1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Introflor Vet 300 mg/ml solution for injection for cattle, sheep and pigs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substances:
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**
Propylene glycol	
N-methylpyrrolidone	250 mg
Macrogol 300	

Clear, light yellow to straw-coloured, slightly viscous solution, free from visible suspended particles.

3. CLINICAL INFORMATION

3.1 Target species

Cattle, sheep and pigs.

3.2 Indications for use for each target species

Cattle
Metaphylactic and therapeutic treatment of respiratory tract infections due to *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*.

The presence of the disease in the group must be established before the product is used.

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

Pigs
Treatment of outbreaks of acute respiratory tract infections due to *Actinobacillus pleuropneumoniae* and *Pasteurella multocida*.

3.3 Contraindications

Do not use in adult bulls, rams and boars intended for collecting sperm or for breeding purposes.
Do not use in piglets weighing less than 2 kg.
Do not use in cases of hypersensitivity to the active substance or to any of the excipients.

3.4 Special warnings

Cross-resistance has been shown between florfenicol and chloramphenicol. Use of the veterinary medicinal product should be carefully considered when susceptibility testing has shown resistance to chloramphenicol because its effectiveness may be reduced.

3.5 Special precautions for use

Special precautions for safe use in the target species:

Use of the veterinary medicinal 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, AMEG - Antimicrobial Advice Ad Hoc Expert Group) should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach.
The safety of the veterinary medicinal product has not been established in sheep younger than 7 weeks of age.
The feeding of waste milk containing residues of florfenicol to calves should be avoided up to the end of the milk withdrawal period (except during the colostral phase), because it could select antimicrobial-resistant bacteria within the intestinal microbiota of the calf and increase the faecal shedding of these bacteria.

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

Laboratory studies in rabbits and rats with the excipient N-methylpyrrolidone have shown evidence of fetotoxic 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.

Personal protective equipment consisting of gloves should be worn when handling the veterinary medicinal product.

People with known hypersensitivity to florfenicol or to propylene glycol and polyethylene glycols should avoid contact with the veterinary medicinal product.

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 direct contact with skin, eyes and mucous membranes. In case of accidental contact with skin or eyes, rinse immediately with plenty of water. 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], Injection site lesion[2]; Anaphylaxis.

[1] Quick and complete recovery upon termination of treatment.
[2] May persist up to 14 days after intramuscular and subcutaneous administration.

Sheep:

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

[1] Quick and complete recovery upon termination of treatment.
[2] Mild and may persist up to 28 days after intramuscular administration.

Pigs:

Common (1 to 10 animals / 100 animals treated):	Diarrhoea[1]; Perianal inflammation[1], Rectal oedema[1]; Pyrexia[2], Depression[2]; Dyspnoea[2].
Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Injection site swelling[3], Injection site lesion[4], Injection site inflammation[4].

[1] Can be observed for one week in 50% of the animals.
[2] Under field conditions in approximately 30% of treated pigs a week or more after administration of the second dose.
[3] Lasting up to 5 days.
[4] 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

Pregnancy, lactation and fertility:
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. Laboratory studies in rabbits and rats with the excipient N-methylpyrrolidone have shown evidence of fetotoxic effects.
Do not use this veterinary medicinal product in pigs during pregnancy and lactation.
Use only according to the benefit-risk assessment by the responsible veterinarian.

3.8 Interaction with other medicinal products and other forms of interaction

None known.

3.9 Administration routes and dosage

Cattle: intramuscular (i.m.) and subcutaneous (s.c.) use.
Sheep and pigs: intramuscular (i.m.) use.

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

Cattle:
Treatment
Intramuscular use: 20 mg florfenicol per 1 kg bodyweight (equivalent to 1 ml veterinary medicinal product per 15 kg bodyweight) to be administered twice 48 hours apart using a 16G needle.
Subcutaneous use: 40 mg florfenicol per 1 kg bodyweight (equivalent to 2 ml veterinary medicinal product per 15 kg bodyweight) to be administered once using a 16G needle.

Metaphylaxis

Subcutaneous use: 40 mg florfenicol per 1 kg bodyweight (equivalent to 2 ml veterinary medicinal product per 15 kg bodyweight) to be administered once using a 16G needle.

The dose volume given at any one injection site should not exceed 10 ml for either route of administration (intramuscular or subcutaneous).
The injection should only be given in the neck.

Sheep:
20 mg florfenicol per 1 kg bodyweight (equivalent to 1 ml veterinary medicinal product per 15 kg bodyweight) to be administered daily for three consecutive days by intramuscular injection.

In sheep, the volume administered per injection site should not exceed 4 ml.
Pharmacokinetic studies showed that mean plasma concentrations remain above MIC_{90} (1 µg/ml) for up to 18 hours after administration of the veterinary medicinal product at the recommended treatment dose. The pre-clinical data support the recommended treatment interval (24 hours) for target pathogens with MIC up to 1 µg/ml.

Pigs:
15 mg florfenicol per 1 kg bodyweight (equivalent to 1 ml veterinary medicinal product per 20 kg bodyweight) to be administered by intramuscular injection into the neck muscle twice 48 hours apart using a 16G needle.

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 second injection, treatment should be changed using another formulation or another antibiotic and continued until clinical signs have resolved.

In pigs, the volume administered per injection site should not exceed 3 ml.

Wipe the rubber stopper before removing each dose. Use a dry sterile needle and syringe.

The rubber stopper can be pierced maximum 15 times.

If the temperature of the veterinary medicinal product drops below 5 °C, administration difficulties may occur due to the increased viscosity. The temperature of the veterinary medicinal product up to approximately 25 °C simplifies the administration.

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

In cattle, no adverse effects have been observed other than those described in section 3.6.

In sheep, after administration of 3 times the recommended dose or more, a transient reduction in feed and water consumption has been observed. Additionally, secondary effects including an increased incidence of lethargy, emaciation and loose faeces have been noted. 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.

In pigs, after administration of 3 times the recommended dose or more, a reduction in feed consumption, dehydration and reduction in 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 periods

Cattle:
Meat and offal: 30 days (intramuscular administration).
44 days (subcutaneous administration).
Milk: Not authorised for use in animals producing milk for human consumption, including pregnant animals intended to produce milk for human consumption.

Sheep:
Meat and offal: 39 days.
Milk: Not authorised for use in animals producing milk for human consumption, including pregnant animals intended to produce milk for human consumption.

Pigs:
Meat and offal: 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 bacteria isolated from domestic animals.
Florfenicol acts by inhibition of bacterial protein synthesis at the ribosomal level and is thereby bacteriostatic.
Laboratory tests have shown that florfenicol is active against the most commonly isolated bacterial pathogens involved in bovine respiratory disease including *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, against bacterial pathogens involved in ovine respiratory disease including *Mannheimia haemolytica*, *Pasteurella multocida* and against bacterial pathogens involved in porcine respiratory disease including *Actinobacillus pleuropneumoniae* and *Pasteurella multocida*.
Florfenicol is considered to be a bacteriostatic agent, but *in vitro* studies of florfenicol demonstrate bactericidal activity against *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni* and *Actinobacillus pleuropneumoniae*.

Acquired resistance to florfenicol is mediated by efflux pumps associated with a *flo* gene.
Florfenicol Minimum Inhibitory Concentrations (MIC) clinical breakpoints (CLSI VET01S, 5th edition, 2020) for the target pathogens are presented in the table below:

Organism	Minimum inhibitory concentrations for florfenicol (µg/ml)		
	susceptible	intermediate	resistant
Mannheimia haemolytica	≤2	4	≥8
Pasteurella multocida	≤2	4	≥8
Histophilus somni	≤2	4	≥8
Actinobacillus pleuropneumoniae	≤2	4	≥8

For pathogens associated with respiratory tract infections in sheep, MIC clinical breakpoints have not yet been established.

4.3 Pharmacokinetics

Cattle

After intramuscular administration at the recommended dose of 20 mg/kg efficacious blood levels are maintained in blood 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 is 0.77 µg/ml.

After subcutaneous administration of the product at the recommended dosage of 40 mg/kg efficacious blood levels are maintained 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 is 18.3 hours.

Sheep
After intramuscular administration of florfenicol at dose 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 is 13.76 ± 6.42 hours. Bioavailability is about 90%.

Pigs
In pigs intravenously administered florfenicol has a mean plasma clearance rate of 5.2 ml/min/kg and a mean volume of distribution at equilibrium of 948 ml/kg. The mean terminal half-life is 2.2 hours. 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 the 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 intramuscular administration. Florfenicol concentrations achieved in lung tissue reflect plasma concentrations, with a lung: plasma concentration ratio of approximately 1.
After intramuscular administration to pigs, florfenicol is rapidly excreted, primarily in urine. 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

Do not store above 30 °C.

5.4 Nature and composition of immediate packaging

Clear type II glass vial closed with a bromobutyl rubber stopper and an aluminium cap or aluminium/polypropylene flip-off cap, packaged in a cardboard box.

Pack size:
Cardboard box with 1 × 100 ml vial.

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

Interchemie Werken De Adelaar Eesti AS

7. MARKETING AUTHORISATION NUMBER(S)

VPA22812/005/001

8. DATE OF FIRST AUTHORISATION

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).