ZELERIS®

Product information

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1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Zeleris 400 mg/ml + 5 mg/ml solution for injection for cattle, pigs and sheep.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:

Florfenicol ..... 400 mg

Meloxicam ..... 5 mg

Excipients:

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear yellow solution.

4. CLINICAL PARTICULARS

4.1 | Target species

Cattle.

4.2 | Indications for use, specifying the target species

For therapeutic treatment of bovine respiratory disease (BRD) associated with pyrexia due to *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni* susceptible to florfenicol.

4.3 | Contraindications

Do not use in adult bulls intended for breeding.

Do not use in animals suffering from impaired hepatic, cardiac or renal function and haemorrhagic disorders, or when there is evidence of ulcerogenic gastrointestinal lesions.

Do not use in case of hypersensitivity to the active substances or to any of the excipients.

4.4 | Special warnings for each target species

None.

4.5 | Special precautions for use

i Special precautions for use in animals

Whenever possible, the veterinary medicinal product should only be used based on susceptibility testing. Official, national and regional antimicrobial policies should be taken into account when the veterinary medicinal product is used.

Avoid use in severely dehydrated, hypovolaemic or hypotensive animals, as there may be a potential risk of renal toxicity. In the absence of safety data it is not recommended to use the product in calves less than 4 weeks old.

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

The product is slightly irritant to the eye. Rinse any splashes from eyes immediately with plenty of water.

In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

People with known hypersensitivity to florfenicol, meloxicam or to any of the excipients should avoid contact with the veterinary medicinal product.

Dose dependent maternotoxic and foetotoxic effects have been observed after oral administration of meloxicam to pregnant rats. Therefore, the veterinary medicinal product should not be administered by pregnant women.

4.6 | Adverse reactions (frequency and seriousness)

Injection site reactions (mostly swelling, induration, heat and pain) were very commonly observed after subcutaneous administration of the product. These effects were transitory and usually resolved without any treatment within 5 to 15 days, but could persist up to 49 days.

During injection of this product animals may exhibit signs of moderate pain, manifested as movement of the head or neck.

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

The safety of the veterinary medicinal product has not been established in breeding, pregnant and lactating animals.
Use only according to the benefit-risk assessment by the responsible veterinarian.

Fertility
Do not use in adult bulls intended for breeding (see section 4.3).

4.8 | Interaction with other medicinal products and other forms of interaction

Do not administer concurrently with glucocorticoids, other non-steroidal anti-inflammatory drugs or with anticoagulant agents.

4.9 | Amounts to be administered and administration route

Subcutaneous use.

A single subcutaneous injection at a dosage of 40 mg florfenicol/kg bodyweight and 0.5 mg meloxicam/ kg bodyweight (i.e. 1 ml/10 kg bodyweight).

The single dose volume should not exceed 15 ml per injection site. The injection should only be given in the neck area.

To ensure a correct dosage, bodyweight should be determined as accurately as possible to avoid underdosing. For the 250 ml vials, the rubber stopper may safely be punctured up to 20 times. Otherwise, the use of a multiple-dose syringe is recommended.

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

In pre-ruminant calves, repeated administration of the recommended dose once per week for three weeks was well tolerated, as well as a single administration of 3 times (3x) the recommended dose. Repeated weekly administration of overdoses (3x and 5x the recommended dose) in calves was associated with decreased milk consumption, decreased weight gain, loose faeces or diarrhoea. Repeated weekly administration of a 3x dose was fatal in 1 out of 8 calves after the third administration. Repeated weekly administration of a 5x dose was fatal in 7 out of 8 calves after the third administration.

The extent of these adverse effects was dose-dependent. Macroscopic intestinal lesions were observed post-mortem (presence of fibrin, abomasal ulcers, haemorrhagic dots and thickening of the abomasal wall).

4.11 | Withdrawal period(s)

Meat and offal: 56 days.

Milk: Not authorised for use in lactating animals producing milk for human consumption. Do not use in pregnant cows, which are intended to produce milk for human consumption, within 2 months of expected parturition.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use, amphenicols, combinations.

ATCvet code: QJ01BA99.

5.1 | Pharmacodynamic properties

Florfenicol is a synthetic broad-spectrum antibiotic effective against most Gram-positive and Gram- negative bacteria isolated from domestic animals. Florfenicol acts by inhibiting protein synthesis at the ribosomal level and its action is bacteriostatic and time-dependent. Laboratory tests have shown that florfenicol is active against the most commonly isolated bacterial pathogens involved in bovine respiratory disease which include *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni.*

Florfenicol is considered to be a bacteriostatic agent, but in vitro studies demonstrate its bactericidal activity against *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni.*

For *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni* the following florfenicol breakpoints have been determined by CLSI (Clinical and Laboratory Standards institute) for bovine respiratory pathogens: susceptible ≤ 2 µg/ml, intermediate : 4 µg/ml, resistant : ≥ 8 µg/ml.

Resistance to florfenicol is mainly mediated by an efflux system due to a specific (Flo-R) or multidrug transporter (AcrAB-TolC). The genes corresponding to these mechanisms are coded on mobile genetic elements such as plasmids, transposon or genes cassettes. Resistance to florfenicol in the target pathogens has only been reported on rare occasions, and was associated with efflux pump and the presence of the floR gene.

Surveillance data of the susceptibility of target field isolates from cattle, collected between 2004 and 2012 across Europe, show consistent efficacy of florfenicol with no finding of resistant isolates. The in vitro Minimum Inhibitory Concentration (MIC) distribution values for these field isolates are presented in the table below.

Species	Range (µg/ml)	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)
Mannheimia haemolytica (n=217)	0.25–4	0.7	0.9
Pasteurella multocida (n=226)	0.125–8	0.3	0.5
Histophilus somni (n=128)	0.125–0.5	0.2	0.3

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class which acts by inhibition of prostaglandin synthesis, thereby exerting anti-inflammatory, anti-exudative, analgesic and antipyretic effects. It reduces leukocyte infiltration into the inflamed tissue. To a minor extent it also inhibits collagen-induced thrombocyte aggregation. Meloxicam also has anti-endotoxic properties, because it has been shown to inhibit production of thromboxane B2 induced by E. coli endotoxin after administration in calves, lactating cows and pigs.

The bioavailability of meloxicam in this combination product is lower compared to the use of meloxicam when administered on its own. The impact of this difference on anti-inflammatory effects has not been investigated in field trials. However, a clear antipyretic effect has been demonstrated in the first 48 hours after administration.

5.2 | Pharmacokinetic particulars

After subcutaneous administration of the product at recommended dose of 1 ml/10 kg bodyweight maximum mean plasma concentration (C_{max}) of 4.6 mg/l and 2.0 mg/l occurred 10 hours (h) and 7 h after dosing for florfenicol and meloxicam, respectively.

Efficacious plasma levels of florfenicol are maintained above the MIC_{90} of 1 µg/ml, 0.5µg/ml and 0.2 µg/ml for 72 h, 120 h and 160 h, respectively.

Florfenicol is largely distributed in the whole body and has a low plasma protein binding (approximately 20%). Meloxicam is extensively bound to plasma proteins (97%) and is distributed in all well-perfused organs.

Florfenicol is mainly excreted via the urine and to a small extent via the faeces with a half-life of about 60 h. Meloxicam excretion is equally divided between urine and faeces, with a half-life of about 23 h.

6. PHARMACEUTICAL PARTICULARS

6.1 | List of excipients

Dimethyl sulfoxide
Glycerol formal, stabilised

6.2 | 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: 3 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

Translucent multi-layered plastic vials (polypropylene/ethylene vinyl alcohol/polypropylene) with chlorobutyl rubber stoppers and aluminium and plastic flip capsules, containing 50 ml, 100 ml or 250 ml.

Pack size:
1 vial per cardboard box

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 in accordance with local requirements.