ANNEX I

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:
Benzyl Alcohol (E 1519)..... 0.014 ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for use in drinking water
An aqueous, clear, yellowish solution

4. CLINICAL PARTICULARS

4.1 Target species

Chickens (broilers)
Turkeys (turkeys for meat production)
Rabbits

4.2 Indications for use, specifying the 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*.

4.3 Contraindications

Do not use for prophylaxis.
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, to any other (fluoro)quinolone or to any of the excipients.

4.4 Special warnings for each target species

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

4.5 Special precautions for use

Special precautions for use in animals

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. Face, lip or eye swelling, as well as difficult breathing, are serious signs requiring urgent medical assistance.

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

4.6 Adverse reactions (frequency and seriousness)

None known.

4.7 Use during pregnancy, lactation or lay

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.

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.

4.8 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.

4.9 Amounts to be administered and administration route

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:

$$\text{ml of the product/L water} = \frac{\text{0.1 ml of the product/kg bw/day x average bw of the animal (kg)}}{\text{average water consumption per animal (L/day)}}$$

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

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

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.

4.11 Withdrawal periods

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

Not authorised for use in birds producing eggs for human consumption.
Do not use within 2 weeks of the start of the laying period.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: quinolone and quinoxaline antibacterials, fluoroquinolones
ATC vet code: QJ01MA90

5.1 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, 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.

5.2 Pharmacokinetic particulars

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%.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol (E 1519)
Potassium hydroxide
Water, purified

6.2 Major incompatibilities

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

6.3 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

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

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.

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 product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

VETPHARMA ANIMAL HEALTH, S.L.
Les Corts, 23
08028 – BARCELONA
Spain

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:
Date of last renewal:

10. DATE OF REVISION OF THE TEXT

PROHIBITION OF SALE, SUPPLY AND/OR USE

[ES]:
Dispensing conditions: **Veterinary medicinal product subject to veterinary prescription**.
Administration conditions: **Administration under the control or direct responsibility of a veterinary surgeon**.

[IT]:
Dispensing conditions: **To be sold only upon presentation of a non-repeatable triplicate veterinary prescription**

[CY, DE, EL, HR, HU, PL, PT]:
To be supplied only on veterinary prescription.