Summary of Product Characteristics

1 NAME OF THE VETERINARY MEDICINAL PRODUCT

Draxxin Plus 100 mg/ml + 120 mg/ml solution for injection for cattle

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substances:
Tulathromycin 100 mg
Ketoprofen 120 mg

Excipients:
Monothioglycerol 5 mg

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection
Clear colourless to yellow/green-yellow solution. Free from visible particles

4 CLINICAL PARTICULARS

4.1 Target Species

Cattle

4.2 Indications for use, specifying the target species

Treatment of bovine respiratory disease (BRD) associated with pyrexia due to *Mannheimia haemolytica*, *Pasteurella multocida, Histophilus somni* and *Mycoplasma bovis* susceptible to tulathromycin.

4.3 Contraindications

Do not use in cases of hypersensitivity to the active substances or to any of the excipients.
Do not use simultaneously with other macrolides or lincosamides (see section 4.4).
Do not administer to animals suffering from gastrointestinal lesions, haemorrhagic diathesis, blood dyscrasia or hepatic, renal or cardiac conditions.

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

This product does not contain any antimicrobial preservative.

Special precautions for use in animals

Use of the product should be based on identification and susceptibility testing of the target pathogen(s). If this is not possible, therapy should be based on epidemiological information and knowledge of susceptibility of the target bacteria at farm level, or at local/regional level.
Use of the product should be in accordance with official, national and regional antimicrobial policies.

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 (MLSB resistance).

Since many NSAIDs possess the potential to induce gastrointestinal ulceration, especially in aged cattle and young calves, concomitant use of the product with other anti-inflammatory drugs (NSAIDs) or steroidal anti-inflammatory drugs (e.g., corticosteroids) should be avoided within the first 24 hours of treatment. Afterwards concurrent treatment with NSAIDs and steroidal anti-inflammatory drugs should be closely monitored. The use of the product (that contains ketoprofen) in aged animals or animals less than 6 weeks should be based on a benefit/risk assessment of the responsible veterinarian.

Avoid use in dehydrated, hypovolaemic or hypotensive animals which require parenteral rehydration, as there may be a potential risk of renal toxicity.

Intra-arterial and intra-venous injection should be avoided.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

- This veterinary medicinal product may cause hypersensitivity (allergy). People with known hypersensitivity to tulathromycin, ketoprofen, or to non-steroidal anti-inflammatory drugs (NSAIDs) should avoid contact with the veterinary medicinal product. In case of accidental spillage onto skin, wash the skin immediately with soap and water.
- This veterinary medicinal product may cause adverse effects after dermal exposure and self-injection. Take care to avoid skin contact and accidental self-injection. In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.
- NSAIDs, such as ketoprofen, may affect fertility and be harmful for the unborn child. Pregnant women, women intending to conceive and men planning to have children should use extreme caution while handling this veterinary medicinal product.
- This veterinary medicinal product is irritating to eyes. Avoid contact with the eyes. In case of accidental eye exposure, flush the eyes immediately with clean water. If irritation persists, seek medical advice and show the package leaflet to the physician.
- Wash hands after use.

4.6 Adverse reactions (frequency and seriousness)

Subcutaneous administration very commonly causes transient pain reactions and local swellings at the injection site that can persist for up to 32 days. Pathomorphological injection site reactions (including reversible changes of congestion, oedema, fibrosis and haemorrhage) are present for approximately 32 days after injection.
In common with all NSAIDs, due to their action of inhibition of prostaglandin synthesis, there can be the possibility in certain individuals of gastric or renal intolerance.

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 with tulathromycin in rats and rabbits have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects. Studies with ketoprofen in laboratory species (rats, mice and rabbits) have not produced any evidence of teratogenic effects, but effects on fertility, maternal toxicity and embryotoxicity has been observed. There are known adverse class-effects of NSAIDS and other prostaglandin inhibitors on pregnancy and/or embryofoetal development. The safety of tulathromycin and ketoprofen combination in the target species 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 interactions

Do not use concurrently with other diuretics, nephrotoxic veterinary medicinal products or anticoagulants.

4.9 Amounts to be administered and administration route

Subcutaneous use.
A single subcutaneous injection of 2.5 mg tulathromycin/kg bodyweight and 3 mg ketoprofen/kg bodyweight (equivalent to 1 ml/40 kg bodyweight). For treatment of cattle over 400 kg bodyweight, divide the dose so that no more than 10 ml are injected at one site.
To ensure correct dosage bodyweight should be determined as accurately as possible to avoid underdosing.

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.
If there is persistent elevated body temperature 24 hours after treatment initiation, the responsible veterinarian must evaluate the necessity of further anti-pyretic treatment.

The stopper 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 or an automatic syringe to avoid excessive broaching of the stopper. The draw-off needle should be removed after treatment.

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

At dosages of 3 and 5 times the recommended dose transient signs of injection site pain and/or swelling which in some instances lasted until day 32. Additionally, transient signs attributed to injection site discomfort (pain) were observed and included restlessness, head-shaking, pawing the ground, and brief decrease in feed intake. Microscopic mucosal erosions of the pylorus of the abomasum were observed at 3 and 5 times the recommended dose. Repeated administration can result in gastric toxicity. Mild myocardial degeneration has been observed in cattle receiving 5 to 6 times the recommended dose.

4.11 Withdrawal period(s)

Meat and offal: 50 days.
Not authorised for use in cattle 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 or IMMUNOLOGICAL PROPERTIES

Pharmacotherapeutic group: Macrolides, combinations with other substances.
ATCvet Code: QJ01FA99.

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* the bacterial pathogens most commonly associated with bovine respiratory disease. Increased minimum inhibitory concentration (MIC) values have been found in some isolates of *Histophilus somni*.

The Clinical and Laboratory Standards Institute CLSI has set the MIC clinical breakpoints for tulathromycin against *M. haemolytica*, *P. multocida*, and *H. somni* of bovine respiratory origin, as ≤ 16 µg/ml susceptible and ≥ 64 µg/ml resistant. CLSI has also published clinical breakpoints for tulathromycin based on a disk diffusion method (CLSI document VET08, 4th ed, 2018). 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 among the BRD pathogens 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 bovine 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.

Ketoprofen is a substance belonging to the group non-steroidal anti-inflammatory drugs (NSAIDs). Ketoprofen has anti-inflammatory, analgesic and antipyretic properties. Not all aspects of its mechanism of action are known. Effects are obtained partially by the inhibition of prostaglandin and leukotriene synthesis by ketoprofen, acting on cyclooxygenase and lipoxygenase respectively. The formation of bradykinin is also inhibited. Ketoprofen inhibits thrombocyte aggregation.

5.2 Pharmacokinetic particulars

When subcutaneously co-administered in the combination formulation, at 2.5 mg tulathromycin/kg body weight, the maximum concentration (C_{max}) in plasma was approximately 0.4 µg/ml, this was achieved approximately 3 hours post-dosing (T_{max}). Peak concentrations were followed by a slow decline in systemic exposure with an apparent elimination half-life ($t_{1/2}$) of 85 hours in plasma.

Furthermore, after subcutaneous injection of the tulathromycin-ketoprofen combination, the AUC_{0-t} of tulathromycin has been shown to be bioequivalent to the AUC_{0-t} after subcutaneous injection of tulathromycin 100 mg/ml for cattle. The combination had a slightly lower tulathromycin C_{max} and the rate of absorption was decreased in comparison with the administration of the compounds separately.

Regarding ketoprofen, following administration of the combination product, at 3 mg ketoprofen/kg body weight, the pharmacokinetics of ketoprofen are driven by flip-flop kinetics. The mean C_{max} in plasma was 2 µg/ml, which was achieved at 4 hours on average. The terminal half-life of ketoprofen is dominated by the slow absorption and was estimated at 6.8 hours.

Furthermore, after subcutaneous injection of the tulathromycin-ketoprofen combination, there was a delay in the absorption, with a lower ketoprofen peak concentration, and a longer elimination half-live, as compared with the compound alone.

Ketoprofen in the combination product is a racemic mixture of two enantiomers, S(+) and R(-). In-vitro models suggest that the S(+) enantiomer is 250 times more potent than the R(-) enantiomer. Inversion of R-ketoprofen to S-ketoprofen has been reported in cattle to be 31% following intravenous dosing of R-ketoprofen.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Monothioglycerol
Propylene glycol
Citric acid (E-330)
Hydrochloric acid, concentrated *(for pH adjustment)*
Sodium hydroxide *(for pH adjustment)*
Pyrrolidone
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: 56 days.

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and composition of immediate packaging

Type I amber glass vial with a fluoropolymer coated chlorobutyl rubber stopper and an aluminium 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 products or waste materials derived from the use of such products

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

7 MARKETING AUTHORISATION HOLDER

Zoetis Belgium S.A.
2nd Floor, Building 10
Cherrywood Business Park, Loughlinstown
Co Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER(S)

VPA10387/099/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25th August 2020

10 DATE OF REVISION OF THE TEXT