ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

[BE, DE, DK, EL, ES, FR, HU, IE, LT, NL, PL, PT, RO]: FLORFENIS 300 mg/ml solution for injection for cattle, sheep and pigs

[IT]: SYVAFLOR 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,

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
N-Methyl pyrrolidone	250 mg
Propylene glycol (E-1520)	
Macrogol 300	

Clear, yellowish solution, free from visible particles in suspension.

3. CLINICAL INFORMATION

3.1 Target species

Cattle, sheep and pigs.

3.2 Indications for use for each 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.

3.3 Contraindications

Do not use in adult bulls, rams and boars intended for breeding purposes. See section 3.7.
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 target species
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.

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 a skin rash, you should seek medical advice and show the physician the package leaflet or the label.

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)	Anaphylactic shock Reduced food intake[1] Loose stool[1,2] Injection site inflammation[3]

[1] Treated animals recover quickly and completely upon termination of treatment.
[2] Transient
[3] After intramuscular and subcutaneous administration. May persist for 14 days.

Sheep:

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

[1] The treated animals recover quickly and completely upon termination of treatment.
[2] After intramuscular administration. Inflammation may persist up to 28 days. Typically, these are mild and transient.

Pigs:

Very common (>1 animal / 10 animals treated)	Diarrhoea[1] Anal and Rectal oedema[1] Erythema[1, 2] Pyrexia, Depression[3] Dyspnoea[3]
Very rare (<1 animal / 10,000 animals treated, including isolated reports)	Injection site swellling[4], Injection site inflammation[5]

[1] These effects are transient and can be observed for one week.
[2] Peri-anal and rectal erythema.
[3] Pyrexia (40ºC) associated with either moderate depression or moderate dyspnoea a week or more after administration of the second dose.
[4] Transient swelling lasting up to 5 days.
[5] Inflammatory lesions 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 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 route and dosage

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.

Pigs:
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. The use of suitably calibrated measuring equipment is recommended. 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.

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 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.

Pigs:
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.

3.11 Special restrictions for use and special conditions for se, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

3.12 Withdrawal periods

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.

Pigs: 18 days.

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

4. PHARMACOLOGICAL INFORMATION

4.1 ATC vet 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 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.

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 0.77 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. 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

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

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.

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

Laboratorios Syva S.A.

7. MARKETING AUTHORISATION NUMBER(S)

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

{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).