

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Draxxin Injectable Solution Veterinary

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Tulathromycin 100 mg/ml

Excipient:

Monothioglycerol 5 mg/ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear colourless to slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Target species

Cattle, pigs

4.2 Indications for use, specifying the target species

Cattle

Treatment and prevention of bovine respiratory disease associated with mannheimia (pasteurella) haemolytica pasteurella multocida haemophilus somnus and mycoplasma bovis sensitive to tulathromycin. The presence of the disease in the herd should be established before preventative treatment.

Pigs

Treatment of swine respiratory disease associated with actinobacillus pleuropneumoniae pasteurella multocida and mycoplasma hyopneumoniae sensitive to tulathromycin.

4.3 Contraindications

Do not use in case of hypersensitivity of the target animals to macrolide antibiotics.

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

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.

4.4 Special warnings for each target species

None

4.5 Special precautions for use

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.

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 resulting in e.g. reddening of the skin (erythema) and/or dermatitis. 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.

If there is suspicion of a hypersensitivity reaction following accidental exposure (recognised by e.g. itching, difficulty in breathing, hives, swelling on the face, nausea, vomitus) appropriate treatment should be administered. Seek medical advice immediately and show the package leaflet or the label to the physician.

4.6 Adverse reactions (frequency and seriousness)

Subcutaneous administration of Draxxin 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 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.

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form sideeffects.health.gov.il

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.

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.

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 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 vocalization and restlessness. Lameness was also observed when the hind leg was used as the injection site.

4.11 Withdrawal period(s)

Cattle (meat and offal): 22 days.

Pigs (meat and offal): 13 days.

Not authorized 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.

ATCvet 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 hyopneumonia*, *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.

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%.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Monothioglycerol

Propylene glycol

Citric acid

Hydrochloric acid

Sodium hydroxide

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

Do not use the veterinary medicinal product after the expiry date (exp. Date) mentioned on the package. The expiry date refers to the last day of that month.

Shelf-life after first opening the immediate packaging: 28 days

6.4 Special precautions for storage

Keep out of the reach of children.

Store below 30°C

6.5 Nature and composition of immediate packaging

Primary packaging: Type I glass vial.

Pack size: Cardboard box containing one vial.

Vial sizes: 20 ml, 50 ml, 100 ml, 250 ml and 500 ml.

The 500 ml vials must not be used for pigs.

Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of as a toxic waste. Do not dispose of in the sewage system.

7. MARKETING AUTHORISATION HOLDER

Zoetis Israel Holding B.V., 5 Atir Yeda Street, Kfar Saba, Israel

8. MARKETING AUTHORISATION NUMBER(S)

083 76 92398 00

083 76 92398 01

083-76-92398-02

9. MANUFACTURER

Fareva Amboise, France

Or

Inovat Industria Farmaceutica LTDA, Brazil

Or

Zoetis Manufacturing & Research Spain, S.L, Spain

10. DATE OF REVISION OF THE TEXT

Revised in 05.10.2021 according to MOH guidelines.