautions for use

This product does not contain any antimicrobial preservative.

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 the target bacteria**.

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

If a hypersensitivity reaction occurs appropriate treatment should be administered without delay.

Use of the veterinary medicinal product deviating from the instruction given in SPC may increase the prevalence of bacteria resistant to the tulathromycin and may decrease the effectiveness of treatment with other macrolides, due to potential for cross resistance

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.

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4.6. Adverse reactions (frequency and seriousness)

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 pig.
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).

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

Cross resistance occurs with other macrolides. Do not administer simultaneously with antimicrobials with a similar mode of action such as other macrolides or lincosamides.

4.9 Amounts to be administered and administration route

Cattle
Subcutaneous use
A single subcutaneous injection of 2.5 mg tulathromycin/kg bodyweight (equivalent to 1 ml/40 kg bodyweight). 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
Intramuscular use
A single intramuscular injection of 2.5 mg tulathromycin/kg bodyweight (equivalent

to 1 ml/40 kg bodyweight) in 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.

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.

Sheep
Intramuscular use.
A single intramuscular injection of 2.5 mg tulathromycin/kg body weight (equivalent to
1 ml/40 kg body weight) in the neck.

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.
The cap may be safely punctured up to 20 times. .

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

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 five to six 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

4.11. 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.

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 *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).

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 or plasmids.

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.

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

5.2 Pharmacokinetic particulars

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 (C_{max}) in plasma was approximately 0.5 µg/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 90 hours in plasma. Plasma protein binding was low, approximately 40%. The volume of distribution at steady-state (V_{ss}) 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 (C_{max}) in plasma was approximately 0.6 µg/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%.

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 (C_{max}) of 1.19 µg/ml in approximately 15 minutes (T_{max}) 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 (V_{ss}) was 31.7 l/kg. The bioavailability of tulathromycin after intramuscular administration in sheep was 100%.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Monothioglyce
rol Propylene
glycol
Citric acid
Hydrochloric acid, dilute (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 rubber 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 Glenoaks Close,

Glenconner, Clonmel

Co Tipperary

Ireland. E91T8Y6.

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