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

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Enroxal 100 mg/ml oral solution for chickens and turkeys (DE, BE, NL, IT)
Enroxil 100 mg/ml oral solution for chickens and turkeys (BG)
Floxatryl 100 mg/ml oral solution for chickens and turkeys (CY)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:
Enrofloxacin 100 mg

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Benzyl alcohol	14 mg
Hypromellose	
Potassium Hydroxide	
Purified, Water	

Clear, yellow solution.

3. CLINICAL INFORMATION

3.1 Target species

Chickens and turkeys.

3.2 Indications for use for each target species

Treatment of infections caused by the following bacteria susceptible to enrofloxacin:

Chickens
Mycoplasma gallisepticum,
Mycoplasma synoviae,
Avibacterium paragallinarum,
Pasteurella multocida.

Turkeys
Mycoplasma gallisepticum,
Mycoplasma synoviae,
Pasteurella multocida.

3.3 Contraindications

Do not use when resistance / cross-resistance to (fluoro)quinolones is known to occur in the flock intended for treatment.
Do not use in cases of hypersensitivity to the active substance, other (fluoro)quinolones or to any of the excipients.

3.4 Special warnings

Treatment of *Mycoplasma* spp. infections may not eradicate the organism.

3.5 Special precautions for use

Special precautions for safe use in the target species:

Before use, header tanks should be emptied, thoroughly cleaned and then filled with a known volume of clean water before adding the required amount of the veterinary medicinal product. The resulting mixture should be stirred. Before use, header tanks should be inspected at regular intervals for presence of dust, algae formation and sedimentation.
Do not use for prophylaxis.
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 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.
Since enrofloxacin was first authorised for use in poultry, there has been widespread reduction in susceptibility of *E. coli* to fluoroquinolones and emergence of resistant organisms. Resistance has also been reported in *Mycoplasma synoviae* in the EU.

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

People with known hypersensitivity to (fluoro)quinolones should avoid contact with this veterinary medicinal product.
Avoid contact with skin and eyes.
Rinse any splashes from skin or eyes immediately with water.
Wash hands and exposed skin after use.
Do not eat, drink or smoke whilst using the veterinary medicinal product.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Chickens, turkeys:

None known.

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

Laying birds:
Do not use in birds in lay and within 2 weeks before the start of the laying period.

3.8 Interaction with other medicinal products and other forms of interaction

In vitro, an antagonism was shown, when combining fluoroquinolones with bacteriostatic antimicrobial agents such as macrolides or tetracyclines and phenicols. The simultaneous application of substances containing aluminium or magnesium can impair the absorption of enrofloxacin.

3.9 Administration routes and dosage

In drinking water use.

10 mg enrofloxacin/kg bodyweight per day for 3–5 consecutive days.

Treatment for 3–5 consecutive days; for 5 consecutive days in mixed infections and chronic progressive forms. If no clinical improvement is achieved within 2–3 days, alternative antimicrobial therapy should be considered based on susceptibility testing.

Always make sure that the entire dose offered has been consumed. The medicated water should be made up fresh each day just before it is offered to the animals. The drinking water must be medicated throughout the treatment period, and no other water source should be available. To ensure a correct dosage, body weight should be determined as accurately as possible.

Use only fresh pre-solutions, prepared every day before start of treatment. Pumping systems should be checked constantly to assure proper medication. Empty the water system and fill it with medicated water before starting the treatment. Based on the recommended dose and the number and weight of animals to be treated, the exact daily concentration of the veterinary medicinal product should be calculated according to the following formula:

Total number of birds	x	Average body weight (kg)	x	0.1	=	Total volume (ml) of the veterinary medicinal product per day

The veterinary medicinal product may be put directly into the header tank or introduced via a water proportioner pump.
Care should be taken that the intended dose is completely ingested.
The use of suitably calibrated measuring equipment is recommended.

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

No adverse clinical symptoms were observed in chickens and turkeys treated respectively with doses up to 10 and 6 times higher than the therapy dose.
The use of fluoroquinolones during the growth phase combined with a marked and prolonged increase in the intake of drinking water, and hence active ingredient, possibly due to high temperatures, may potentially be associated with damage of the articular cartilage.

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

Chickens: Meat and offal: 7 days.
Turkeys: Meat and offal: 13 days.

Not for use in birds producing or intended to produce eggs for human consumption.
Do not use within 2 weeks before the start of the laying period.

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. They modulate the topological state of DNA through cleaving and resealing reactions. Initially, both strands of the DNA double helix are cleaved. Then, a distant segment of DNA is passed through this break before the strands are resealed. Target inhibition is caused by non-covalent binding of fluoroquinolone molecules to an intermediate state in this sequence of reactions, in which DNA is cleaved, but both strands are retained covalently attached to the 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.

Antibacterial spectrum
Enrofloxacin is active against many Gram-negative bacteria, against Gram-positive bacteria and *Mycoplasma* spp. In vitro susceptibility has been shown in strains of (i) Gram-negative species such as *Pasteurella multocida* and *Avibacterium (Haemophilus) paragallinarum* and (ii) *Mycoplasma gallisepticum* and *Mycoplasma synoviae*. (See section 3.5)

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.

4.3 Pharmacokinetics

Enrofloxacin administered via drinking water to poultry is rapidly and very well absorbed with a bioavailability of approx. 90 %. Maximum plasma concentrations of 2 mg/L are reached within 1.5 hours after a single bolus dose rate of 10 mg/kg body weight with a total systemic availability of 14.4 mg·hr/L. Enrofloxacin is eliminated from the body with a total body clearance of 10.3 mL/min·kg. If dosed as continuous drinking water medication (multiple dosing) steady-state concentrations of 0.5 mg (turkeys) to 0.8 mg (chickens) enrofloxacin per litre are achieved. A high mean volume of distribution (5 L/kg) indicates good tissue penetration of enrofloxacin. Concentrations in target tissues like lungs, liver, kidney, intestine and muscle tissue, exceed plasma concentrations by far. In poultry enrofloxacin is poorly metabolized to its active metabolite ciprofloxacin (approximately 5 %). Enrofloxacin is eliminated from the body at a half-life of 6 hours. Protein binding in poultry is approximately 25 %.

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: 5 years.

Shelf life after first opening the immediate packaging: 3 months.
Shelf life after dilution according to directions: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

Carton box containing 100 ml amber type III glass vial with HDPE cap and LDPE sealing liner. A 25 ml polypropylene dosing cup is included.
1000 ml HDPE bottle with HDPE screw cap. A 50 ml polypropylene dosing cup is included.

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

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

Box 100 ml
Bottle 1000 ml

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Enroxal 100 mg/ml oral solution (DE, BE, NL, IT)
Enroxil 100 mg/ml oral solution (BG)
Floxatryl 100 mg/ml oral solution (CY)

2. STATEMENT OF ACTIVE SUBSTANCES

Each ml contains 100 mg of enrofloxacin.

3. PACKAGE SIZE

100 ml
1000 ml

4. TARGET SPECIES

Chickens and turkeys

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

In drinking water use.

7. WITHDRAWAL PERIODS

Withdrawal period:
Chickens: Meat and offal: 7 days.
Turkeys: Meat and offal: 13 days.

Not for use in birds producing or intended to produce eggs for human consumption.
Do not use within 2 weeks before the start of the laying period.

8. EXPIRY DATE

Exp. {mm/yyyy}

Once opened use within 3 months.
Once diluted 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

14. MARKETING AUTHORISATION NUMBERS

15. BATCH NUMBER

Lot {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

Vial 100 ml

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Enroxal 100 mg/ml oral solution (DE, BE, NL, IT)
Enroxil 100 mg/ml oral solution (BG)
Floxatryl 100 mg/ml oral solution (CY)

2. STATEMENT OF ACTIVE SUBSTANCES

Each ml contains 100 mg of enrofloxacin.

100 ml

3. TARGET SPECIES

Chickens and turkeys

4. ROUTES OF ADMINISTRATION

In drinking water use.
Read the package leaflet before use.

5. WITHDRAWAL PERIODS

Withdrawal period:
Chickens: Meat and offal: 7 days.
Turkeys: Meat and offal: 13 days.

Not for use in birds producing or intended to produce eggs for human consumption.
Do not use within 2 weeks before the start of the laying period.

6. EXPIRY DATE

Exp. {mm/yyyy}

Once opened use within 3 months.
Once diluted use within 24 hours.

7. SPECIAL STORAGE PRECAUTIONS

8. NAME OF THE MARKETING AUTHORISATION HOLDER

9. BATCH NUMBER

Lot {number}

B. PACKAGE LEAFLET

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

Enroxal 100 mg/ml oral solution for chickens and turkeys (DE, BE, NL, IT)
Enroxil 100 mg/ml oral solution for chickens and turkeys (BG)
Floxatryl 100 mg/ml oral solution for chickens and turkeys (CY)

2. Composition

Each ml contains:

Active substance:
Enrofloxacin 100 mg

Excipients:
Benzyl alcohol 14 mg

Clear, yellow solution.

3. Target species

Chickens and turkeys.

4. Indications for use

Treatment of infections caused by the following bacteria susceptible to enrofloxacin:

Chickens
Mycoplasma gallisepticum,
Mycoplasma synoviae,
Avibacterium paragallinarum,
Pasteurella multocida.

Turkeys
Mycoplasma gallisepticum,
Mycoplasma synoviae,
Pasteurella multocida.

5. Contraindications

Do not use when resistance / cross-resistance to (fluoro)quinolones is known to occur in the flock intended for treatment.
Do not use in cases of hypersensitivity to the active substance, other (fluoro)quinolones or to any of the excipients.

6. Special warnings

Special warnings:
Treatment of *Mycoplasma* spp. infections may not eradicate the organism.

Special precautions for safe use in the target species:
Before use, header tanks should be emptied, thoroughly cleaned and then filled with a known volume of clean water before adding the required amount of the veterinary medicinal product. The resulting mixture should be stirred. Before use, header tanks should be inspected at regular intervals for presence of dust, algae formation and sedimentation.
Do not use for prophylaxis.
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 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.
Since enrofloxacin was first authorised for use in poultry, there has been widespread reduction in susceptibility of *E. coli* to fluoroquinolones and emergence of resistant organisms. Resistance has also been reported in *Mycoplasma synoviae* in the EU.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
People with known hypersensitivity to (fluoro)quinolones should avoid contact with this veterinary medicinal product.
Avoid contact with skin and eyes.
Rinse any splashes from skin or eyes immediately with water.
Wash hands and exposed skin after use.
Do not eat, drink or smoke whilst using the veterinary medicinal product.

Laying birds:
Do not use in birds in lay and within 2 weeks before the start of the laying period.

Interaction with other medicinal products and other forms of interaction:
In vitro, an antagonism was shown, when combining fluoroquinolones with bacteriostatic antimicrobial agents such as macrolides or tetracyclines and phenicols. The simultaneous application of substances containing aluminium or magnesium can impair the absorption of enrofloxacin.

Overdose:
No adverse clinical symptoms were observed in chickens and turkeys treated respectively with doses up to 10 and 6 times higher than the therapy dose.
The use of fluoroquinolones during the growth phase combined with a marked and prolonged increase in the intake of drinking water, and hence active ingredient, possibly due to high temperatures, may potentially be associated with damage of the articular cartilage.

Major incompatibilities:
In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

7. Adverse events

Chickens, turkeys:

None known.

Reporting adverse events is important. It allows continuous safety monitoring of a 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}*[listed in Appendix I*]*>.

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

In drinking water use.

10 mg enrofloxacin/kg bodyweight per day for 3–5 consecutive days.

Treatment for 3–5 consecutive days; for 5 consecutive days in mixed infections and chronic progressive forms. If no clinical improvement is achieved within 2–3 days, alternative antimicrobial therapy should be considered based on susceptibility testing.

Always make sure that the entire dose offered has been consumed. The medicated water should be made up fresh each day just before it is offered to the animals. The drinking water must be medicated throughout the treatment period, and no other water source should be available. To ensure a correct dosage, body weight should be determined as accurately as possible.

Use only fresh pre-solutions, prepared every day before start of treatment. Pumping systems should be checked constantly to assure proper medication. Empty the water system and fill it with medicated water before starting the treatment. Based on the recommended dose and the number and weight of animals to be treated, the exact daily concentration of the veterinary medicinal product should be calculated according to the following formula:

Total number of birds	x	Average body weight (kg)	x	0.1	=	Total volume (ml) of the veterinary medicinal product per day

The veterinary medicinal product may be put directly into the header tank or introduced via a water proportioner pump.
Care should be taken that the intended dose is completely ingested.
The use of suitably calibrated measuring equipment is recommended.

9. Advice on correct administration

Please refer to section 8.

10. Withdrawal periods

Chickens: Meat and offal: 7 days.
Turkeys: Meat and offal: 13 days.

Not for use in birds producing or intended to produce eggs for human consumption.
Do not use within 2 weeks before the start of the laying period.

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.

Shelf life after first opening the immediate packaging: 3 months.
Shelf life after dilution according to directions:24 hours.

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

100 ml amber type III glass vial with polypropylene measuring cup in carton.
1000 ml high density polyethylene bottle and polypropylene measuring cup.

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:

Manufacturer responsible for batch release:
KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia
TAD Pharma GmbH, Heinz-Lohmann-Straße 5, 27472 Cuxhaven, Germany

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>