B. PACKAGE LEAFLET

PACKAGE LEAFLET:

1. Name of the veterinary medicinal product

Draxxin Plus 100 mg/ml + 120 mg/ml solution for injection for cattle
(AT, BE, BG, CY, CZ, DE, EE, EL, ES, HR, HU, IE, IT, LT, LU, LV, NL, PL, PT, RO, SI, SK, UK)

Draxxin KP 100 mg/ml + 120 mg/ml solution for injection for cattle
(FR)

2. Composition

Each ml contains:

Active substances:	
Tulathromycin	100 mg
Ketoprofen	120 mg
Excipients:	
Monothioglycerol	5 mg

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

3. Target species

Cattle.

4. Indications for use

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

5. 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.
Do not administer to animals suffering from gastrointestinal lesions, haemorrhagic diathesis, blood dyscrasia or hepatic, renal or cardiac conditions.

6. Special warnings

This product does not contain any antimicrobial preservative.

Special warnings:
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 safe use in the target species:

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 package leaflet 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.

Special precautions for the protection of the environment:
None.

Pregnancy and lactation:
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.

Interaction with other medicinal products and other forms of interaction:

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

Overdose:
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.

Special restrictions for use and special conditions for use:
To be completed in accordance with national requirements.

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

7. Adverse events

Cattle:

Very common (>1 animal / 10 animals treated):
injection site pain[1] injection site swelling[1,2] injection site reaction[2] injection site oedema[2] injection site fibrosis[2] injection site haemorrhage[2]
Very rare (<1 animal / 10,000 animals treated, including isolated reports):
digestive tract disorder renal disorder hypersensitivity reactions (e.g. anaphylaxis, dyspnoea, collapse)[3]

[1] May persist for up to 32 days after injection.
[2] Pathomorphological injection site reactions are present for approximately 32 days after injection.
[3] In case of such an allergic or anaphylactic reaction, appropriate symptomatic treatment should be administered immediately.

Reporting adverse events is important. It allows continuous safety monitoring of a product. 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 contact, in the first instance, your veterinarian. You can also report any adverse events to the marketing authorisation holder using the contact details at the end of this leaflet, or via your national reporting system *{national system details}*.

8. Dosage for each species, routes and method of administration

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.

9. Advice on correct administration

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.

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

10. Withdrawal periods

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.

11. Special storage precautions

Keep out of the sight and reach of children.

Do not freeze.

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 immediate packaging: 56 days.

12. Special precautions for disposal

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any applicable national collection systems.
Medicines should not be disposed of via wastewater or household waste.
These measures should help to protect the environment. Ask your veterinary surgeon or pharmacist how to dispose of medicines no longer required.

13. Classification of veterinary medicinal products

Veterinary medicinal product subject to prescription.

14. Marketing authorisation numbers and pack sizes

Marketing authorisation numbers:
To be completed in accordance with national requirements.

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.

15. Date on which the package leaflet was last revised

{DD/MM/YYYY}
To be completed in accordance with national requirements.
Detailed information on this veterinary medicinal product is available in the Union Product Database (*https://medicines.health.europa.eu/veterinary*).

16. Contact details

Marketing authorisation holder and contact details to report suspected adverse reactions:
To be completed nationally

Manufacturer responsible for batch release:
Zoetis Manufacturing & Research Spain, S.L.
Ctra. Camprodón s/n, Finca La Riba.
17813 Vall de Bianya (Gerona)
SPAIN

<Local representative and contact details to report suspected adverse reactions:>
To be completed nationally

17. Other information

Pharmacodynamics:
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.

Pharmacokinetics:

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-life, 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.