ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Enrox Flavour 50 mg tablets for dogs (UK (NI), AT, BE, DE, DK, EL, IE, IT, LUX, NL)
Enrox Sabor 50 mg tablets for dogs (ES, PT)
Enroxil Flavour 50 mg tablets for dogs (BG, CZ, HU, LT, LV, PL, RO, SI, SK)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Active substances:
Enrofloxacin 50 mg

Excipients:

Qualitative composition of excipients and other constituents
Mannitol
Maize starch
Sodium starch glycolate (type A)
Meat flavour 10022
Sodium laurilsulphate
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. The tablets can be divided into halves.

3. CLINICAL INFORMATION

3.1 Target species

Dogs.

3.2 Indications for use for each target species

The veterinary medicinal product is for use in dogs for the treatment of bacterial infections of the alimentary, respiratory and urogenital tracts, skin, secondary wound infections and otitis externa where clinical experience, supported where possible by sensitivity testing of the causal organism, indicates enrofloxacin as the drug of choice.

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 for prophylaxis.

3.4 Special warnings

None.

3.5 Special precautions for use

Special precautions for safe use in the target species:

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, use of fluoroquinolones should be based on susceptibility testing. Use of the veterinary medicinal product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to the fluoroquinolones and may decrease the effectiveness of treatment with other quinolones due to the potential for cross-resistance. Official and local antimicrobial policies should be taken into account when the veterinary medicinal product is used.
Do not use in case of resistance to quinolones, as there exists almost complete cross resistance to other quinolones and complete cross resistance to other fluoroquinolones.
Do not exceed the recommended dosage.
Use the veterinary medicinal product with caution in dogs with severe renal or hepatic impairment.

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

Wash hands after use.
In case of contact with the eyes, wash with plenty of clean water.
In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
People with known hypersensitivity to (fluoro)quinolones should avoid contact with 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):	Anorexia Vomiting
Undetermined frequency (cannot be estimated from the available data)	Joint cartilage disorder[1]

[1]During the period of rapid growth, articular cartilage development may be affected.

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

Lactation:

Enrofloxacin passes into maternal milk. Use only according to the benefit-risk assessment by the responsible veterinarian.

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.
Concurrent administration of fluoroquinolones may increase the action of oral anticoagulants.
Do not combine with theophylline as this could lead to a prolonged elimination of this substance.
Concurrent administration of magnesium or aluminum containing substances may be followed by retarded absorption of enrofloxacin.

3.9 Administration routes and dosage

Oral use.

Do not exceed the recommended dose. The dosage rate of enrofloxacin is 5 mg/kg given orally once daily or as a divided dose twice daily for 5 to 10 days with or without food.

The duration of treatment in dogs may be extended depending on the clinical response and the judgement of the responsible veterinary surgeon.

To ensure a correct dosage, body weight should be determined as accurately as possible.

The daily dose is achieved as follows:
Medium dogs: one tablet per 10 kg body weight.

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

In accidental overdose vomiting, diarrhoea and CNS/behavioural changes may occur. There is no antidote and treatment should be symptomatic. If necessary, administration of aluminium- or magnesium-containing antacids or activated carbon can be used to reduce absorption of enrofloxacin.

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 bactericidal in action with activity against Gram positive and Gram negative bacteria and mycoplasmas. The mechanism of action of the quinolones is unique among antimicrobials – they act primarily to inhibit bacterial DNA gyrase, an enzyme responsible for

controlling the super coiling of bacterial DNA during replication. Resealing of the double standard helix is inhibited resulting in irreversible degradation of the chromosomal DNA. The fluoroquinolones also possess activity against bacteria in the stationary phase by an alteration of the permeability of the outer membrane phospholipid cell wall.

Susceptibility of selected canine pathogens (MIC) is as follows:
– *Pasteurella multocida*: 0.03 mg/L;
– *Escherichia coli*: 0.03-0.06 mg/L;
– *Staphylococcus pseudointermedius*: 0.125 mg/L;
– *Pseudomonas aeruginosa*: 2.0 mg/L.
Susceptibility breakpoints are: sensitive ≤0.5 mg/L; intermediate 1-2 mg/L; resistant ≥4 mg/L.

Bacterial resistance to fluoroquinolones most commonly occurs by alteration of the target, DNA-gyrase, via mutation. Less commonly mutation occurs at the topoisomerase-IV target. Other mechanisms of resistance occur when bacteria decrease the ability of the drug to enter the cell or increase active transport out of the cell. Resistance is usually chromosomally developed and, therefore, remains after antimicrobial therapy ends. Cross-resistance of enrofloxacin with other fluoroquinolones can occur. Changes in levels of resistance to fluoroquinolones over time by *Campylobacter* and *Salmonella* species are being monitored because of their possible impact on human health.

4.3 Pharmacokinetics

The pharmacokinetics of enrofloxacin in dogs is such that oral and parenteral administration leads to similar serum levels.
Enrofloxacin is rapidly absorbed after oral, intramuscular and subcutaneous administration.
In the study conducted in dogs the dose of enrofloxacin administered was 4.91 mg/kg. The maximal plasma concentration was 1179.94 ± 260.83 ng/ml, T_{max} was 1.57 ± 0.62 hours, half life 3.78 hours (harmonic mean) and AUC_{tot} value 4037 ± 1155.82 ngh/ml.
Approximately 40% of the oral or intravenous enrofloxacin dose administered in dogs is metabolised to ciprofloxacin.
The mean maximal concentration for ciprofloxacin reached 491.99 ± 57.95 ng/ml, T_{max} 1.79 ± 2.6 hours and the apparent terminal half-life was 5.10 hours (harmonic mean). The mean AUC_{tot} for ciprofloxacin was 3737.21 ± 562.65 ngh/ml.
Enrofloxacin possesses a high distribution volume. Tissue levels 2-3 times higher than that found in the serum, have been demonstrated in laboratory animals and target species. Organs in which high levels can be expected are the lungs, liver, kidney, skin, bone and lymphatic system. Enrofloxacin also distributes into the cerobrospinal fluid, the aqueous humour and the foetus in pregnant animals.
The elimination of enrofloxacin is renal, primarily through glomerular filtration and tubular secretion.

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. Each cardboard carton contains 100 tablets in 10 blister packs.
Polyamide/Aluminium/Polyvinyl chloride film (OPA/Al/PVC), heat sealed with aluminium foil containing 10 tablets / blister. Each cardboard carton contains 10 tablets in 1 blister pack.

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

KRKA, d.d., Novo mesto

7. MARKETING AUTHORISATION NUMBER(S)

{To be completed nationally}

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: DD/MM/YYYY
{To be completed nationally}

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).

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

{Cardboard box}

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Enrox Flavour 50 mg tablets

2. STATEMENT OF ACTIVE SUBSTANCES

Each tablet contains: Enrofloxacin 50 mg.

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

KRKA, d.d., Novo mesto

14. MARKETING AUTHORISATION NUMBERS

{To be completed nationally}

15. BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

{Blister}

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Enrox Flavour

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

50 mg

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}

B. PACKAGE LEAFLET

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

Enrox Flavour 50 mg tablets for dogs

2. Composition

Each tablet contains:

Active substances:
Enrofloxacin 50 mg

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

3. Target species

Dogs.

4. Indications for use

The veterinary medicinal product is for use in dogs for the treatment of bacterial infections of the alimentary, respiratory and urogenital tracts, skin, secondary wound infections and otitis externa where clinical experience, supported where possible by sensitivity testing of the causal organism, indicates enrofloxacin as the drug of choice.

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 for prophylaxis.

6. Special warnings

Special precautions for safe use in the target species:
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, use of fluoroquinolones should be based on susceptibility testing. Use of the veterinary medicinal product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to the fluoroquinolones and may decrease the effectiveness of treatment with other quinolones due to the potential for cross-resistance. Official and local antimicrobial policies should be taken into account when the veterinary medicinal product is used.

Do not use in case of resistance to quinolones, as there exists almost complete cross resistance to other quinolones and complete cross resistance to other fluoroquinolones.
Do not exceed the recommended dosage.
Use the veterinary medicinal product with caution in dogs with severe renal or hepatic impairment.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
Wash hands after use.
In case of contact with the eyes, wash with plenty of clean water.
In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
People with known hypersensitivity to (fluoro)quinolones should avoid contact with the veterinary medicinal product.

Lactation:
Enrofloxacin passes into maternal milk. Use only according to the benefit-risk assessment by the responsible veterinarian.

Interaction with other medicinal products and other forms of interaction:
Do not combine with tetracyclines, phenicols or macrolides because there is a potential that these drugs nullify the desired effect.
Concurrent administration of fluoroquinolones may increase the action of oral anticoagulants.
Do not combine with theophylline as this could lead to a prolonged elimination of this substance.
Concurrent administration of magnesium or aluminum containing substances may be followed by retarded absorption of enrofloxacin.

Overdose:
In accidental overdose vomiting, diarrhoea and CNS/behavioural changes may occur. There is no antidote and treatment should be symptomatic. If necessary, administration of aluminium- or magnesium-containing antacids or activated carbon can be used to reduce absorption of enrofloxacin.

7. Adverse events

Dogs:

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Anorexia Vomiting
Undetermined frequency (cannot be estimated from the available data)	Joint cartilage disorder[1]

[1]During the period of rapid growth, articular cartilage development may be affected.

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

Oral use.

Do not exceed the recommended dose. The dosage rate of enrofloxacin is 5 mg/kg given orally once daily or as a divided dose twice daily for 5 to 10 days.

The duration of treatment in dogs may be extended depending on the clinical response and the judgement of the responsible veterinary surgeon.

To ensure a correct dosage, body weight should be determined as accurately as possible.

The daily dose is achieved as follows:
Medium dogs: one tablet per 10 kg body weight.

9. Advice on correct administration

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

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

{To be completed nationally}

100 tablets in 10 blister packs.
10 tablets in 1 blister pack.

Not all pack sizes may be marketed.

15. Date on which the package leaflet was last revised

MM/YYYY

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:
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
Virbac S.A., 1ère avenue, 2065 m L.I.D., 06516 Carros Cedex, France
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