MACROSYN

100 mg/ml Solution for Injection for Cattle, Pigs and Sheep

Tulathromycin

DATA SHEET

INDICATIONS FOR USE

Cattle
Treatment and metaphylaxis of bovine respiratory disease (BRD). The presence of the disease in the herd should be established before metaphylactic treatment.

Treatment of infectious bovine keratoconjunctivitis (IBK).

Pigs
Treatment and metaphylaxis of swine respiratory disease (SRD). The presence of the disease in the herd should be established before metaphylactic treatment.

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

BENEFITS

- **Multi-species use**
- **Short meat withdrawal time in cattle, sheep and pigs of 22, 16 and 13 days respectively**
- **Small dose size**

LIST No	UNIT PACKAGE	CASE SIZE
1MAC025	100 ml	12

Please see full details overleaf.

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ACTIVE SUBSTANCE
Tulathromycin 100 mg per ml

PHARMACEUTICAL FORM
Clear colourless to slightly yellow solution for injection.

TARGET SPECIES
Cattle, pigs and sheep

INDICATIONS FOR USE
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 herd should be established before metaphylactic treatment.
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 herd should be established before metaphylactic treatment. The 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.

DOSAGE
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 50 ml and 100 ml vials can be punctured up to 30 times and the 250 ml and 500 ml vials up to 50 times. The 500 ml vials must not be used for pigs and sheep.

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.

CONTRAINDICATIONS
Do not use in cases of hypersensitivity to macrolide antibiotics or to any of the excipients. Do not use simultaneously with other macrolides or lincosamides. Do not 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.

Special Warnings - 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.

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, due to the potential for cross resistance.

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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.

ADVERSE REACTIONS

Subcutaneous administration of the product to cattle very commonly causes 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.

USE DURING 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.

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.

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.

OVERDOSE

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.

PHARMACODYNAMIC PROPERTIES

Tulathromycin is a semi-synthetic macrolide antimicrobial agent, which originates from a fermentation product. 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 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, Mycoplasma bovis, Actinobacillus pleuropneumoniae, Pasteurella multocida, Mycoplasma hyopneumonia, Haemophilus parasuis* and *Bordetella bronchiseptica* the bacterial pathogens most commonly associated with bovine and swine respiratory disease. 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 (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 or plasmids.

In addition to its antimicrobial properties, tulathromycin demonstrates immune-modulating and anti-inflammatory actions in experimental studies.

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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.

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 (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%.

EXCIPIENTS

Monothioglycerol
Propylene glycol
Citric acid, anhydrous
Hydrochloric acid
Sodium hydroxide
Water for injection

MAJOR INCOMPATIBILITIES

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

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.

SPECIAL PRECAUTIONS FOR STORAGE

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

DISPOSAL OF UNUSED VETERINARY MEDICINAL PRODUCT OR WASTE MATERIALS

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

LEGAL CATEGORY

POM-V

MARKETING AUTHORISATION NUMBER

Vm 50146/4042

DISTRIBUTOR

Bimeda UK
Unit 2, Bryn Cefni Industrial Park
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