1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Enrocill Flavour 15 mg Tablets for dogs and cats (ES, PT)
Enro-Sleecol Flavour 15 mg Tablets for dogs and cats (DE)
Enroxil Flavour 15 mg Tablets for dogs and cats (EL)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Each tablet contains:

Active substance:
Enrofloxacin 15 mg

Excipients:

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
Round slightly biconvex, cream to light brownish tablets with possible visible white or darker spots and bevel-edged.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs and cats.

4.2 Indications for use, specifying the target species

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

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

4.3 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 cats less than 8 weeks of age.

Do not use in cases of hypersensitivity to the active substance, to any other quinolone or to any of the excipients.
Do not use in animals having seizure disorders, since enrofloxacin may cause CNS stimulation.
Do not use in cases of known resistance to (fluoro)quinolones.
Please, see section 4.7.

4.4 Special warnings for each target species

Retinotoxic effects including blindness can occur in cats if recommended dose is exceeded.

4.5 Special precautions for use

i) Special precautions for use in animals

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 product is used. Use of the 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 product with caution in cats or dogs with severe renal or hepatic impairment.

ii) 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 product.

4.6 Adverse reactions (frequency and seriousness)

Gastrointestinal disturbances may occur very rarely. Hypersensitivity reactions and central nervous system disorders may be observed very rarely.
Joint cartilage alterations are possible in growing puppies (see 4.3 contraindications).

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

4.7 Use during pregnancy, lactation or lay

Do not use in pregnant or lactating bitches and queens.

4.8 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.

4.9 Amounts to be administered and administration route

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 15 mg tablet per 3 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.

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

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

Do not exceed recommended doses. In cats, higher doses (20 mg / kg bw day or more) can cause ocular damage (see section 4.4).

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use. Fluoroquinolones.
ATCvet code: QJ01MA90

5.1 Pharmacodynamic properties

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. Enrofloxacin exerts its antimicrobial action at low concentrations. It is effective against most Gram-negative bacteria and many Gram positive bacteria, both aerobes and anaerobes.

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

The enrofloxacin *in vitro* activity against pathogens isolated from canine and feline respiratory, urinary and soft tissue infections in Europe, is good: MIC_{50} 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 and cats) 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 and cats respiratory pathogens

Bacteria	Resistant (%)	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)
S. intermedius – dogs	4.1	0.12	0.5
E. colli – dogs	12.5	0.06	>8
P. multocida – dogs	NA	0.015	0.015
P. multocida – cats	NA	0.015	0.03

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

Susceptibility of dogs and cats urinary tract pathogens

Bacteria	Resistant (%)	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)
E. colli – dogs	3.9	0.03	0.06
S. intermedius – dogs	3.0	0.12	0.25
E. coli – cats	7.5	0.03	0.25

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

Susceptibility of dogs and cats pathogens involved in skin infections

Bacteria	Resistant (%)	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)
S. pseudointermedius – dogs	5.2	0.12	0.5
S. pseudointermedius – cats	10.2	0.12	>8
S. aureus – dogs	2.2	0.12	0.25
S. aureus – cats	3.4	0.12	0.25
E. coli – dogs	3.7	0.06	0.12
E. coli – cats	7.1	0.03	0.5
Pasteurella spp. – dogs	NA	0.015	0.015
Pasteurella spp. – cats	NA	0.015	0.03

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.

5.2 Pharmacokinetic particulars

Enrofloxacin has relatively high bioavailability after oral administration in almost all of the species studied. In dogs and cats, orally dosed with enrofloxacin, the maximum plasma concentration of enrofloxacin is reached after 1 and 2 hours, respectively. The 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%.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Major incompatibilities

Not applicable.

6.3 Shelf life

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

6.4. Special precautions for storage

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

6.5 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 carton with 10 blister packs
Cardboard carton with 1 blister pack

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 products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Hifarmax, Produtos e Serviços Veterinários, Lda, Rua do Fojo 136, Pavilhão B - Trajouce
2785-615 S. Domingos de Rana – Portugal

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Carton box

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Enrocill Flavour 15 mg Tablets for dogs and cats (ES, PT)
Enro-Sleecol Flavour 15 mg Tablets for dogs and cats (DE)
Enroxil Flavour 15 mg Tablets for dogs and cats (EL)
Enrofloxacin

2. STATEMENT OF ACTIVE SUBSTANCES

Each tablet contains:

Active substance:
Enrofloxacin 15 mg

3. PHARMACEUTICAL FORM

Tablet

4. PACKAGE SIZE

10 tablets
100 tablets

5. TARGET SPECIES

Dogs and cats.

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
The tablet is given orally once daily or as a divided dose twice daily with or without food.

8. WITHDRAWAL PERIOD(S)

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

User warnings - please read the package leaflet.

10. EXPIRY DATE

EXP:

11. SPECIAL STORAGE CONDITIONS

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Dispose of waste material in accordance with local requirements.

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only. To be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Hifarmax, Produtos e Serviços Veterinários, Lda, Rua do Fojo 136, Pavilhão B - Trajouce
2785-615 S. Domingos de Rana – Portugal

16. MARKETING AUTHORISATION NUMBER(S)

17. MANUFACTURER'S BATCH NUMBER

Lot:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blisters

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Enrocill Flavour 15 mg Tablets for dogs and cats (ES, PT)
Enro-Sleecol Flavour 15 mg Tablets for dogs and cats (DE)
Enroxil Flavour 15 mg Tablets for dogs and cats (EL)
Enrofloxacin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Hifarmax, Lda, Portugal

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

PACKAGE LEAFLET:

Enrocill Flavour 15 mg Tablets for dogs and cats (ES, PT)
Enro-Sleecol Flavour 15 mg Tablets for dogs and cats (DE)
Enroxil Flavour 15 mg Tablets for dogs and cats (EL)

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder:
Hifarmax, Produtos e Serviços Veterinários, Lda, Rua do Fojo 136, Pavilhão B - Trajouce
2785-615 S. Domingos de Rana – Portugal

Manufacturer responsible for the batch release:
KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Enrocill Flavour 15 mg Tablets for dogs and cats (ES, PT)
Enro-Sleecol Flavour 15 mg Tablets for dogs and cats (DE)
Enroxil Flavour 15 mg Tablets for dogs and cats (EL)
Enrofloxacin

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

Each tablet contains 15 mg of Enrofloxacin.
Round slightly biconvex, cream to light brownish tablets with possible visible white or darker spots and bevel-edged.

4. INDICATION(S)

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

The 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

Articular cartilage may be affected during the period of rapid growth, therefore 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.
Do not use in cats less than 8 weeks of age.

Do not use in cases of hypersensitivity to the active substance, to any other quinolone or to any of the excipients.
Do not use in animals having seizure disorders, since enrofloxacin may cause stimulation of the central nervous system.
Do not use in cases of known resistance to (fluoro)quinolones.
Please, see section 12 regarding use in pregnant and lactating animals.

6. ADVERSE REACTIONS

Gastrointestinal disturbances may occur very rarely. Hypersensitivity reactions and central nervous system disorders may be observed very rarely.
Joint cartilage alterations are possible in growing puppies (see 5. Contraindications).

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

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 inform your veterinary surgeon.

7. TARGET SPECIES

Dogs and cats.

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

The dosage rate of enrofloxacin is 5 mg/kg/day (i.e. one 15 mg tablet per 3 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 PERIOD(S)

Not applicable.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.
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 label after EXP.The expiry date refers to the last day of that month.

12. SPECIAL WARNING(S)

Special warnings for each target species
Retinotoxic effects including blindness can occur in cats if recommended dose is exceeded.

Special precautions for use in animals
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 product is used. Use of the 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 product with caution in cats 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 product.

Use during pregnancy, lactation or lay
Do not use in pregnant or lactating bitches and queens.

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 (symptoms, emergency procedures, antidotes), if necessary
In case of overdose, sickness, vomiting, diarrhoea, and CNS/behavioural changes may occur and the treatment must be suspended.
In cats, higher doses (20 mg / kg bw day or more) can cause ocular damage (see sec. Special warnings for each target species).
Do not exceed recommended doses.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

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

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

15. OTHER INFORMATION

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

Package sizes:
Cardboard carton with 10 blister packs
Cardboard carton with 1 blister pack

Not all pack sizes may be marketed.