SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Resflor Veterinary

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains:

Active substances:

Florfenicol 300.0 mg
Flunixin meglumine 27.4 mg (equivalent to 16.5 mg of free flunixin)

Excipients:
N-Methyl-2-Pyrrolidone 250.0 mg
Propylene Glycol 150.0 mg

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for injection
Clear, light yellow to straw coloured liquid

4. CLINICAL PARTICULARS

4.1 Target species

Cattle.

4.2 Indications for use, specifying the target species

Therapeutic treatment of febrile respiratory tract infections caused by Mannheimia haemolytica, Pasteurella multocida, Mycoplasma bovis or histophilus somni in cattle.

4.3 Contraindications

Do not use in adult bulls intended for breeding purposes.
Do not use in animals suffering from hepatic and renal diseases.
Do not use if there is a risk of gastrointestinal bleeding or in cases where there is evidence of altered hemostasis.
Do not use in animals suffering from cardiac diseases.
Do not use in cases of hypersensitivity to the active substances or to any of the excipientslisted in section 6.1.

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

Special precautions for use in animals
Use of the 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 and local 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.
Avoid use in dehydrated, hypovolaemic or hypotensive animals as there is a potential risk of increased renal toxicity. Concurrent administration of potentially nephrotoxic drugs should be avoided.
Repeated daily dosing has been associated with abomasal erosions in the pre-ruminant calf. The product should be used with caution in this age group.
The safety of the product has not been tested in calves of 3 weeks of age or less.
Flunixin is toxic to avian scavengers. Do not administer to animals susceptible to enter wild fauna food chain. In case of death or sacrifice of treated animals, ensure that they are not made available to wild fauna.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
Care should be taken to avoid accidental self-injection.
People with known hypersensitivity to propylene glycol and polyethylene glycols should avoid contact with the veterinary medicinal product.
Wash hands after use.
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.

Special precautions for the protection of the environment:
Not applicable.

4.6 Adverse reactions (frequency and seriousness)

Cattle:

Very common (>1 animal / 10 animals treated):	Injection site swelling[1]
Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Anaphylactic-type reaction[2]

[1]becomes palpable 2-3 days after subcutaneous injection. The duration of the injection site swellings ranged from 15-36 days post-injection. Grossly, this is associated with minimal to mild irritation of the subcutis. Extension into the underlying muscle was noted in only a few

instances. By 56 days post-dosing, no gross lesions were observed that would require any trim-out at slaughter.
[2]these reactions may be fatal.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form **https://sideeffects.health.gov.il/**

4.7 Use during pregnancy, lactation or lay

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.

4.8 Interaction with other medicinal products and other forms of interaction

Concurrent use of other active substances that have a high degree of protein binding may compete with flunixin for binding and thus lead to toxic effects. Pre-treatment with other anti-inflammatory substances may result in additional or increased adverse effects and accordingly a treatment-free period with such drugs should be observed for at least 24 hours before the commencement of treatment. The treatment-free period, however, should take into account the pharmacokinetic properties of the products used previously.
The product must not be administered in conjunction with other NSAIDs or glucocorticosteroids. Gastrointestinal tract ulceration may be exacerbated by corticosteroids in animals given NSAIDs.

4.9 Amounts to be administered and administration route

Subcutaneous use.
40 mg/kg florfenicol and 2.2 mg/kg flunixin (2 mL/15 kg body weight) to be administered by a single injection.
The dose volume given at any one injection site should not exceed 10 mL.

It is recommended to treat animals in the early stages of the disease and to evaluate the response to treatment 48 hours after injection. The anti-inflammatory component of the veterinary medicinal product, flunixin, may mask a poor bacteriological response to florfenicol in the first 24 hours after 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.

The injection should only be given in the neck.

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

To ensure a correct dosage, body weight should be determined as accurately as possible.

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

Overdose studies in the target species for 3 times the duration of treatment showed decreased food consumption in the groups given 3 and 5 times the recommended dose. Decreased body weights were observed in the 5 times overdose group (secondary to decreased food consumption). Decreased water consumption was observed in the 5 times overdose group. Tissue irritation increases with injection volume.
Treatment at 3 times the recommended treatment duration was associated with dose-related erosive and ulcerative abomasum lesions.

4.11 Withdrawal periods

Meat and offal: 46 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 within 2 months of expected parturition.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: antibacterials for systemic use, amphenicols, combinations
ATCvet code: QJ01BA99

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 bacterial 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 bovine respiratory disease which include *Mycoplasma bovis, Mannheimia haemolytica, Pasteurella multocida* and *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*.

Florfenicol bactericidal activity was characterised as essentially time dependant against the three target pathogens with the possible exception of *H. somni* where a concentration dependency was observed.
During the florfenicol susceptibility monitoring program (2000-2003) a total of 487 *M. haemolytica*, 522 *P. multocida* and 25 *H. somni* isolates were collected. MIC values ranged between <0.12 and 2 µg/ml for *M. haemolytica* (MIC_{90} = 1 µg/ml), between <0.12 and 2 µg/ml for *P. multocida* (MIC_{90} = 0.50 µg/ml) and between 0.12 and 0.5 µg/ml for *H. somni*.

Breakpoints have been established by the CLSI (Clinical and Laboratory Standard Institute) for bovine respiratory pathogens as follows:

Pathogen	Florfenicol Disk Concentration (µg)	Diameter (mm)			MIC (µg/ml)		
		S	I	R	S	I	R
M. haemolytica *P. multocida* *H. somni*	30	≥ 19	15-18	≤ 14	≤ 2	4	≥ 8

There are no established breakpoints for *Mycoplasma bovis* nor have culture techniques been standardized by CLSI. Despite a reduction in *Mycoplasma bovis* pathogen load, *Mycoplasma bovis* may not be fully eliminated from the lungs after treatment with the veterinary medicinal product.

The only mechanisms of chloramphenicol resistance that are known to have significant clinical relevance are CAT-mediated inactivation and efflux-pump resistance. Of these, only some of the efflux mediated resistance would also confer resistance to florfenicol and thus have the potential to be affected by florfenicol use in animals. Resistance to florfenicol in the target pathogens has only been reported on rare occasions and was associated with efflux pump and the presence of the *flo*R gene.

Flunixin meglumine is a non-steroidal anti-inflammatory drug with analgesic and antipyretic activity.
Flunixin meglumine acts as a reversible non-selective inhibitor of cyclo-oxygenase (both COX 1 and COX 2 forms), an important enzyme in the arachidonic acid cascade pathway which is responsible for converting arachidonic acid to cyclic endoperoxides. Consequently, synthesis of eicosanoids, important mediators of the inflammatory process involved in central pyresis, pain perception and tissue inflammation is inhibited. Through its effects on the arachidonic acid cascade, flunixin also inhibits the production of thromboxane, a potent platelet pro-aggregator and vasoconstrictor which is released during blood clotting. Flunixin exerts its antipyretic effect by inhibiting prostaglandin E2 synthesis in the hypothalamus. Although flunixin has no direct effect on endotoxins after they have been produced, it reduces prostaglandin production and hence reduces the many effects of the prostaglandin cascade. Prostaglandins are part of the complex processes involved in the development of endotoxic shock.

5.2 Pharmacokinetic particulars

The administration of the product by the subcutaneous route at the recommended dosage of 40 mg/kg florfenicol maintained efficacious plasma levels in cattle above a MIC_{90} of 1 µg/mL for approximately 50 hours and above a MIC_{90} of 2 µg/mL for approximately 36 hours. Maximum plasma concentration (Cmax) of approximately 9.9 µg/mL occurred approximately 8 hours (Tmax) after dosing.

After administration of the product by the subcutaneous route at the recommended dosage of 2.2 mg/kg flunixin, peak plasma concentrations of 2.8 µg/mL were achieved after 1 hour.

The binding of florfenicol on proteins is approximately 20% and for flunixin > 99%. The degree of elimination of florfenicol residues in urine is approximately 68% and in faeces approximately 8%. The degree of elimination of flunixin residues in urine is approximately 34% and for faeces approximately 57%.

5.3 Environmental properties

Flunixin is toxic to avian scavengers although foreseen low exposure leads to low risk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipientsN-methyl-2-pyrrolidone
Propylene glycol
Citric acid
Macrogol

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

The expiry date of the product is indicated on the packaging materials.
Shelf life after first opening the immediate packaging: 28 days.

6.4 Special precautions for storage

Do not store above 25°C.
Do not freeze. Protect from frost.

6.5 Nature and composition of immediate packaging

Type I glass vials closed with bromobutyl stoppers and aluminium seals.

Carton box containing 100 mL vial
Carton box containing 250 mL vial

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

Medicines should not be disposed of via wastewater.

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MANUFACTURER

Vet Pharma Friesoythe
Sedelsbergerstrasse 2, 26169 Friesoythe, Germany

8. NAME OF REGISTRATION HOLDER

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9. LICENSE NUMBER
146-43-92424-00

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