ANNEX I

SUMMARY OF PRODUCT CHARACTERSTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Cadorex 300 mg/ml solution for injection for cattle, sheep and pigs [AT, BG, CY, CZ, DE, EE, EL, FR, HR, HU, IE, IT, LT, LV, NL, PL, PT, RO, SI, SK, UK (NI)]
Flodoex 300 mg/ml solution for injection for cattle, sheep and pigs [BE]
Cadorex vet, 300 mg/ml solution for injection for cattle, sheep and pigs [DK]
Cadorex vet 300 mg/ml solution for injection [FI]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:
Florfenicol 300 mg

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
N-Methylpyrrolidone	250 mg
Propylene glycol	
Macrogol 300	

Clear, light yellow to straw-coloured, somewhat viscous solution, free from foreign matter.

3. CLINICAL INFORMATION

3.1 Target species
Cattle, sheep and pigs.

3.2 Indications for use for each target species

Cattle:
Diseases caused by florfenicol susceptible bacteria: Metaphylactic and therapeutic treatment of respiratory tract infections in cattle due to *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni.* The presence of the disease in the group must be established before the veterinary medicinal product is used.

Sheep:
Treatment of ovine respiratory tract infections due to *Mannheimia haemolytica* and *Pasteurella multocida*.

Pigs:
Treatment of acute outbreaks of swine respiratory disease caused by strains of *Actinobacillus pleuropneumoniae* and *Pasteurella multocida*.

3.3 Contraindications

Do not use in adult bulls and rams intended for breeding purposes.
Do not use in boars intended for breeding.
Do not use in cases of hypersensitivity to the active substance or to any of the excipients.

3.4 Special warnings

None.

3.5 Special precautions for use

Special precautions for safe use in the target species:
This veterinary medicinal product does not contain any antimicrobial preservative.
The safety of the veterinary medicinal product has not been established in sheep under 7 weeks of age.
Do not use in piglets of less than 2 kg.
Use of the veterinary medicinal product should be based on identification and susceptibility testing of the target pathogens. Use of the veterinary medicinal product should be in accordance with official, national and regional antimicrobial policies.
Use of the veterinary medicinal product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to the florfenicol and may decrease the effectiveness of treatment with amphenicols due to the potential for cross-resistance.

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 florfenicol, propylene glycol or polyethylene glycols should avoid contact with the veterinary medicinal product.

Laboratory studies in rabbits and rats with the excipient N-methyl pyrrolidone have shown evidence of foetotoxic effects. Women of childbearing age, pregnant women or women suspected of being pregnant should use the veterinary medicinal product with serious caution to avoid accidental self-injection.

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

Avoid skin or eye contact with the veterinary medicinal product. In case of contact with the skin or eyes, rinse the affected area immediately with plenty of clean water.

If you develop symptoms following exposure such as skin rash, you should seek medical advice and show the physician the package leaflet or the label.

Wash hands after use.

Special precautions for the protection of the environment:
The use of this veterinary medicinal product may pose a risk for terrestrial plants, cyanobacteria and groundwater organisms.

3.6 Adverse events

Cattle:

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Reduced food intake[1] Loose stool[1] Injection site inflammation[2]

	Anaphylactic shock

[1] The treated animals recover quickly and completely upon termination of treatment.
[2] It may persist for 14 days.

Sheep:

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Reduced food intake[3] Injection site inflammation[4]

[3] The treated animals recover quickly and completely upon termination of the treatment.
[4] It may persist up to 28 days. Typically, these are mild and transient.

Pigs:

Very common (>1 animal / 10 animals treated):	Pyrexia[5,6] Respiratory depression[7], dyspnoea[7] Diarrhoea[8], anal and rectal disorder (erythema/oedema)[8]
Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Injection site swelling[9], injection site inflammation[10]

[5] 40ºC
[6] These effects were observed in approximately 30% of treated pigs associated with either moderate depression or moderate dyspnoea a week or more after administration of the second dose.
[7] Moderate
[8] These effects, may affect 50% of the animals. These effects can be observed for one week (transient).
[9] It may be observed up to 5 days.
[10] It may be seen up to 28 days.

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 its local representative> or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established in cattle, sheep and pigs during pregnancy, lactation or in animals intended for breeding.
Pregnancy and lactation:
Studies in laboratory animals have not revealed any evidence of embryo- or foetotoxic potential for florfenicol. Laboratory studies in rabbits and rats with the excipient N-methyl pyrrolidone have shown evidence of foetotoxic effects. Use only according to the benefit-risk assessment by the responsible veterinarian.
Fertility:
Do not use in adult bulls, rams and boars intended for breeding (see section 3.3).

3.8 Interaction with other medicinal products and other forms of interaction

None known.

3.9 Administration routes and dosage

For intramuscular and subcutaneous use in cattle.
For intramuscular use in sheep and pigs.

For treatment
Cattle:
Intramuscular route: 20 mg of florfenicol/kg bodyweight (equivalent to 1 ml of the veterinary medicinal product/15 kg bodyweight) to be administered twice 48 hours apart using a 16 gauge needle.
Subcutaneous route: 40 mg of florfenicol/kg bodyweight (equivalent to 2 ml of the veterinary medicinal product/15 kg bodyweight) to be administered once using a 16 gauge needle. The dose volume given at any one injection site should not exceed 10 ml.
The injection should only be given in the neck.

Sheep:
20 mg of florfenicol/kg bodyweight (equivalent to 1 ml of the veterinary medicinal product/15 kg bodyweight) by intramuscular injection daily for three consecutive days. The volume administered per injection site should not exceed 4 ml.

Pigs:
15 mg of florfenicol/kg bodyweight (equivalent to 1 ml of the veterinary medicinal product/20 kg bodyweight) by intramuscular injection into the neck muscle twice at 48 hours intervals using a 16-gauge needle.
The volume administered per injection site should not exceed 3 ml.
For intramuscular, it is recommended to treat animals in the early stages of disease and to evaluate the response to treatment within 48 hours after the second injection. If clinical signs of respiratory disease persist 48 hours after the last injection, treatment should be changed using another formulation or another antibiotic and continued until clinical signs have resolved.

For metaphylaxis
Cattle:
Subcutaneous use: 40 mg florfenicol/kg bodyweight (equivalent to 2 ml of the veterinary medicinal product/15 kg bodyweight) to be administered once only using a 16-gauge needle. The dose volume given at any one injection site should not exceed 10 ml.
The injection should only be given in the neck.

Wipe the stopper before removing each dose. Use a dry sterile needle and syringe.
To ensure a correct dosage, body weight should be determined as accurately as possible.
As the vial should not be broached more than 25 times, the user should select the most appropriate vial size according to the target species to be treated. When treating groups of animals in one run, use a draw-off needle that has been placed in the vial stopper to avoid excess broaching of the stopper. The draw-off needle should be removed after treatment.

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

Cattle:
No symptoms other than those described in section 3.6.
Sheep:
After administration of 3 times the recommended dose or more, a transient reduction in feed and water consumption has been observed. Additional secondary effects that were noted included an increased incidence of lethargy, emaciation and loose faeces.
Head tilt was seen after administration of 5 times the recommended dose and was considered most likely a result of irritation at the injection site.
Swine:

After administration of 3 times the recommended dose or more, a reduction in feeding, hydration and weight gain has been observed.
After administration of 5 times the recommended dose or more, vomiting has also been noted.

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 period(s)

Cattle:

Meat and offal:	by IM route:	30 days
	by SC route:	44 days

Milk: Not authorized for use in animals producing milk for human consumption. Do not use in pregnant animals which are intended to produce milk for human consumption.

Sheep:

Meat and offal:	by IM route:	39 days

Milk: Not authorized for use in animals producing milk for human consumption. Do not use in pregnant animals which are intended to produce milk for human consumption.

Pigs:

Meat and offal:	by IM route:	18 days

4. PHARMACOLOGICAL INFORMATION

4.1 ATCVet code: QJ01BA90

4.2 Pharmacodynamics

Florfenicol is a synthetic broad spectrum antibiotic effective against most Gram-positive and Gram-negative isolated from domestic animals. Florfenicol acts by inhibiting protein synthesis at ribosomal level and is bacteriostatic. Laboratory tests have shown that florfenicol is active against the most commonly isolated bacterial pathogens involved in ovine and bovine respiratory disease which include *Mannheimia haemolytica, Pasteurella multocida,* and for cattle *Histophilus somni.* Florfenicol is considered to be a bacteriostatic agent, but *in vitro* studies of florfenicol demonstrate bactericidal activity against *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni.*

Mechanisms of resistance to florfenicol include specific and non-specific drug transporters and RNA methyltransferases. In general, the specific efflux proteins provide levels of resistance greater than that of the multidrug efflux proteins. A number of genes (including floR gene) mediate combined resistance to florfenicol. Resistance to florfenicol and other antimicrobials has been firstly detected on a plasmid in *Photobacterium damselae* subsp. *Piscida*, then as part of a chromosomal multiresistance gene cluster in *Salmonella enterica* serovar *Typhimurium* and serovar Agona, but also on multiresistance plasmids of *E. coli*. Co-resistance with the third-generation cephalosporins has been observed in respiratory and digestive *E. coli.*

For florfenicol in cattle respiratory disease for *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni* CLSI breakpoints (CLSI-2018) are: susceptible ≤ 2 µg/ml, intermediate 4 µg/ml and re-sistant ≥ 8 µg/ml.
For florfenicol in swine respiratory disease for *Pasteurella multocida* CLSI breakpoints (CLSI-2018) are: susceptible ≤ 2 µg/ml, intermediate 4 µg/ml and resistant ≥ 8 µg/ml.

4.3 Pharmacokinetics

Cattle:
Intramuscular administration at the recommended dose of 20 mg/kg maintains efficacious blood levels in cattle for 48 hours. Maximum mean serum concentration (C_{max}) of 3.37 µg/ml occurs at 3.3 hours (T_{max}) after dosing. The mean serum concentration 24 hours after dosing was 0.77µg/ml.

The administration of the veterinary medicinal product by subcutaneous route at the recommended dosage of 40 mg/kg maintains efficacious blood levels in cattle (i.e. above the MIC_{90} of the main respiratory pathogens) for 63 hours. Maximum serum concentration (C_{max}) of approximately 5 µg/ml occurs approximately 5.3 hours (T_{max}) after dosing. The mean serum concentration 24 hours after dosing is approximately 2 µg/ml.
The harmonic mean elimination half-life was 18.3 hours.

Sheep:
After initial intramuscular administration of florfenicol (20 mg/kg) the mean maximum serum concentration of 10.0 µg/ml is reached after 1 hour. Following the third intramuscular administration, the maximum serum concentration of 11.3 µg/ml is reached after 1.5 hours. The elimination half-life was estimated to be 13.76 ± 6.42 h. Bioavailability is about 90%.

Pigs:
After initial intramuscular administration of florfenicol, maximum serum concentrations of between 3.8 and 13.6 µg/ml are reached after 1.4 hours and the concentrations deplete with a terminal mean half-life of 3.6 hours. After a second intramuscular administration, maximum serum concentrations of between 3.7 and 3.8 µg/ml are reached after 1.8 hours. Serum concentrations drop below 1 µg/ml, the MIC_{90} for the target porcine pathogens, 12 to 24 hours following IM administration. Florfenicol concentrations achieved in lung tissue reflect plasma concentrations, with a lung: plasma concentration ratio of approximately 1.

After administration to pigs by the intramuscular route, florfenicol is rapidly excreted, primarily in urine. The florfenicol is extensively metabolised.

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: 2 years
Shelf life after first opening the immediate packaging: 28 days

5.3 Special precautions for storage

Store below 30ºC.

Do not freeze.

5.4 Nature and composition of immediate packaging

Polypropylene vial of 100 ml, closed with bromobutyl rubber stopper and sealed with an aluminium tear-off cap or aluminium/plastic flip-off cap.
Polypropylene vial of 250 ml, closed with bromobutyl rubber stopper and sealed with an aluminium/plastic flip-off cap.

Package sizes:
Cardboard box containing 1 vial of 100 ml
Cardboard box containing 1 vial of 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.

The veterinary medicinal product should not enter water courses as florfenicol may be dangerous for fish and other aquatic organisms.
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

Industrial Veterinaria, S.A.

7. MARKETING AUTHORISATION NUMBER

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: {DD/MM/YYYY}

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

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).