SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Flovuxin 300/16.5 mg/ml solution for injection for cattle

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substances:

Florfenicol	300.0 mg
Flunixin (as flunixin meglumine)	16.5 mg

Excipients:

Propylene glycol E1520	150.0 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection
Solution for injection is a clear, slightly yellow to yellow or to greenish yellow solution or to brownish yellow solution.

4. CLINICAL PARTICULARS

4.1 Target species

Cattle

4.2 Indications for use, specifying the target species

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

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 excipients.

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

i) 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.

ii) Special precautions to be taken by the person administering the veterinary medicinal product to animals

This product may cause adverse effects. 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 veterinary medicinal product may cause hypersensitivity reactions (allergy). People with known hypersensitivity to propylene glycol and polyethylene glycols should avoid contact with the veterinary medicinal product. If you develop symptoms following exposure, such as skin rash, swelling of the face, lips or eyes or difficulty with breathing, you should seek medical advice immediately and show the package leaflet or the label to the physician.
Wash hands after use.

4.6 Adverse reactions (frequency and seriousness)

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

[1]Those reactions might be fatal.
[2]Subcutaneous administration of the product may result in application site swelling that become palpable 2-3 days after injection. The duration of the application site swelling 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.

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 also section 16 of the package leaflet for respective contact details.

4.7 Use during pregnancy, lactation or lay

The effect of florfenicol on bovine reproductive performance, pregnancy and lactation has not been assessed. Use only accordingly 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 Amount to be administered and administration route

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

The cap may be safely punctured up to 25 times. 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.
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 this veterinary product, flunixin, may mask resistance 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 to avoid underdosing.

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 period(s)

Meat and offal: 46 days.
Milk: Not authorised for use in animals producing milk for human consumption. Do not use during lactation or drying off periods. 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 *Mannheimia haemolytica, Pasteurella multocida, Mycoplasma bovis* 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 dependent against the three target pathogens with the possible exception of *H. somni* where a concentration dependency was observed.
Surveillance data of the susceptibility of target field isolates from cattle, collected between 2009 and 2012 across Europe, show consistent efficacy of florfenicol with no finding of resistant isolates. The in vitro Minimum Inhibitory Concentration (MIC) values for these field isolates are presented in the table below.

Species	MIC50 (µg/ml)	MIC90 (µg/ml)
Mannheimia haemolytica (n=149)	1.0	1.0
Pasteurella multocida (n=152)	0.5	0.5
Histophilus somni (n=66)	0.25	0.25

Breakpoints have been established by the Clinical and Laboratory Standard Institute (CLSI VET08 ED4: 2018) 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.

Resistance to florfenicol is mainly mediated by an efflux system due to a specific (Flo-R) or multidrug transporter (AcrAB-TolC). The genes corresponding to these mechanisms are coded on mobile genetic elements such as plasmids, transposon or genes cassettes. 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. Cross resistance with the third-generation cephalosporins is possible and has been observed in respiratory and digestive *E. coli*.

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 (C_{max}) of approximately 9.9 µg/mL occurred approximately 8 hours (T_{max}) 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 excipients

Propylene glycol (E1520)
N-methylpyrrolidone
Citric acid
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

Do not store above 25 °C.
Store in the original package.

6.5 Nature and composition of immediate packaging

Type II clear glass bottles of 100 ml and type I clear glass bottles of 250 ml with type I bromobutyl rubber stoppers and aluminium caps with plastic tear/flip-off tabs, in a cardboard box.

Package sizes:
Cardboard box containing 1 bottle of 100 ml.
Cardboard box containing 1 bottle 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

KRKA, d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

8. MARKETING AUTHORISATION NUMBER/RENEWAL OF THE AUTHORISATION

Vm 01656/5033

9. DATE OF FIRST AUTHORISATION

21 December 2020

10. DATE OF REVISION OF THE TEXT

March 2023

11. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Approved 17 March 2023