

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Flortekxin 300 mg/ml + 16.5 mg/ml solution for injection for cattle

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substances:

Florfenicol 300.0 mg

Flunixin 16.5 mg

(as flunixin meglumine)

Excipients:

Qualitative composition of excipients and other constituents	Quantitative composition if that information is essential for proper administration of the veterinary medicinal product
Propylene glycol (E1520)	150.0 mg
N-methylpyrrolidone	250.0 mg
Citric acid	-
Macrogol 300	-

Clear, yellow, free from visible particles solution for injection.

3. CLINICAL INFORMATION

3.1 Target species

Cattle

3.2 Indications for use for each target species

Treatment of respiratory infections caused by *Histophilus somni*, *Mannheimia haemolytica*, *Pasteurella multocida* and *Mycoplasma bovis*, associated with pyrexia.

3.3 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 excipients.

3.4 Special warnings

Cross-resistance has been shown between florfenicol and chloramphenicol. Use of the veterinary medicinal product should be carefully considered when susceptibility testing has shown resistance to florfenicol and other amphenicols because its effectiveness may be reduced.”.

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.

There is no bacterial eradication of *Mycoplasma bovis*.

3.5 Special precautions for use

Special precautions for safe use in the target species:

Use of the veterinary medicinal product should be based on identification and susceptibility testing of the target pathogen(s). If this is not possible, therapy should be based on epidemiological information and knowledge of susceptibility of the target pathogens at farm level, or at local/regional level. Use of the product should be in accordance with official, national and regional antimicrobial policies. Use of the veterinary medicinal product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to florfenicol.

An antibiotic with a lower risk of antimicrobial resistance selection (lower AMEG category) should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach.

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 veterinary medicinal product should be used with caution in this age group.

The safety of the veterinary medicinal product has not been tested in calves of 3 weeks of age or less.

Not for use for prophylaxis or metaphylaxis.

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. 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 hypersensitivity. People with known hypersensitivity to propylene glycol and 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.

Wash hands after use.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Cattle:

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Anaphylactic reactions (sometimes fatal)
Undetermined frequency (cannot be estimated from the available data)	Injection site swelling ¹ , injection site irritation ²

¹Become palpable 2-3 days after injection. The duration ranged from 15-36 days post-injection.

²Minimal to mild irritation of the subcutis. Extension into the underlying muscle was note only a few instances. By 56 days post-dosing, no gross lesions were observed that would require any trim-out at slaughter.

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 the 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 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.

Fertility:

Do not use in adult bulls intended for breeding (see section 3.3)

3.8 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 veterinary medicinal products used previously. The veterinary medicinal product must not be administered in conjunction with other NSAIDs or glucocorticosteroids. Gastrointestinal tract ulceration may be exacerbated by corticosteroids in animals given NSAIDs.

3.9 Administration routes and dosage

Subcutaneous use.

40 mg/kg florfenicol and 2.2 mg/kg flunixin (2 ml/15 kg body weight) to be administered by a single subcutaneous injection. The dose volume given at any one injection 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 within the 48 hours after injection. The anti-inflammatory component of this 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 persists or increases, or if relapse occurs, treatment should be changed, using another antibiotic, and continue 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.

For 100 ml vial: The cap may be safely punctured up to 20 times.

For 250 ml vial: The cap may be safely punctured up to 40 times.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

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.

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

Not applicable.

3.12 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.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QJ01BA99

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 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 *Histophilus somni*, *Mannheimia haemolytica*, *Pasteurella multocida* and *Mycoplasma bovis*.

Florfenicol is considered to be a bacteriostatic agent, but in vitro studies of florfenicol demonstrate bactericidal activity against *Histophilus somni*, *Mannheimia haemolytica* and *Pasteurella multocida*. 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.

Breakpoints have been established by the CLSI (Clinical and Laboratory Standard Institute) in 2018 for bovine respiratory pathogens as follows:

Pathogen	Florfenicol Disk Concentration (µg)	MIC (µg/ml)		
		S	I	R
<i>M. haemolytica</i> <i>P. multocida</i> <i>H. somni</i>	30	≤ 2	4	≥ 8

There are no established breakpoints for *Mycoplasma bovis* nor have culture techniques been standardized by CLSI. The only mechanisms of chloramphenicol resistance that are known to have significant clinical relevance are CAT (Chloramphenicol acetyltransferases)-mediated inactivation and efflux-pump resistance and RNA methyltransferases. 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 *floR* 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.

4.3 Pharmacokinetics

The administration of the veterinary medicinal product by the subcutaneous route at the recommended dosage of 40 mg/kg florfenicol maintained efficacious plasma levels in cattle above a MIC90 of 1 microgram/mL for approximately 50 hours and above a MIC90 of 2 microgram/mL for approximately 36 hours. Maximum plasma concentration (C_{max}) of approximately 9.9 microgram/mL occurred approximately 8 hours (T_{max}) after dosing. After administration of the veterinary medicinal product by the subcutaneous route at the recommended dosage of 2.2 mg/kg flunixin, peak plasma concentrations of 2.8 microgram/mL were achieved after 1 hour. The binding of florfenicol on proteins is approximately 20% and for flunixin > 99%. The degree of excretion of florfenicol residues in urine is approximately 68% and in faeces approximately 8%. The degree of excretion of flunixin residues in urine is approximately 34% and for faeces approximately 57%.

Environmental properties

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

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: 26 months

Shelf life after first opening the immediate packaging: 28 days

5.3 Special precautions for storage

Do not store above 30 °C.

5.4 Nature and composition of immediate packaging

COEX (PP/Adhesive/EVOH/Adhesive/PP) vial closed with bromobutyl rubber stopper type I and aluminium cap with plastic lid.

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.

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.

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 Karizoo, S.A.

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

Date of first authorisation

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

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 \(https://medicines.health.europa.eu/veterinary\)](https://medicines.health.europa.eu/veterinary).