SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Nifencol 300 mg/ml solution for injection for cattle and pigs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:
Florfenicol .....300 mg

Excipients:
N-methylpyrrolidone……..250 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

Solution for injection.
Clear slightly yellowish solution.

4. CLINICAL PARTICULARS

4.1 Target species

Cattle and pigs.

4.2 Indications for use, specifying the target species

Cattle:
Metaphylaxis and treatment of respiratory tract infections in cattle due to *Histophilus somni*, *Mannheimia haemolytica* and *Pasteurella multocida*, susceptible to florfenicol.
The presence of the disease in the herd should be established before the product is used.

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

4.3 Contraindications

Do not use in adult bulls and boars intend for breeding purposes.
Do not use in cases of hypersensitivity to florfenicol or to any of the excipients.

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

This veterinary medicinal product does not contain an antimicrobial preservative.

Special precautions for use in animals
Do not administer to piglets of less than 2 kg.
Whenever possible, the veterinary medicinal product should be used based on susceptibility testing. Official, national and regional antimicrobial policies should be taken into account when the product is used.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
Care should be taken 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 water. Wash the hands after use.
People with known hypersensitivity to 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.

4.6 Adverse reactions (frequency and seriousness)

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.

Administration of the product by the intramuscular and subcutaneous routes may cause inflammatory lesions at injection site which persist for 14 days.

On very rare occasions, anaphylactic reactions have been reported in cattle.
In 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 dyspnea 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 and lactation

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

Cattle:
The safety of the veterinary medicinal product has not been established in cattle during pregnancy, lactation or in animals intended for breeding. 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.
Pig:
The safety of the veterinary medicinal product has not been established in pigs during pregnancy, lactation or in animals intended for breeding. 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..

4.8 Interaction with other medicinal products and other forms of interaction

None known.

4.9 Amounts to be administered and administration route

Cattle: Intramuscular or subcutaneous injection
Pig: intramuscular injection

Cattle:
<u>Treatment</u>
IM route: 20 mg florfenicol /kg bodyweight (1ml of the product/15kg) to be administered twice 48 hours apart using a 16 gauge needle.

SC route: 40 mg florfenicol /kg bodyweight (2ml of the product/15kg) to be administered once only using a 16 gauge needle.

<u>Metaphylaxis</u>
SC route: 40 mg florfenicol/kg bodyweight (2ml of the product/15kg) to be administered once only using a 16 gauge needle.

Pigs:
15 mg florfenicol/kg bodyweight (1 ml of the product / 20 kg) by intramuscular injection twice at 48 hour intervals using a 16-gauge needle.

The dose volume given at any one injection site should not exceed 10ml for both routes of administration (intramuscular and subcutaneous) in cattle and 3 ml in pigs. The injection should only be given in the neck in both target species.

To ensure a correct dosage body weight of the animals should be determined as accurately as possible to avoid underdosing.

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 or if relapse occurs, treatment should be changed using another formulation or another antibiotic and continued until clinical signs have resolved.

Swab septum before removing each dose. Use a dry sterile needle and syringe.

Do not broach the stopper of vial more than 25 times.

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

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

Cattle:
Meat and offal: by IM (at 20 mg/kg bodyweight, twice): 30 days
by SC (at 40 mg/kg bodyweight, once): 44 days

Milk: Not authorised for use in cattle producing milk for human consumption, including during the dry period.

Pigs:
Meat and offal: 18 days

5 PHARMACOLOGICAL 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 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 drugs 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 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

In cattle, intramuscular administration at the recommended dose of 20mg/kg maintains efficacious blood levels in cattle for 48 hours. Maximum mean plasma concentration (C_{max}) of 3.37µg/ml occurs at 3.3 hours (T_{max}) after dosing.
The mean plasma concentration 24 hours after dosing was 0.77µg/ml.

The administration of the product by subcutaneous route at the recommended dosage of 40mg/kg maintains bovine efficacious blood levels in cattle (ie above the MIC_{90} of the main respiratory pathogens) for 63 hours. Maximum plasma concentration (C_{max}) of approximately 5 µg/ml occurs approximately 5.3 hours

(T_{max}) after dosing. The mean plasma concentration 24 hours after dosing is approximately 2 µg/ml.

The elimination half life was 18.3 hours.

In pigs intravenously administered 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 plasma 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 plasma concentrations of between 3.7 and 3.8 µg/ml are reached after 1.8 hours. Plasma 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 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

Keep the vial in the outer carton in order to protect from light.

6.5 Nature and composition of immediate packaging

Polypropylene vial of 100 ml and 250 ml, closed with bromobutyl stopper secured with flip-off aluminium collar.
Package sizes:
Cardboard box with 1 vial of 100 ml

Cardboard box with 1 vial of 250 ml
Not all pack sizes may be marketed.

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

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

Vetpharma Animal Health, S.L.
Les Corts, 23
08028 Barcelona
Spain

8. MARKETING AUTHORISATION NUMBER

Vm 32509/4011

9. DATE OF FIRST AUTHORISATION

24 October 2013

10. DATE OF REVISION OF THE TEXT

November 2023

PROHIBITION OF SALE, SUPPLY AND/OR USE

Under veterinary prescription

Approved 23 January 2024