SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

LEVOFLOK 100 mg/ml Solution for use in drinking water for chickens, turkeys and rabbits [ES, CY, EL, HR, HU, IT, PT, PL]
FLUONIX 100 mg/ml Solution for use in drinking water for chickens, turkeys and rabbits [DE]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:
Enrofloxacin 100.0 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 (E 1519)	0.014 ml

An aqueous, clear, yellowish solution

3. CLINICAL INFORMATION

3.1 Target species

Chickens (broilers)
Turkeys (for meat production)
Rabbits

3.2. Indications for use for each target species

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

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

Turkey
Mycoplasma gallisepticum,
Mycoplasma synoviae,
Pasteurella multocida,

Rabbits:
Treatment of respiratory infections caused by *P. multocida*.

3.3. Contraindications

Do not use in cases of hypersensitivity to the active substance, to any other (fluoro)quinolones or to any of the excipients.

3.4 Special warnings

Treatment of *Mycoplasma* spp infections may not eradicate the organism.
Do not use when resistance/ cross-resistance to (fluoro)quinolones is known to occur in the flock intended for treatment.

3.5 Special precautions for use

Special precautions for safe use in the target species:

Official and local antimicrobial policies should be taken into account when the 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.

Wherever possible, fluoroquinolones should be used based on susceptibility testing.

Use of the product deviating from 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 for cross resistance.

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.

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

(Fluoro)quinolones may cause hypersensitivity (allergy) in sensitised people. People with known hypersensitivity to (fluoro)quinolones should avoid contact with the veterinary medicinal product.

Avoid contact with skin and eyes. Personal protective equipment consisting of protective gloves should be worn when handling the veterinary medicinal product. In case of accidental contact, rinse immediately with plenty of water. If such symptoms as skin rash appear after being exposed to this product, seek for medical advice and show the package leaflet or the label to the physician. Swelling of the face, lip or eye or difficulty with breathing are more serious symptoms and require urgent medical attention.

Do not smoke, eat or drink while handling this product.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

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 on this label, 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><the local representative of the marketing authorisation holder> using the contact details on this label, or via your national reporting system <{national system details}.>

3.7 Use during pregnancy, lactation or lay

Pregnancy:

Laboratory studies in rats have not produced any evidence of teratogenic effects. Studies performed in female rabbits do not show teratogenic effects for the foetus.

Lactation:

Studies carried out in lactating rabbits do not show toxic effects for the lactating young rabbits within the first 16 days. Rabbits older than this age have the ability to eliminate enrofloxacin.

Use only accordingly to the benefit/risk assessment by the responsible veterinarian.

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 aluminum, ferrum or calcium can reduce absorption of enrofloxacin. Don’t combine in solution or vials with aluminum, calcium, ferrum and zinc because chelate compounds may be formed.

3.9 Administration routes and dosage

In drinking water use.

Chickens and turkeys
10 mg enrofloxacin/kg bodyweight per day (equivalent to 0.1 ml product/kg b.w./day) for 3-5 consecutive days. Administer 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.

Rabbits
10 mg enrofloxacin/kg bodyweight per day for 5 consecutive days (equivalent to 0.1 ml product/kg b.w./day).

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

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

According to the recommended dose, the number and weight of the animals which should be treated, the exact daily dose of the product should be calculated using the following formula:

$$\frac{\text{ml veterinary medicinal product/kg body weight day} \times \text{Average body weight (kg) of animals to be treated}}{\text{average daily water intake (l/animal)}} = \text{ml veterinary medicinal product per litre of drinking water}$$

The medicated water should be made up fresh each day just before it is offered to the animals. Sufficient access to the system of water 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.

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

At the dosage of 20 mg/kg b.w. (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.

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

[ES]: Administration under the control or direct responsibility of a veterinary surgeon.

3.12 Withdrawal periods

Chickens (broilers):
Meat and offal: 7 days
Turkeys:
Meat and offal: 13 days
Rabbits:
Meat and offal: 2 days

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

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 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, drug 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*.

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.
Resistance has been reported in *Mycoplasma synoviae* in the EU.

4.3 Pharmacokinetics

Enrofloxacin has relatively high bioavailability by oral, intramuscular and subcutaneous route in almost all tested species.

After oral administration of enrofloxacin to chickens and rabbits, the maximum concentration is achieved between 0.5 and 2.5 hours. Maximum concentration after the administration of a therapeutical dosage ranges between 1-2.5 µg/ml.

Concomitant administration of compounds containing polyvalent cations (antiacids, milk or milk replacer) reduces oral bioavailability of fluoroquinolones.

Fluoroquinolones have a great diffusion into body fluids and tissues, achieving higher concentrations than those found in plasma. Moreover, they are widely distributed in skin, bones and semen, reaching the anterior and posterior eye chambers; they cross the placenta and thebrain barrier. They also accumulate in phagocytes (alveolar macrophages, neutrophils) and this explains their efficacy against intracellular microorganisms.

The degree of metabolism varies between species and it is about 50–60%. Biotransformation at hepatic level of enrofloxacin results in the active metabolite, ciprofloxacin. In general, metabolism is by hydroxylation and oxidation processes to oxofluoroquinolones. Other reactions that also occur are N-desalkylation and conjugation with glucuronic acid.

Excretion occurs by biliary and renal route, being the latest the main one. Renal excretion is carried out by glomerular filtration and also by active tubular secretion through organic anions pump.

CHICKENS

After the oral administration of 10 mg/Kg it was observed a maximum concentration of 2.5 μg/ml at 1.6h post-administration, with a bioavailability around 64%. The plasma half-life was 14 h and the mean residence time was 15 h.

RABBITS

Within the administration of the product at the recommended dosage, 10 mg enrofloxacin/kg b.w./day, for 5 consecutive days administered in drinking water, there were found values of Cmax around 350 ng/ml and a mean metabolization of enrofloxacin into ciprofloxacin of 26.5%.

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: 3 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

White high-density polyethylene containers closed with a seal screw cap of the same material with induction disk.

Package sizes:
Bottle of 250 mL
Bottle of 1 L
Barrel of 5 L

Not all pack sizes may be marketed.

5.5 Special precautions for the disposal of unused veterinary medicinal product 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 MARKETING AUTHORIZATION HOLDER

VETPHARMA ANIMAL HEALTH, S.L.

7. MARKETING AUTHORISATION NUMBER

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: DD/MM/YYYY

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

<{DD/MM/YYYY}>

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

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

[CY, DE, EL, ES, HR, HU, IT, PT]:
Veterinary medicinal product subject to prescription