[Version 9,07/2021]

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Florfeksyl 300 mg/ml solution for injection for cattle, sheep and pigs [ES, PL, RO, IT]

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	250.0 mg
Propylene glycol	
Macrogol 300	

Clear yellow solution, free from visible particles.

3. CLINICAL INFORMATION

3.1 Target species

Cattle, sheep and pigs.

3.2 Indications for use for each target species

Cattle:
Treatment of respiratory tract infections in cattle due to *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni* susceptible to florfenicol.

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

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

3.3 Contraindications

Do not use in adult bulls and rams intended for breeding purposes.
Do not administer to 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

Do not exceed the recommended treatment dose or the recommended duration of treatment.

3.5 Special precautions for use

This medicinal product does not contain any antimicrobial preservative.

Special precautions for safe use in the target species:
The safety of the 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 susceptibility testing of the bacteria isolated from the animal. If this is not possible, therapy should be based on local (regional, farm level) epidemiological information about susceptibility of the target bacteria.
Official, national and regional antimicrobial policies should be taken into account when the product is used.
Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to 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 product may cause hypersensitivity (allergy). People with known hypersensitivity to florfenicol, polyethylene glycol or propylene glycol 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.
Administer the veterinary medicinal product with caution 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.
This product may cause skin and eye irritation. Avoid contact with skin or eyes. In case of accidental contact, wash immediately exposed area with plenty of clean water.
If you develop symptoms following exposure such as skin rash, seek medical advice and take the package leaflet or the label with you.

Special precautions for the protection of the environment:
Florfenicol is toxic for terrestrial plants, cyanobacteria and groundwater organisms.

3.6 Adverse events

Cattle:

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Anaphylaxis Anorexia (decrease appetite) and loose stool[1]. * Injection site inflammation[2].

[1]The treated animals recover quickly and completely upon termination of treatment.
[2] It persist for 14 days may be observed after intramuscular and subcutaneous administration of the product.

Sheep:

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Anorexia (decrease appetite)[3]. Injection site inflammation[4].

[3] The treated animals recover quickly and completely upon termination of the treatment.
[4] It may be observed after administration of the product by the intramuscular route. Typically, these are mild and transient. It may persist up to 28 days

Pigs:

Very common (>1 animal / 10 animals treated):	Transient diarrhea and/or anal and rectal disorder NOS (peri-anal and rectal erythema/oedema)[5]. Hyperthermia (40ºC) associated with either moderate depression or moderate dyspnoea[6].
Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Application site oedema[7]. Injection site inflammation[8].

[5] These effects are commonly observed adverse effects, which may affect 50% of the animals. They can be observed for one week.
[6] These effects were observed in approximately 30% of treated pigs a week or more after administration of the second dose under field conditions.
[7] It may be observed up to 5 days.
[8] 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 also the last section of 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. 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

Cattle –intramuscular or subcutaneous use
Sheep, pigs -intramuscular use

For treatment
Cattle:
Intramuscular use: 20 mg of florfenicol/kg bodyweight (equivalent to 1 ml of the product/15 kg bodyweight) to be administered twice 48 hours apart using a 16 gauge needle.
Subcutaneous use: 40 mg of florfenicol/kg bodyweight (equivalent to 2 ml of the 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 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 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.

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

To ensure a correct dosage bodyweight should be determined as accurately as possible to avoid underdosing.

As the vial should not be broached more than 20 times in case of 100 ml vial and 40 times in case of 250 vial, 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)

In cattle, a decrease in food consumption and transient softening of the faeces may occur during the treatment period. The treated animals recover quickly and completely upon termination of treatment.
In 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.
In 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

Use of the veterinary medicinal product should be based on susceptibility testing of the bacteria isolated from the animal. If this is not possible, therapy should be based on local (regional, farm level) epidemiological information about susceptibility of the target bacteria.
Official, national and regional antimicrobial policies should be taken into account when the product is used.
Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to florfenicol and may decrease the effectiveness of treatment with amphenicols due to the potential for cross-resistance.

3.12 Withdrawal periods

Withdrawal period:
Meat and offal

Cattle:	IM use (20 mg/kg bodyweight, twice):	30 days.
	SC use (40 mg/kg bodyweight, once):	44 days.

Sheep:	39 days.
Pig:	18 days.

Milk
Not authorised for use in animals producing milk for human consumption including pregnant animals intended to produce milk for human consumption.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code:QJ01BA90

4.2 Pharmacodynamic

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 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.*
In vitro testing has shown that florfenicol is active against the bacterial pathogens most commonly isolated in respiratory diseases in pigs, 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* and *Histophilus somni.*

Florfenicol resistance is mainly due to the presence of specific efflux pumps (e.g. florR) or multi-substrate (e.g. AcrAB-TolC). The genes corresponding to these mechanisms are encoded in genetic elements such as plasmids, transposons or gene cassettes. Cross resistance with chloramphenicol is possible. The floR gene and its analogs have mainly been identified in gram-negative bacteria, whereas the other resistance genes have mainly been detected in gram-positive bacteria.

For florfenicol in cattle respiratory disease for *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni* CLSI breakpoints (CLSI-2018) are: susceptible $\leq$ 2 µg/ml, intermediate 4 µg/ml and resistant $\geq$ 8 µg/ml.

For florfenicol in swine respiratory disease for *Pasteurella multocida* CLSI breakpoints (CLSI-2018) are: susceptible $\leq$ 2 µg/ml, intermediate 4 µg/ml and resistant $\geq$ 8 µg/ml.

4.3 Pharmacokinetic

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 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 decrease 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.

Environmental properties
Florfenicol is toxic for terrestrial plants, cyanobacteria and groundwater organisms.

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: 30 months
Shelf life after first opening the immediate packaging: 28 days

5.3 Special precautions for storage

Keep the vial in the outer carton in order to protect from light.
This veterinary medicinal product does not require any special temperature storage conditions.

5.4 Nature and composition of immediate packaging

(COEX) PP/HV/EVOH/HV/PP vial of capacity 100 and 250 ml closed with Type I bromobutyl rubber stopper and sealed with an aluminium/plastic flip-off cap packed individually in carboard box.

Package sizes:
Cardboard box containing 1 vial of capacity 100 ml.
Cardboard box containing 1 vial of capacity 250 ml.
Not all pack sizes may be marketed.

5.5 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 or household waste.
The veterinary medicinal product should not enter water courses as florfenicol may be dangerous for 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

Vet-Agro Multi-Trade Company Sp. z o.o.

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

Date of first authorisation:

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

09/2023

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.
Administration under the supervision of a veterinary surgeon.

Detailed information on this veterinary medicinal product is available in the Union Product Database.