Summary of Product Characteristics

1 NAME OF THE VETERINARY MEDICINAL PRODUCT

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

4 CLINICAL PARTICULARS

4.1 Target Species

Cattle, sheep and pigs.

4.2 Indications for use, specifying the target species

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

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.

4.3 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 case of hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings for each target species

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

4.5 Special precautions for use

This medicinal product does not contain any antimicrobial preservative.

Special precautions for use in animals
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.
The product should be used in conjunction with susceptibility testing and take into account official and local antimicrobial policies.
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 or propylene glycol should avoid contact with the 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 skin or eye contact with the 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, seek medical advice and take the package leaflet or the label with you.
Wash hands after use.

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.
Administration of the product by the intramuscular and subcutaneous routes may cause inflammatory lesions at injection site which persist for 14 days.
In very rare cases, anaphylactic shocks have been reported in bovines.

Sheep:
A decrease in food consumption may occur during the treatment period. The treated animals recover quickly and completely upon termination of the treatment.
Administration of the product by the intramuscular route 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 (40ºC) 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.

4.7 Use during pregnancy, lactation or lay

Studies in laboratory animals have not revealed any evidence of embryo- or foetotoxic potential for florfenicol.

Cattle and Sheep
The effect of florfenicol on bovine and ovine reproductive performance and pregnancy has not been assessed. Use only accordingly to the benefit/risk assessment by the responsible veterinarian.

Pigs
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 interaction

None known.

4.9 Amounts to be administered and administration route

For treatment

Cattle:
Intramuscular route: 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 route: 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.
Pharmacokinetic studies showed that mean plasma concentrations remain above MIC_{90} (1 µg/ml) for up to 18 hours after administration of the product at the recommended treatment dose. The pre-clinical data provided support the recommended treatment interval (24 hours) for target pathogens with MIC up to 1 µg/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 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.

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

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.

4.11 Withdrawal Period(s)

Cattle:
Meat and offal: by IM route: 30 days
by SC route: 44 days
Milk: Not authorised for use in lactating animals producing milk for human consumption including pregnant animals intended to produce milk for human consumption.
Sheep:
Meat and offal: by IM route: 39 days
Milk: Not authorised for use in lactating animals producing milk for human consumption including pregnant animals intended to produce milk for human consumption.
Pigs:
Meat and offal: by IM route: 18 days

5 PHARMACOLOGICAL or IMMUNOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterial for systemic use (Amphenicols)

ATCVet code: QJ01BA90

5.1 Pharmacodynamic properties

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.*
In cattle, 99% of *P. multocida* isolates (n=156) and 98% of *M. haemolytica* isolates (n=109) were susceptible to florfenicol (strains isolated in France in 2012).
In sheep, 99% of *M. haemolytica* isolates (n=71) were susceptible to florfenicol (strains isolated in France in 2012).

In pigs, 99% of *A. pleuropneumoniae* isolates (n=159) and 99% *P. multocida* isolates (n=150) were susceptible to florfenicol (strains isolated in France in 2012).
MIC_{90} values of florfenicol against bovine and porcine respiratory pathogens

Microorganism	MIC_{90} (µg/ml)
Cattle	
Mannheimia haemolytica	2
Pasteurella multocida	1
Pigs	
Actinobacillus pleuropneumoniae	0.5

Organisms were isolated from clinical cases of bovine and porcine respiratory disease in Czech Republic and Germany during the years 2007 to 2011.
CLSI breakpoints: S ≤ 2 µg/ml, I = 4 µg/ml and R ≥ 8 µg/ml.

5.2 Pharmacokinetic properties

Cattle:
Intramuscular administration at the recommended dose of 20 mg/kg maintains efficacious blood levels in cattle for 48 hours. Maximum mean serum concentration (Cmax) of 3.37 µg/ml occurs at 3.3 hours (Tmax) 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 (Cmax) 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 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

N-Methylpyrrolidone

Propylene glycol

Macrogol 300

6.2 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

Store below 30ºC.

Do not freeze.

6.5 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.
Pack sizes:
Cardboard box containing 1 vial of 100 ml
Cardboard box containing 1 vial 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

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

LIVISTO Int'l, S.L.
Av. Universitat Autònoma, 29
08290 Cerdanyola del Vallès
Barcelona E-08950
Spain

8 MARKETING AUTHORISATION NUMBER(S)

VPA 10425/002/001

9 DATE OF THE FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th May 2017

10 DATE OF REVISION OF THE TEXT