SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Zeleris 400 mg/ml + 5 mg/ml solution for injection for cattle

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:
Active substances:
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) due to *Histophilus somni, Mannheimia haemolytica, Pasteurella multocida* and *Mycoplasma bovis*associated with pyrexia.

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

There is no bacterial eradication of *Mycoplasma bovis.* Clinical efficacy against *M. bovis* has only been demonstrated in mixed infections.

4.5 Special precautions for use

i) 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 pathogens at farm level, or at local/regional level.
Use of the product should be in accordance with official, national and regional antimicrobial policies.
An antibiotic with a lower risk of antimicrobial resistance selection (lower AMEG category) should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach.
Not for use for prophylaxis or metaphylaxis.
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.

Special precautions for the protection of the environment:
Not applicable.

4.6 Adverse reactions (frequency and seriousness)

Cattle:

Very common (>1 animal / 10 animals treated):	Injection site swelling, Injection site induration, Injection site warmth, Injection site pain*
Undetermined frequency (cannot be estimated from the available data):	Immediate pain upon injection**

* Usually resolve without treatment within 5 to 15 days but could persist up to 49 days.
** Pain at injection site is of moderate severity and manifested as head or neck movement.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or the national competent authority via the national reporting system. See also the last section ‘Contact details’ of the package leaflet

4.7 Use during pregnancy, lactation or lay

Pregnancy and lactation
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 Amount(s) 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.
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).

Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

Not applicable.

4.11 Withdrawal period(s)

Meat and offal: 56 days.
Milk: Not authorised for use in 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

QJ01BA99.

5.1 Pharmacodynamic properties

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

For *Histophilus somni, Mannheimia haemolytica and Pasteurella multocida* the following florfenicol breakpoints have been determined by CLSI (Clinical and Laboratory Standards institute) in 2020 for bovine respiratory pathogens: susceptible ≤ 2 µg/ml, intermediate : 4 µg/ml, resistant : ≥ 8 µg/ml.

Surveillance data of the susceptibility of target field isolates from cattle, collected in 2019 and 2020 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)
Histophilus somni (n=29)	0.125–0.25	0.1	0.2
Mannheimia haemolytica (n=132)	0.25–16	0.7	1.1
Pasteurella multocida (n=144)	0.125–32	0.3	0.5

There are no established breakpoints for *Mycoplasma bovis* nor have culture techniques been standardized by CLSI.
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.
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 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: 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: Cardboard box with 1 vial of 50 ml, 100 ml or 250 ml.

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

Medicines should not be disposed of via wastewater. Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Ceva Animal Health Ltd
Explorer House
Mercury Park
Wycombe Lane
Wooburn Green
High Wycombe
Buckinghamshire
HP10 0HH
United Kingdom

8. MARKETING AUTHORISATION NUMBER

Vm 15052/5026

9. DATE OF FIRST AUTHORISATION

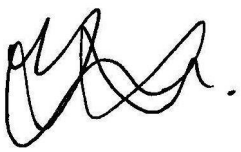
15 May 2017

10. DATE OF REVISION OF THE TEXT

August 2023

PROHIBITION OF SALE, SUPPLY AND/OR USE

Veterinary medicinal product subject to prescription.



Approved: 08 August 2023