[Version 9.1,11/2024]

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Interflox-100 100 mg/ml solution for injection for cattle, sheep, goats and pigs (BG, CY, CZ, EE, EL, FR, HU, IT, LV, MT, PT, RO, SI, SK)
Interflox 100 mg/ml solution for injection for cattle, sheep, goats and pigs (AT, ES, HR, PL)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substances:
Enrofloxacin 100,0 mg

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
n-butanol	30,0 mg
Potassium hydroxide (for pH adjustment)	
Water for injections	

Clear, light-yellow solution, free from visible particles.

3. CLINICAL INFORMATION

3.1 Target species

Cattle, sheep, goats, pigs.

3.2 Indications for use for each target species

Cattle
Treatment of infections of the respiratory tract caused by enrofloxacin susceptible strains of *Pasteurella multocida*, *Mannheimia haemolytica* and *Mycoplasma* spp.
Treatment of acute severe mastitis caused by enrofloxacin susceptible strains of *Escherichia coli*.
Treatment of infections of the alimentary tract caused by enrofloxacin susceptible strains of *Escherichia coli*.
Treatment of septicaemia caused by enrofloxacin susceptible strains of *Escherichia coli*.
Treatment of acute mycoplasma-associated arthritis due to enrofloxacin susceptible strains of *Mycoplasma bovis* in cattle less than 2 years old.

Sheep
Treatment of infections of the alimentary tract caused by enrofloxacin susceptible strains of *Escherichia coli*.
Treatment of septicaemia caused by enrofloxacin susceptible strains of *Escherichia coli*.
Treatment of mastitis caused by enrofloxacin susceptible strains of *Staphylococcus aureus* and *Escherichia coli*.

Goats
Treatment of infections of the respiratory tract caused by enrofloxacin susceptible strains of *Pasteurella multocida* and *Mannheimia haemolytica*.

Treatment of infections of the alimentary tract caused by enrofloxacin susceptible strains of *Escherichia coli*.
Treatment of septicaemia caused by enrofloxacin susceptible strains of *Escherichia coli*.
Treatment of mastitis caused by enrofloxacin susceptible strains of *Staphylococcus aureus* and *Escherichia coli*.

Pigs
Treatment of infections of the respiratory tract caused by enrofloxacin susceptible strains of *Pasteurella multocida*, *Mycoplasma* spp. and *Actinobacillus pleuropneumoniae*.
Treatment of infections of the urinary tract caused by enrofloxacin susceptible strains of *Escherichia coli*.
Treatment of post-partum dysgalactiae syndrome, PDS (MMA syndrome) caused by enrofloxacin susceptible strains of *Escherichia coli* and *Klebsiella* spp.
Treatment of infections of the alimentary tract caused by enrofloxacin susceptible strains of *Escherichia coli*.
Treatment of septicaemia caused by enrofloxacin susceptible strains of *Escherichia coli*.

3.3 Contraindications

Do not use in cases of hypersensitivity to the active substance or other fluoroquinolones or to any of the excipients.

Do not use in growing horses because of possible deleterious damage on articular cartilage.

3.4 Special warnings

None.

3.5 Special precautions for use

Special precautions for safe use in the target species:

Official and local antimicrobial policies should be taken into account when the veterinary medicinal product is used.

Fluoroquinolones should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to other classes of antimicrobials.

Whenever possible, fluoroquinolones should only be used based on susceptibility testing.

Use of the veterinary medicinal product including use deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to enrofloxacin and may decrease the effectiveness of treatment with all fluoroquinolones due to the potential for cross-resistance.

Degenerative changes of articular cartilage were observed in calves treated orally with 30 mg enrofloxacin/kg body weight during 14 days.

The use of enrofloxacin in growing lambs at the recommended dose for 15 days caused histological changes in the articular cartilage, not associated with clinical signs.

Enrofloxacin is eliminated renally. As with all fluoroquinolones, delayed excretion can therefore be expected in the presence of existing renal damage.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
People with known hypersensitivity to fluoroquinolones should avoid any contact with the veterinary medicinal product.

Avoid skin and eye contact. Wash any splashes from skin or eyes immediately with water. Wash hands after use. Do not eat, drink or smoke whilst handling the veterinary medicinal product.

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.

Special precautions for the protection of the environment:

Not applicable.

Other precautions:

In countries where feeding of fallen stock to scavenger bird populations is permitted as a conservation measure (see Commission Decision 2003/322/EC), the possible risk to hatching success should be considered before feeding carcasses of livestock recently treated with this veterinary medicinal product.

3.6 Adverse events

Cattle, sheep, goats, pigs:

Very rare (<1 animal / 10 000 animals treated, including isolated reports):	Shock[1] Digestive tract disorders (e.g. Diarrhoea)[2]
Undetermined frequency (cannot be estimated from the available data):	Injection site inflammation[3]

[1] In cattle, after intravenous administration, presumably as a result of circulatory impairment.
[2] Generally mild and transient.
[3] In pigs, after intramuscular administration, may persist up to 28 days after the injection.

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 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

Pregnancy and lactation:

Cattle:
The safety of the veterinary medicinal product has been established in pregnant cows during the 1st quarter of pregnancy. The veterinary medicinal product can be used in pregnant cows during the 1st quarter of pregnancy.
The use of the veterinary medicinal product in cows during the 3 last quarters of pregnancy should be based on a benefit-risk assessment by the responsible veterinarian.
Can be used in cows during lactation.

Sheep and goats:
The safety of the veterinary medicinal product has not been established during pregnancy and lactation. Use only accordingly to the benefit-risk assessment by the responsible veterinarian.

Pigs:
The safety of the veterinary medicinal product has not been established during pregnancy. Use only accordingly to the benefit-risk assessment by the responsible veterinarian.

Can be used in sows during lactation.

3.8 Interaction with other medicinal products and other forms of interaction

Do not use enrofloxacin concomitantly with antimicrobial substances acting antagonistically to quinolones (e.g. macrolides, tetracyclines or phenicols).

Do not use concurrently with theophylline as the elimination of theophylline may be delayed.

3.9 Administration routes and dosage

Cattle: intravenous use.
Cattle, sheep, goats: subcutaneous use.
Pigs: intramuscular use.

Repeated injections should be made at different injection sites.
To ensure a correct dosage, body weight (bw) should be determined as accurately as possible to avoid underdosing.

Cattle
5 mg of enrofloxacin per 1 kg bw, corresponding to 1 ml of product per 20 kg bw, once daily for up to 3–5 consecutive days.

Acute mycoplasma-associated arthritis due to enrofloxacin susceptible strains of *Mycoplasma bovis* in cattle less than 2 years old: 5 mg of enrofloxacin per 1 kg bw, corresponding to 1 ml of product per 20 kg bw, once daily for up to 5 consecutive days.

The product can be administered by slow intravenous or subcutaneous administration.

Acute mastitis caused by *Escherichia coli*: 5 mg enrofloxacin per 1 kg bw, corresponding to 1 ml of product per 20 kg bw, by slow intravenous injection once daily for up to 2 consecutive days.
The second dose may be administered by the subcutaneous route. In this case, the withdrawal period following subcutaneous injection applies.

Not more than 10 ml should be administered at one subcutaneous injection site.

Sheep and goats
5 mg of enrofloxacin per 1 kg bw, corresponding to 1 ml of product per 20 kg bw, once daily by subcutaneous injection for up to 3 consecutive days.
Not more than 6 ml should be administered at one subcutaneous injection site.

Pigs
2.5 mg of enrofloxacin per 1 kg bw, corresponding to 0.5 ml of product per 20 kg bw, once daily by intramuscular injection for up to 3 consecutive days.

Alimentary tract infection, or septicaemia caused by *Escherichia coli*: 5 mg of enrofloxacin per 1 kg bw, corresponding to 1 ml of product per 20 kg bw, once daily by intramuscular injection for up to 3 consecutive days.
In pigs, the injection should be made in the neck at the ear base.
Not more than 3 ml should be administered at one intramuscular injection site.

The rubber stopper can be safely punctured for up to 15 times.

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

In cases of accidental overdoses, digestive tract disorders (e.g. vomiting, diarrhoea) and neurological disorders may occur.

In pigs, no adverse effects were reported after the administration of 5 times the recommended dose.

In cattle, sheep and goats, overdose has not been documented.

In accidental overdose, there is no antidote and treatment should be symptomatic.

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

Cattle: *Following intravenous injection:*
Meat and offal: 5 days.
Milk: 3 days.

Following subcutaneous injection:
Meat and offal: 12 days.
Milk: 4 days.

Sheep: Meat and offal: 4 days.
Milk: 3 days.

Goats: Meat and offal: 6 days.
Milk: 4 days.

Pigs: Meat and offal: 13 days.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QJ01MA90

4.2 Pharmacodynamics

Mode of action
Two enzymes essential in DNA replication and transcription, DNA gyrase and topoisomerase IV, have been identified as the molecular targets of fluoroquinolones. Target inhibition is caused by non-covalent binding of fluoroquinolone molecules to these enzymes. Replication forks and translational complexes cannot proceed beyond such enzyme- DNA-fluoroquinolone complexes, and inhibition of DNA and mRNA synthesis triggers events resulting in a rapid, drug concentration- dependent killing of pathogenic bacteria. The mode of action of enrofloxacin is bactericidal and bactericidal activity is concentration dependent.

Antibacterial spectrum
Enrofloxacin is active against many Gram-negative bacteria such as *Escherichia coli*, *Klebsiella* spp., *Actinobacillus pleuropneumoniae*, *Mannheimia haemolytica*, *Pasteurella* spp. (e.g. *Pasteurella multocida*), against Gram-positive bacteria such as *Staphylococcus* spp. (e.g. *Staphylococcus aureus*) and against *Mycoplasma* spp. at the recommended therapeutic doses.

Types and mechanisms of resistance

Resistance to fluoroquinolones has been reported to arise from five sources, (i) point mutations in the genes encoding for DNA gyrase and/or topoisomerase IV leading to alterations of the respective enzyme, (ii) alterations of drug permeability in Gram-negative bacteria, (iii) efflux mechanisms, (iv) plasmid mediated resistance and (v) gyrase protecting proteins. All mechanisms lead to a reduced susceptibility of the bacteria to fluoroquinolones. Cross-resistance within the fluoroquinolone class of antimicrobials is common.

The following Minimum Inhibitory Concentrations (MIC) have been determined for enrofloxacin in European isolates of target bacteria, isolated from diseased animals:

Cattle							
Species	**Country**	**Period**	**Number of isolates**	**MIC_{50} (µg/ml)**	**MIC_{90} (µg/ml)**	**Resistance (%)**	**Ref**
Pasteurella multocida	EU	2009 – 2012	134	0.015	0.03	3.0	(1)
	Czech Rep.	2017	41	≤ 0.06	0.25	2.4	(2)
Mannheimia haemolytica	EU	2009 – 2012	149	0.03	0.25	0.7	(1)
	Czech Rep.	2017	26	≤ 0.06	1	7.7	(2)
Mycoplasma bovis (respiratory)	EU	2010 – 2012	156	0.25	4	n.a.	(3)
Mycoplasma bovis (various infections)	France	2010 – 2012	143 (136 resp, 3 arthritis, 3 otitis, 1 mastitis)	0.5	0.5	n.a.	(4)
Escherichia coli (mastitis)	EU	2009 – 2012	207	0.03	0.06	n.a.	(5)
	Czech Rep.	2017	57	≤ 0.03	0.06	n.a.	(6)
Escherichia coli	Czech Rep.	2017	73	≤ 0.03	> 4	n.a.	(6)
Pigs							
Species	**Country**	**Period**	**Number of isolates**	**MIC_{50} (µg/ml)**	**MIC_{90} (µg/ml)**	**Resistance (%)**	**Ref**
Pasteurella multocida	EU	2009 – 2012	152	0.008	0.03	0.0	(1)
	Czech Rep.	2017	31	≤ 0.06	0.125	0.0	(2)
Actinobacillus pleuropneumoniae	EU	2009 – 2012	158	0.03	0.06	1.3	(1)
	Czech Rep.	2017	27	≤ 0.06	0.25	0.0	(2)
Mycoplasma hyopneumoniae	EU	2010 – 2012	50	0.03	0.5	n.a.	(3)
Escherichia coli	Czech Rep.	2017	108	≤ 0.03	0.5	n.a.	(6)
Sheep							
Species	**Country**	**Period**	**Number of isolates**	**MIC_{50} (µg/ml)**	**MIC_{90} (µg/ml)**	**Resistance (%)**	**Ref**
Staphylococcus aureus (mastitis)	Spain	n.d.	12	0.25	0.5	n.a.	(7)
Goats							
Species	**Country**	**Period**	**Number of isolates**	**MIC_{50} (µg/ml)**	**MIC_{90} (µg/ml)**	**Resistance (%)**	**Ref**
Staphylococcus aureus (mastitis)	Spain	n.d.	12	0.125	0.18	n.a.	(7)

n.a. – not applicable; n.d. – not determined; (1) Veterinary Microbiology 2016, 194:11-22; (2) State Veterinary Institute Jihlava, Czech Republic. Národní program sledování rezistencí k antimikrobikům u veterinárně významných patogenů za rok 2017 část I; (3) Veterinary Microbiology 2017, 204:188-193; (4) PLOS One, 2014, 9:e87672; (5) Veterinary Microbiology 2018, 213:73-81; (6) State Veterinary Institute Jihlava, Czech Republic. Národní program sledování rezistencí k antimikrobikům u veterinárně významných patogenů za rok 2017 část II; (7) Veterinary Record 2017, 180:376.

Enrofloxacin resistance breakpoints (R) are available for *Mannheimia haemolytica* and *Pasteurella multocida* isolated from cattle (R ≥ 2 µg/ml, CLSI document VET08, 4th ed., 2018) and for *Pasteurella multocida* and *Actinobacillus pleuropneumoniae* isolated from pigs (R ≥ 1 µg/ml, CLSI document VET08, 4th ed., 2018).

4.3 Pharmacokinetics

Enrofloxacin is rapidly absorbed after parenteral injection. Bioavailability is high (approximately 100% in pig and cattle) with a low to moderate plasma protein binding (approximately 20 to 50%). Enrofloxacin is metabolised to the active substance ciprofloxacin at approximately 40% in ruminants and less than 10% in pigs.
Enrofloxacin and ciprofloxacin distribute well into all target tissues, e.g. lung, kidney, skin and liver, reaching 2- to 3-fold higher concentrations than in plasma. Parent substance and active metabolite are cleared from the body via urine and faeces.

Accumulation in plasma does not occur following a treatment interval of 24 h.
In milk, most of drug activity consists on ciprofloxacin. Overall drug concentrations peak at 2 hours after treatment showing an approximately 3-fold higher total exposure over the 24 hours dosing interval compared to plasma.

	Pigs	Pigs	Cattle	Cattle
Dose rate (mg/kg bw)	2.5	5	5	5
Route of administration	im	im	iv	sc
Tmax (h)	2	2	/	3.5
Cmax (µg/ml)	0.7	1.6	/	0.733
AUC (µg·h/ml)	6.6	15.9	9.8	5.9
Terminal half-life (h)	13.12	8.10	/	7.8
Elimination half-life (h)	7.73	7.73	2.3	/
F (%)	95.6	/	/	88.2

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: 3 years.
Shelf life after first opening the immediate packaging: 28 days.

5.3 Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.
After first opening the immediate packaging do not store above 25 °C.

5.4 Nature and composition of immediate packaging

100 ml amber glass bottles (type I) closed with bromobutyl rubber stopper and aluminium cap or flip-off cap with aluminium seal and polypropylene cover in cardboard box.

Pack size:
Cardboard box with 1 glass bottle of 100 ml.

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

Interchemie Werken De Adelaar Eesti AS

7. MARKETING AUTHORISATION NUMBER(S)

To be completed in accordance with national requirements after conclusion of the MR phase.

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: *To be completed in accordance with national requirements after conclusion of the MR phase.*

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

{MM/YYYY}

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).