Summary of Product Characteristics

1 NAME OF THE VETERINARY MEDICINAL PRODUCT

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:
Florfenicol..... 300 mg

Excipients,
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.
Clear, yellowish solution, free from visible particles in suspension.

4 CLINICAL PARTICULARS

4.1 Target Species

Cattle, sheep and pigs.

4.2 Indications for use, specifying the target species

Cattle: Treatment and metaphylaxis of bovine respiratory disease associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni* susceptible to florfenicol. The presence of the disease in the group must be established before metaphylactic treatment.

Sheep**:** Treatment of ovine respiratory disease associated with *Mannheimia haemolytica* and *Pasteurella multocida* susceptible to florfenicol.

Pigs: Treatment of acute outbreaks of swine respiratory disease associated with *Actinobacillus pleuropneumoniae* and *Pasteurella multocida* susceptible to florfenicol.

4.3 Contraindications

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

See section 4.7.

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

Special precautions for use in animals
Do not use in piglets of less than 2 kg.

The safety of the veterinary medicinal product has not been established in sheep younger than 7 weeks of age.

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 de effectiveness of treatment with amphenicols due to the potential cross-resistance.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
The product can cause hypersensitivity (allergy). People with known hypersensitivity to florfenicol, propylene glycol or polyethylene glycols should avoid contact with the veterinary medicinal product.

This product contains N-methylpyrrolidone which may be harmful for the unborn child; therefore, women of child-bearing age must be very careful to avoid exposure via spillage onto the skin or accidental self-injection when administering the product. If you are pregnant, think you may be pregnant or are attempting to conceive, you should not administer the product.
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 a skin rash, you should seek medical advice and show the physician the package leaflet or the label.

Other precautions:
Florfenicol is toxic for terrestrial plants, cyanobacteria and groundwater organisms.

4.6 Adverse reactions (frequency and seriousness)

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.
Intramuscular and subcutaneous administration may cause inflammatory lesions at the injection site which may persist for 14 days.
In very rare cases, anaphylactic shock has been reported in cattle.

Sheep:
A decrease in food consumption may occur during the treatment period. The treated animals recover quickly and completely upon termination of treatment.
Intramuscular administration may cause inflammatory lesions at the injection site which may persist up to 28 days. Typically, these are mild and transient.

Pigs:
Commonly observed adverse effects are transient diarrhoea and/or peri-anal and rectal erythema/oedema which may affect 50% of the animals. These effects can be observed for one week.
Under field conditions approximately 30% of treated pigs presented with pyrexia (40°C) associated with either moderate depression or moderate dyspnoea a week or more after administration of the second dose.
Transient swelling lasting up to 5 days may be observed at the site of injection. Inflammatory lesions at the injection site may be seen up to 28 days.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

4.7 Use during pregnancy, lactation or lay

Studies in laboratory animals with florfenicol have not revealed any evidence of teratogenic or foetotoxic effects.

Laboratory studies with the excipient N-methylpyrrolidone in rabbits and rats have shown evidence of teratogenic, foetotoxic, maternotoxic and reprotoxic effects.

Cattle and sheep: the effect of florfenicol on bovine and ovine reproductive performance and pregnancy has not been assessed. Do not use the product during pregnancy and lactation.

Pig: the safety of the product in sows during pregnancy and lactation has not been demonstrated. Do not use the product during pregnancy and lactation.

4.8 Interaction with other medicinal products and other forms of interactions

None known.

4.9 Amounts to be administered and administration route

Administration route: For intramuscular and subcutaneous use in cattle.
For intramuscular use in sheep and pigs.

For treatment:
Cattle**:**
Intramuscular use: 20 mg florfenicol/kg bodyweight (equivalent to 1 ml of the veterinary medicinal product/15 kg bodyweight) to be administered twice 48 hours apart.
Subcutaneous use: 40 mg florfenicol/kg bodyweight (equivalent to 2 ml of the veterinary medicinal product/15 kg bodyweight) to be administered once only.
For both routes: use 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:
Intramuscular use: 20 mg florfenicol/kg bodyweight (equivalent to1 ml of the veterinary medicinal product/15 kg bodyweight) to be administered daily for three consecutive days.
The volume administered per injection site should not exceed 4 ml.

Pig:
Intramuscular use: 15 mg 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-hour intervals using a 16-gauge needle.
The volume administered per injection site should not exceed 3 ml.
It is recommended to treat animals in the early stages of the disease and to evaluate the response to treatment within 48 hours after the last injection. If clinical signs of respiratory disease persist or increase, or if relapse occurs, treatment should be changed, using 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.

For all target species: To ensure a correct dosage body weight should be determined as accurately as possible to avoid underdosing. The closure must not be punctured more than 50 times.
When treating groups of animals at the same time, use of a draw-off needle in the vial stopper is recommended to avoid excess stopper broaching. The draw-off needle should be removed after treatment.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

Cattle:
No symptoms other than those described in section 4.6.

Sheep:
After administration of 3 times the recommended dose or more, a transient reduction in feed and water consumption has been observed. Additional effects 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.

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

4.11 Withdrawal period(s)

Meat and offal

Cattle:	IM use (20 mg/kgbodyweight, twice):	30 days.
	SC use (40 mg/kgbodyweight, 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.

5 PHARMACOLOGICAL or IMMUNOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterial for systemic use (Amphenicols).
ATC vet code: QJ01BA90

5.1 Pharmacodynamic properties

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 most commonly isolated bacterial pathogens involved in ovine and bovine (including *Pasteurella multocida*, *Mannheimia haemolytica*, and for cattle *Histophilus somni*) and in swine respiratory disease (including *Actinobacillus pleuropneumoniae* and *Pasteurella multocida*).

Although considered to be a bacteriostatic agent, bactericidal activity of florfenicol has been demonstrated *in vitro* against *Mannheimia haemolytica*, *Pasteurella multocida*, *Actinobacillus pleuropneumoniae* 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. *piscicida*, then as part of a chromosomal multi-resistance gene cluster in *Salmonella enterica* serovar *Typhimurium* and serovar *Agona*, but also on multi-resistance 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 resistant ≥ 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.

5.2 Pharmacokinetic particulars

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 0.77 µg/ml.

Subcutaneous administration at the recommended dose of 40 mg/kg maintains efficacious blood levels in cattle (ie 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 (tmax) 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 intravenous administration florfenicol had 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 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.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

N-Methylpyrrolidone
Propylene glycol (E-1520)
Macrogol 300

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: 2 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 temperature storage conditions.
Keep the vial in the outer carton in order to protect from light.

6.5 Nature and composition of immediate packaging

Colourless type II glass vial (100 ml or 250 ml), closed with type I bromobutyl rubber stoppers with aluminium seals.

Pack sizes:
Carton box with 1 vial of 100 ml
Carton box with 1 vial of 250 ml
Cardboard box with 6 vials of 100 ml
Cardboard box with 6 vials of 250 ml

Not all pack sizes may be marketed.

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

This veterinary medicinal product is dangerous for aquatic organisms (such as cyanobacteria). Do not contaminate surface waters or ponds with used product or containers.

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

Laboratorios SYVA, S.A.U
Avda. Párraco Pablo Díez
49-57 León
24010
Spain

8 MARKETING AUTHORISATION NUMBER(S)

VPA10495/007/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 February 2021

10 DATE OF REVISION OF THE TEXT