[Version 9,03/2022] corr. 11/2022

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Enrocill Flavour 150 mg tablets for dogs (ES, PT)
Enro-Sleecol Flavour 150 mg tablets for dogs (DE)
Enroxil Flavour 150 mg tablets for dogs (EL)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Active substance:
Enrofloxacin 150 mg

Excipients:

Qualitative composition of excipients and other constituents
Mannitol
Maize starch
Sodium starch glycolate (type A)
Meat flavour 10022
Sodium laurilsulfate
Basic butylated methacrylate copolymer
Dibutyl sebacate
Croscarmellose sodium
Silica, colloidal anhydrous
Talc
Magnesium stearate

Round slightly biconvex, cream to light brownish tablets with possible visible white or darker spots, one side scored and bevel-edged.
The tablets can be divided into halves.

3. CLINICAL INFORMATION

3.1 Target species

Dogs.

3.2 Indications for use for each target species

In dogs:
Treatment of infections caused by strains of *Staphylococcus* spp., *E. coli, Haemophilus* spp. *Pasteurella* spp. and *Salmonella* spp. susceptible to enrofloxacin.

The veterinary medicinal product is indicated for treatment of mono or mixed bacterial infections of the respiratory, digestive and urinary tract, otitis externa, skin and wound infections.

3.3 Contraindications

Do not use in dogs less than 1 year of age or in exceptionally large breeds of dog with a longer growth period less than 18 months of age, as articular cartilage may be affected during the period of rapid growth.

Do not use in cases of hypersensitivity to the active substance or to any of the excipients.
Do not use in dogs having seizure disorders, since enrofloxacin may cause CNS stimulation.
Do not use in cases of known resistance to (fluoro)quinolones.
Please, see section 3.7.

3.4 Special warnings

None.

3.5 Special precautions for use

Special precautions for safe use in the target species:

Flouroquinolones should be reserved for the treatment of clinical conditions that 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. Official and local antimicrobial policies should be taken into account when the veterinary medicinal product is used. Use of the veterinary medicinal product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to fluoroquinolones and may decrease the effectiveness of treatment with other quinolones due to the potential cross resistance.
If there is no clinical improvement within three days, further susceptibility testing and possibly a change in antimicrobial therapy should be considered.
Use the veterinary medicinal product with caution in or dogs with severe renal or hepatic impairment.

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

People with known hypersensitivity to fluoroquinolones should avoid contact with the veterinary medicinal product.
In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
Avoid contact with the eyes. In case of contact with the eyes, wash immediately with water.
Wash hands after use.
Do not smoke, eat or drink while handling the veterinary medicinal product.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Dogs:

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Central nervous system disorder Digestive tract disorder Hypersensitivity reaction
Undetermined frequency (cannot be estimated from the available data):	Joint cartilage disorder[1]

[1]In growing puppies (see section 3.3).

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

Do not use during pregnancy and lactation.

3.8 Interaction with other medicinal products and other forms of interaction

Do not combine with tetracyclines, phenicols or macrolides because of potential antagonistic effects.
Do not combine with theophylline as this could lead to a prolonged elimination of this substance.
Do not use simultaneously with NSAIDs (convulsions may occur).
Concurrent use of flunixin and enrofloxacin should be under careful veterinary monitoring, as the interactions between these drugs may lead to adverse events related to delayed elimination.
Concurrent administration of magnesium, calcium or aluminum containing substances may be followed by retarded absorption of enrofloxacin.
Excessive alkalinisation of the urine should be avoided in animals subjected to rehydration.

3.9 Administration routes and dosage

Tablets may be given directly into the mouth or masked in food.

The dosage rate of enrofloxacin is 5 mg/kg/day (i.e. one 150 mg tablet per 30 kg per day), for 5 days. In chronic and severe cases, treatment duration can be extended to 10 days.

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

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

In case of overdose, sickness, vomiting, diarrhoea, and CNS/behavioural changes may occur and the treatment must be suspended.

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

Not applicable.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QJ01MA90.

4.2 Pharmacodynamics

Enrofloxacin is an antibiotic that belongs to the chemical class of fluoroquinolones. The compound exerts bactericidal activity via mechanism of action based on the inhibition of the A subunit of DNA gyrase (topoisomerase II). In Gram positive bacteria the primary target is topoisomerase IV instead of topoisomerase II. With this mechanism enrofloxacin blocks the replication, transcription and recombination of bacterial DNA.

Fluoroquinolones also act on bacterial cells during stationary phase by changing the permeability in the phospholipid cellular membranes. These mechanisms explain the rapid loss of viability of the

bacteria exposed to enrofloxacin. Inhibitory and bactericidal concentrations of enrofloxacin are strongly correlated. They are either equal, or differ in 1-2 dilution steps.

Antibacterial spectrum: *Staphylococcus* spp, *Escherichia coli, Haemophilus* spp., *Pasteurella* spp., *Salmonella* spp.

The enrofloxacin *in vitro* activity against pathogens isolated from canine respiratory, urinary and soft tissue infections in Europe, is good: MIC50 values are comprised between 0.03 and 0.12 µg/ml for *Escherichia coli*, 0.015 µg/ml for *Pasteurella* spp., and 0.12 µg/ml for *Staphylococcus* spp. Susceptibility breakpoints for enrofloxacin used in Enterobacteriaceae and *Staphylococcus* spp. (in dogs) have been determined as ≤ 0,5 µg/ml for sensitive, 1-2 µg/ml for intermediate and ≥ 4 µg/ml for resistant bacterial strains (CLSI, 2013).

Several Susceptibility pan-European surveillances to investigate the susceptibility to enrofloxacin of bacterial strains isolated to several pathologies in target species have been conducted. See main results below.

Susceptibility of dogs' respiratory pathogens

Bacteria	Resistant (%)	MIC50	MIC90
S. intermedius	4.1	0.12	0.5
E. colli	12.5	0.06	>8
P. multocida	NA	0.015	0.015

NA: No breakpoints were available; standardised agar dilution methodology (Morrisey et al., 2016)

Susceptibility of dogs' urinary tract pathogens

Bacteria	Resistant (%)	MIC50	MIC90
E. colli	3.9	0.03	0.06
S. intermedius	3.0	0.12	0.25

Standardized agar dilution methodology (Moyaert et al., 2017)

Susceptibility of dogs' pathogens involved in skin infections.

Bacteria	Resistant (%)	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)
S. pseudointermedius	5.2	0.12	0.5
S. aureus	2.2	0.12	0.25
E. coli	3.7	0.06	0.12
Pasteurella spp.	NA	0.015	0.015

NA: No breakpoints were available (Ludwig et al., 2016)

Resistance to fluoroquinolones occurs by chromosomal mutation with following mechanisms: decrease of the bacterial cell wall permeability, expression change of genes coding for efflux pumps or mutations in genes encoding enzymes responsible for molecule binding. Plasmid-mediated resistance to fluoroquinolones confer only decreased susceptibility of bacteria, however, it can facilitate development of mutations in genes of target enzymes and can be transferred horizontally. Depending on the underlying resistance mechanism cross-resistance to other (fluoro)quinolones and co-resistance to other antimicrobial classes can occur.

4.3 Pharmacokinetics

Enrofloxacin has relatively high bioavailability after oral administration in almost all of the species studied. In dogs, orally dosed with enrofloxacin, the maximum plasma concentration of enrofloxacin is reached after 1 hour, and antibacterial activity is still maintained after 24 hours. Concomitant administration of compounds containing multivalent cations (antacids, milk or milk replacers) decreases the oral bioavailability of fluoroquinolones.

Fluoroquinolones are characterized by extensive distribution to body fluids and tissues, reaching in some concentrations higher than those found in plasma. Fluoroquinolones are widely distributed in skin, bone and semen as well as in the anterior and posterior chambers of the eye; they cross the

placenta and brain barrier. High levels are found in phagocytic cells (alveolar macrophages, neutrophils); therefore fluoroquinolones are effective against intracellular microorganisms.
The degree of metabolism varies between species and is around 50-60%. Enrofloxacin is biotransformed in the liver, to an active metabolite ciprofloxacin. In general, metabolism occurs via hydroxylation and oxidation reactions. Other reactions involved are N-dealkylation and glucuronic acid conjugation.
Excretion occurs via the bile and kidney, the latter being predominant. The renal excretion is by glomerular filtration and tubular excretion.
In dogs, orally administered 5 mg / kg enrofloxacin rapid absorption was observed and concentrations of enrofloxacin after 4 h were 0.3 µg / ml in plasma, 3.3 µg / ml in alveolar macrophages and 4.8 µg / ml in lung epithelial fluid. The bioavailability was approximately 80%.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

Not applicable.

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.

Return any halved tablet to the opened blister pack and use within 24 hours.

5.3 Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.

5.4 Nature and composition of immediate packaging

Polyamide/Aluminium/Polyvinyl chloride film (OPA/Al/PVC), heat sealed with aluminium foil containing 10 tablets / blister.

Package sizes:
Cardboard box with 10 blister packs (100 tablets).
Cardboard box with 1 blister pack (10 tablets).

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

Hifarmax, Produtos e Serviços Veterinários, Lda.
KRKA, d.d., Novo mesto

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).

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

{Cardboard box}

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Enrocill Flavour 150 mg tablets

2. STATEMENT OF ACTIVE SUBSTANCES

Each tablet contains 150 mg of enrofloxacin.

3. PACKAGE SIZE

10 tablets
100 tablets

4. TARGET SPECIES

Dogs

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

Oral use.
The tablet is given orally once daily or as a divided dose twice daily with or without food.

7. WITHDRAWAL PERIODS

8. EXPIRY DATE

Exp. {mm/yyyy}

Return any halved tablet to the opened blister pack and use within 24 hours.

9. SPECIAL STORAGE PRECAUTIONS

10. THE WORDS "READ THE PACKAGE LEAFLET BEFORE USE"

Read the package leaflet before use.

11. THE WORDS “FOR ANIMAL TREATMENT ONLY”

For animal treatment only.

12. THE WORDS “KEEP OUT OF THE SIGHT AND REACH OF CHILDREN”

Keep out of the sight and reach of children.

13. NAME OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder:
Hifarmax, Produtos e Serviços Veterinários, Lda.
KRKA, d.d., Novo mesto

14. MARKETING AUTHORISATION NUMBERS

15. BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

{Blisters}

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Enrocill Flavour

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

150 mg

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}

B. PACKAGE LEAFLET

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

Enrocill Flavour 150 mg tablets for dogs

2. Composition

Each tablet contains:

Active substance:
Enrofloxacin 150 mg

Round slightly biconvex, cream to light brownish tablets with possible visible white or darker spots, one side scored and bevel-edged.
The tablets can be divided into halves.

3. Target species

Dogs.

4. Indications for use

In dogs:
Treatment of infections caused by strains of *Staphylococcus* spp., *E. coli, Haemophilus* spp. *Pasteurella* spp. and *Salmonella* spp. susceptible to enrofloxacin.

The veterinary medicinal product is indicated for treatment of mono or mixed bacterial infections of the respiratory, digestive and urinary tract, otitis externa, skin and wound infections.

5. Contraindications

Do not use in dogs less than 1 year of age or in exceptionally large breeds of dog with a longer growth period less than 18 months of age, as articular cartilage may be affected during the period of rapid growth.
Do not use in cases of hypersensitivity to the active substance or to any of the excipients.
Do not use in dogs having seizure disorders, since enrofloxacin may cause CNS stimulation.
Do not use in cases of known resistance to (fluoro)quinolones.
Please, see section 6, “Pregnancy and lactation.”

6. Special warnings

Special precautions for safe use in the target species:
Flouroquinolones should be reserved for the treatment of clinical conditions that 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. Official and local antimicrobial policies should be taken into account when the veterinary medicinal product is used. Use of the veterinary medicinal product deviating from the instructions given in the SPC may increase the

prevalence of bacteria resistant to fluoroquinolones and may decrease the effectiveness of treatment with other quinolones due to the potential cross resistance.
If there is no clinical improvement within three days, further susceptibility testing and possibly a change in antimicrobial therapy should be considered.
Use the veterinary medicinal product with caution in dogs with severe renal or hepatic impairment.
Pyoderma is mostly secondary to an underlying disease. It is advisable to determine the un-derlying cause and to treat the animal accordingly.
The veterinary medicinal product is flavoured. To avoid accidental ingestion, the tablets should be stored out of reach of animals.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
People with known hypersensitivity to fluoroquinolones should avoid contact with the veterinary medicinal product.
In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
Avoid contact with the eyes. In case of contact with the eyes, wash immediately with water.
Wash hands after use.
Do not smoke, eat or drink while handling the veterinary medicinal product.

Pregnancy and lactation:
Do not use during pregnancy and lactation.

Interaction with other medicinal products and other forms of interaction:
Do not combine with other drugs, such as tetracyclines, phenicols or macrolides because there is a potential that these drugs nullify the desired effect.
Do not combine with theophylline (a drug used in medicine as a bronchial dilator) as this could lead to a prolonged elimination of this substance.
Do not use simultaneously with NSAIDs (convulsions may occur).
Concurrent use of flunixin and enrofloxacin should be under careful veterinary monitoring, as the interactions between these drugs may lead to adverse events related to delayed elimination.
Concurrent administration of magnesium, calcium or aluminum containing substances may be followed by retarded absorption of enrofloxacin.
Excessive alkalinisation of the urine should be avoided in animals subjected to rehydration.

Overdose:
In case of overdose, sickness, vomiting, diarrhoea, and CNS/behavioural changes may occur and the treatment must be suspended.

7. Adverse events

Dogs:

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Central nervous system disorder Digestive tract disorder Hypersensitivity reaction
Undetermined frequency (cannot be estimated from the available data):	Joint cartilage disorder[1]

[1]In growing puppies (see section “Contraindications”).

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. If you notice any side effects, even those not already listed in this package leaflet,

or you think that the medicine has not worked, please contact, in the first instance, your veterinarian. You can also report any adverse events to the marketing authorisation holder or the local representative of the marketing authorisation holder using the contact details at the end of this leaflet, or via your national reporting system: {national system details}.

8. Dosage for each species, routes and method of administration

The dosage rate of enrofloxacin is 5 mg/kg/day (i.e. one 150 mg tablet per 30 kg per day), for 5 days. In chronic and severe cases, treatment duration can be extended to 10 days.

9. Advice on correct administration

Tablets may be given directly into the mouth or masked in food.
To ensure a correct dosage body weight should be determined as accurately as possible to avoid underdosing.

10. Withdrawal periods

Not applicable.

11. Special storage precautions

Keep out of the sight and reach of children.

Return any halved tablet to the opened blister pack and use within 24 hours.

This veterinary medicinal product does not require any special storage conditions.

Do not use this veterinary medicinal product after the expiry date which is stated on the box and blister after Exp. The expiry date refers to the last day of that month.

12. Special precautions for disposal

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 applicable national collection systems. These measures should help to protect the environment.

Ask your veterinary surgeon or pharmacist how to dispose of medicines no longer required.

13. Classification of veterinary medicinal products

Veterinary medicinal product subject to prescription.

14. Marketing authorisation numbers and pack sizes

Package sizes:

Cardboard box with 10 blister packs (100 tablets).
Cardboard box with 1 blister pack (10 tablets).

Not all pack sizes may be marketed.

15. Date on which the package leaflet was last revised

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).

16. Contact details

Marketing authorisation holder and contact details to report suspected adverse reactions:
Hifarmax, Produtos e Serviços Veterinários, Lda, Rua do Fojo 136, Pavilhão B - Trajouce
2785-615 S. Domingos de Rana – Portugal
Tel:
KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia
Tel:

Manufacturer responsible for batch release:
KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia
KRKA - FARMA d.o.o., V. Holjevca 20/E, 10450 Jastrebarsko, Croatia

Local representatives and contact details to report suspected adverse reactions:

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.

17. Other information