ANNEX I

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:

Qualitative composition of excipients and other constituents
Dimethyl sulfoxide
Glycerol formal, stabilised

Clear yellow solution.

3. CLINICAL INFORMATION

3.1 Target species

Cattle.

3.2 Indications for use for each target species

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

3.3 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.

3.4 Special warnings

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

3.5 Special precautions for use

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 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.

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.

3.6 Adverse events

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 section ‘Contact details’ of the package leaflet.

3.7 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 3.3).

3.8 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.

3.9 Administration routes and dosage

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.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

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).

3.11 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.

3.12 Withdrawal periods

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.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QJ01BA99

4.2 Pharmacodynamics

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 multocida* and *Mycoplasma bovis*.
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.

4.3 Pharmacokinetics

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.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

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

5.2 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.

5.3 Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.

5.4 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.

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

Medicines should not be disposed of via wastewater or household waste.
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 national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

Ceva Santé Animale

7. MARKETING AUTHORISATION NUMBER(S)

EU/2/17/210/001–003

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: 15/05/2017

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

{DD/MM/YYYY}

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).

ANNEX II

OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

None

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Cardboard box of 50 ml, 100 ml and 250 ml vials

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCES

Florfenicol 400 mg/ml
Meloxicam 5 mg/ml

3. PACKAGE SIZE

50 ml
100 ml
250 ml

4. TARGET SPECIES

Cattle

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

Subcutaneous use.

7. WITHDRAWAL PERIODS

Withdrawal period:
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.

8. EXPIRY DATE

Exp. {mm/yyyy}
Once broached, use within 28 days, by __/__/__.

9. SPECIAL STORAGE PRECAUTIONS

10. THE WORDS “READ THE PACKAGE LEAFLET BEFORE USE”

Read the package leaflet before use.

11. THE WORDS “FOR ANIMAL TREATMENT ONLY”

For animal treatment only.

12. THE WORDS “KEEP OUT OF THE SIGHT AND REACH OF CHILDREN”

Keep out of the sight and reach of children.

13. NAME OF THE MARKETING AUTHORISATION HOLDER

Ceva Santé Animale

14. MARKETING AUTHORISATION NUMBERS

EU/2/17/210/001 50 ml
EU/2/17/210/002 100 ml
EU/2/17/210/003 250 ml

15. BATCH NUMBER

Lot {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

Vial of 100 ml and 250 ml

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCES

Florfenicol 400 mg/ml
Meloxicam 5 mg/ml

3. TARGET SPECIES

Cattle

4. ROUTES OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

5. WITHDRAWAL PERIODS

Withdrawal period:
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.

6. EXPIRY DATE

Exp. {mm/yyyy}
Once broached, use within 28 days.

7. SPECIAL STORAGE PRECAUTIONS

8. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ceva Santé Animale

9. BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial 50 ml

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Zeleris

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

Florfenicol 400 mg/ml
Meloxicam 5 mg/ml

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}
Once broached, use within 28 days.

B. PACKAGE LEAFLET

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

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

2. Composition

Each ml contains:

Active substances:
Florfenicol 400 mg
Meloxicam 5 mg

Clear yellow solution.

3. Target species

Cattle.

4. Indications for use

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

5. 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.

6. Special warnings

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

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 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.

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.

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 "Contraindications").

Interactions 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.

Overdose:
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).

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 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 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 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.

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.

9. Advice on correct administration

To ensure a correct dosage, bodyweight should be determined as accurately as possible.

10. Withdrawal periods

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.

11. Special storage precautions

Keep out of the sight and reach of children.

This veterinary medicinal product does not require any special storage conditions.

Do not use this veterinary medicinal product after the expiry date which is stated on the carton after "Exp". The expiry date refers to the last day of that month.
Shelf life after first opening the immediate packaging: 28 days.

12. Special precautions for disposal

Medicines should not be disposed of via wastewater or household waste.
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. 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

EU/2/17/210/001-003

Pack size:
Cardboard box with 1 vial of 50 ml, 100 ml or 250 ml.

Not all pack sizes may be marketed.

15. Date on which the package leaflet was last revised

{MM/YYYY}
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 manufacturer responsible for batch release and contact details to report suspected adverse reactions:

Ceva Santé Animale
10 av. de La Ballastière
33500 Libourne
France
Tel: +800 35 22 11 51
E-mail: pharmacovigilance@ceva.com

17. Other information

Pharmacodynamics
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 multocida* and *Mycoplasma bovis*.
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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 flo-R gene.

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Pharmacokinetics
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.