Proposed Package Insert for

KARIFLOXX 100 mg/mL oral solution for chickens and rabbits

VETERINARY MEDICINE

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

KARIFLOXX 100 mg/mL oral solution for chickens and rabbits.

COMPOSITION

Each 1 mL solution contains 100 mg enrofloxacin.

Other ingredients:

Benzyl alcohol 1,4 % *m/v* (preservative), potassium hydroxide and purified water.

PHARMACOLOGICAL CLASSIFICATION

C 17.1.6 Antimicrobials (quinolones)

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

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 fluroquinolone

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-fluroquinolone complexes, and inhibition of DNA and mRNA synthesis triggers events resulting in a rapid, medicine concentration-dependant 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 **Special precautions for use in animals**).

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 medicine permeability in Gram-negative bacteria.

(iii) Efflux mechanisms.

(iv) Plasmid mediated resistance.

(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.

Pharmacokinetic properties

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 mass 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 medicine (multiple dosing) steady-state concentrations of 0,8 mg (chicken) enrofloxacin per litre are achieved. A high mean volume of distribution (5 L/kg) indicated 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 metabolised 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 %.

INDICATIONS

Target species

Chickens (broilers) and rabbits.

Indications for use, specifying the target species

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

Chickens

Mycoplasma gallisepticum

Mycoplasma synoviae

Avibacterium paragallinarum

Pasteurella multocida

Rabbits

For the treatment infectious diseases due to *Pasteurella multocida.*

Enrofloxacin should be used where clinical experience, supported where possible by sensitivity testing of the causal organism, indicates enrofloxacin as the active substance of choice.

CONTRAINDICATIONS

- Do not use in the case of known hypersensitivity to enrofloxacin, other (fluoro)quinolones or to any of the excipients of KARIFLOXX 100 mg/mL.
- Do not use when resistance / cross-resistance to (fluoro)quinolones is known to occur in the flock intended for treatment.
- Do not use for prophylaxis.

WARNINGS

Special warnings for each target species

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

Withdrawal period:

Meat and offal:	Chickens (broilers):	7 days
	Rabbits:	3 days

INTERACTIONS

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

PREGNANCY, LACTATION OR LAY

- Do not use in laying hens producing eggs for human consumption.
- Do not administer to layer replacement birds within 14 days of coming into lay.

DOSAGE AND DIRECTIONS FOR USE

For oral administration via the drinking water.

Chickens

KARIFLOXX 100 mg/mL is applied via the drinking water. The basic dosage is 1 mL per 10 kg (10 mg per kg) live mass given in a 6 to 8 hour water supply over 3 consecutive days.

Diseases such as colibacillosis, fowl cholera, infectious coryza and mycoplasmosis (MG/MS) should be treated continuously for 3 consecutive days.

In mycoplasmosis, treat whenever symptoms occur or positive seroconversion is diagnosed.

Salmonellosis should be treated for 5 consecutive days.

Average live mass (g)	mg AI/ 1 000 birds	mL KARIFLOXX 100 mg/mL / 1 000 birds	Total KARIFLOXX 100 mg/mL volume (mL) for 1 000 birds for 3 treatment days
140	1 400	14	42
340	3 400	34	102
650	6 500	65	195
1 000	10 000	100	300
1 400	14 000	140	420
1 800	18 000	180	540
2 200	22 000	220	660

Rabbits

10 mg/kg body mass per day for 5 consecutive days.

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

The intake of medicated water depends on the clinical condition of the animals and the time of year. In order to obtain the correct dosage, the concentration of enrofloxacin has to be adjusted accordingly.

According to the recommended dose, the number and mass of the animals which should be treated, the exact daily dose of KARIFLOXX 100 mg/mL should be calculated using the following formula:

$$\text{mL of product/L water} = \frac{\text{10 mg/kg/day x average body mass of the animals}}{\text{100 mg/mL x average water consumption (L/day)}}$$

The medicated water should be made up fresh each day just before it is offered to the animals. Sufficient access to the system of supply should be available for the animals to be treated to ensure adequate water consumption. The drinking water must be medicated throughout the treatment period, and no other water source should be available.

Use appropriate and properly calibrated dosing equipment.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

Side effects

None known.

If you notice any serious effects or other effects, please inform your veterinarian.

Special precautions for use in animals

Official and local antimicrobial policies should be taken into account when the KARIFLOXX 100 mg/mL 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 product deviating from the instructions given in this Package Insert 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 synovia* in the EU.

Special precautions to be taken by the person administering KARIFLOXX 100 mg/mL

- People with known hypersensitivity to (fluoro)quinolones should avoid contact with KARIFLOXX 100 mg/mL.
- Avoid contact with skin and eyes. Use gloves and carefully handle KARIFLOXX 100 mg/mL to avoid getting in contact with it when introducing it into drinking water. In case of accidental contact, rinse immediately with plenty of water.
- If such symptoms as skin rash appear after being exposed to this KARIFLOXX 100 mg/mL, seek for medical advice. Face, lip or eye swelling, as well as difficult breathing, are serious signs requiring urgent medical assistance.
- Wash hands and exposed skin after use.
- Do not eat, drink or smoke while using KARIFLOXX 100 mg/mL

KNOWN SIGNS OF OVERDOSE AND PARTICULARS OF ITS TREATMENT

At the dosage of 20 mg/kg body mass (twice the recommended dosage) administered for 15 days (3 times the recommended duration of treatment) adverse reactions were not observed. In case of overdosage, the symptoms would be a weak stimulation of the spontaneous motility, so the treatment should be ceased.

Overdose by fluoroquinolones may cause sickness, vomiting and diarrhoea.

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.

IDENTIFICATION

An aqueous, clear, yellowish solution.

PRESENTATION

White high-density polyethylene container closed with a high-density polyethylene screw cap and induction disk.

Pack sizes: 1 L and 5 L.

Not all pack sizes may be marketed.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Shelf-life as packaged for sale: 36 months

Shelf-life after fist opening of container: 3 months.

Shelf-life after dilution or reconstitution according to directions: 24 hours.

KEEP OUT OF REACH OF CHILDREN AND UNINFORMED PERSONS.

REGISTRATION NUMBER

21/27

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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DATE OF NOTIFICATION OF APROVAL OF THIS SCIENTIFIC PACKAGE INSERT

25 March 2025.

Signed: