

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

CENFLOX 100 mg/ml solution for injection for cattle and pigs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:

Enrofloxacin 100 mg

Excipients:

n-Butanol 30 mg

Benzyl alcohol (E1519) 20 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, yellow solution.

4. CLINICAL PARTICULARS

4.1 Target species

Cattle and pigs.

4.2 Indications for use, specifying the target species

Cattle:

For the treatment of respiratory tract infections caused by enrofloxacin-sensitive *Histophilus somni*, *Mannheimia haemolytica*, *Pasteurella multocida* and *Mycoplasma* spp.

For the treatment of Mastitis caused by enrofloxacin-sensitive *E.coli*.

Pigs:

For the treatment of bacterial bronchopneumonia caused by enrofloxacin-sensitive *Actinobacillus pleuropneumoniae*, *Pasteurella multocida* and *Haemophilus parasuis*.

4.3 Contraindications

Do not use in cases of hypersensitivity to the active substance or to any of the excipient.

Do not use in animals with central nervous system-associated seizure disorders.

Do not use in the presence of existing disorders of cartilage development or musculoskeletal damage around functionally significant or weight-bearing joints.

Do not use in case of resistance against other fluoroquinolone due to the potential for cross-resistance.

4.4 Special warnings for each target species

None.

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.

Whenever possible, fluoroquinolones should only be used based on susceptibility testing.

Use of the 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.

For repeated injection or for injection volumes exceeding 15 ml (cattle) or 7.5 ml (pigs, calves) in divided doses, a new site must be chosen for each injection.

Enrofloxacin is eliminated renally. As with all fluoroquinolones, delayed excretion can therefore be expected in the presence of existing renal damage.

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

Direct contact with the skin should be avoided due to sensitisation, contact dermatitis and possible hypersensitivity reactions.

People with known hypersensitivity to (fluoro)quinolones should avoid contact with the product.

Wash hands after use.

In the event of accidental splash into the eye, rinse with large amounts of clean water. If irritation occurs, seek medical advice.

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

Take care to avoid accidental self-injection.

In case of accidental self-injection, seek medical advice immediately and show the package leaflet or label to the physician.

4.6 Adverse reactions (frequency and seriousness)

Transitory inflammatory reactions (swelling, redness) can occur at the injection site in very rare cases. These regress within a few days without further therapeutic measures.

Intravenous treatment can cause shock reactions in cattle, probably as a result of circulatory disturbances, in very rare cases.

Gastrointestinal disturbances may occur in very rare cases during treatment of calves.

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

4.7 Use during pregnancy, lactation or lay

May be used during pregnancy and lactation.

4.8 Interaction with other medicinal products and other forms of interaction

Antagonist effects due to concurrent administration of macrolides and tetracyclines may occur.

Enrofloxacin may interfere with the metabolism of theophylline, decreasing theophylline clearance resulting in increased plasma levels of theophylline.

4.9 Amounts to be administered and administration route

Cattle

The dosage for respiratory disease is 7.5 mg enrofloxacin per kg body weight (bw) for a single treatment by subcutaneous administration (s.c.). This is equivalent to 7.5 ml of the product per 100 kg bw and day.

Do not administer more than 15 ml (cattle) or 7.5 ml (calf) per injection site (subcutaneous).

In case of serious or chronic respiratory disease a second injection may be required after 48 hours.

The dosage for the treatment of colimastitis is 5 mg enrofloxacin per kg body weight (bw) by intravenous administration (i.v.). This is equivalent to 5 ml of the product per 100 kg bw and day.

The treatment of colimastitis should be exclusively by intravenous application on 2 to 3 consecutive days.

Pigs

The dosage for respiratory tract infections is 7.5 mg enrofloxacin per kg body weight for a single administration. This is equivalent to 0.75 ml of the product per 10 kg bw and day.

Do not administer more than 7.5 ml per injection site (intramuscular).

In case of serious or chronic respiratory disease a second injection may be required after 48 hours.

Method of administration:

Cattle:

For subcutaneous injection (respiratory disease) or for intravenous injection (colimastitis).

Pig:

For intramuscular injection into the neck muscles behind the ear.

To ensure administration of the correct dosage, body weight should be determined as accurately as possible to avoid underdosing.

The stopper may be safely punctured up to 30 times.

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

In cattle a dose of 25 mg/kg bodyweight administered by the subcutaneous route for 15 consecutive days is tolerated without any clinical symptoms. Higher doses in cattle and doses of around 25 mg/kg and above in pig may cause lethargy, lameness, ataxia, slight salivation and muscle tremors.

Do not exceed the recommended dose. In accidental overdose there is no antidote and treatment should be symptomatic.

4.11 Withdrawal periods

Cattle:

Meat and offal:

s.c. 14 days
i.v.: 7 days
Milk: s.c.: 120 hours (5 days)
i.v.: 72 hours (3 days)

Pig:

Meat and offal: i.m.: 12 days.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Fluoroquinolones.
ATCvet code: QJ01MA90.

5.1 Pharmacodynamic properties

Enrofloxacin belongs to the fluoroquinolone group of antibiotics. The substance has bactericidal activity targeting DNA gyrase and topoisomerase IV with the resulting selective inhibition of these enzymes.

DNA gyrase and topoisomerase IV are the two type II topoisomerases present in bacteria. These enzymes are involved in the replication, transcription and recombination of bacterial DNA. Fluoroquinolones also influence bacteria in the stationary phase by altering cell wall permeability.

The inhibitory and bactericidal concentrations of enrofloxacin are very close, being either identical or differing by no more than 1-2 dilution steps.

Enrofloxacin has a spectrum of activity which includes enrofloxacin-sensitive *Histophilus somni*, *Mannheimia haemolytica*, *Pasteurella multocida*, *Mycoplasma* spp., *E. coli* in cattle as well as *Actinobacillus pleuropneumoniae*, *Pasteurella multocida* and *Haemophilus parasuis* in pigs.

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.

Enrofloxacin clinical breakpoints (Susceptible, Intermediate, Resistant) are available for: *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni* isolated from cattle (S \leq 0.25 μ g/ml; I = 0.5-1 μ g/ml; R \geq 2 μ g/ml, CLSIVET08ED4-2018 document), *Pasteurella multocida* and *Actinobacillus pleuropneumoniae* isolated from pigs (S \leq 0.25 μ g/ml; I = 0.5 μ g/ml; R \geq 1 μ g/ml, CLSIVET08ED4-2018 document).

No clinical breakpoints are available for *E.coli* isolates from cattle/mastitis (ECOFF = 0.125 μ g/ml, EUCAST 2019).

MIC₉₀ for isolates *E.coli* from clinical mastitis 0.06 - 0.125 μ g/ml (SE: 0.125 μ g/ml 2013-2017, No isolates 503; CZ: 0.125 μ g/ml 2015-2017, No isolates 192); DE: 0.06 μ g/ml 2004 – 2014, No isolates 1756).

5.2 Pharmacokinetic particulars

Following subcutaneous administration of the product in cattle or intramuscular administration in pigs, the active ingredient, enrofloxacin, is absorbed very rapidly and almost completely (high bioavailability).

Cattle:

After subcutaneous administration at a dose rate of 7.5 mg enrofloxacin per kg body weight to non-lactating cattle peak plasma concentrations of 0.82 mg/L are reached within 5 hours. The overall drug exposure in plasma is 9.1 mg*h/L. Enrofloxacin is excreted from the body at a half-life of 6.4 h. Approximately 50% of enrofloxacin is metabolized to the active substance ciprofloxacin. Ciprofloxacin is excreted from the body at a half-life of 6.8 h.

After intravenous injection at a dose rate of 5.0 mg enrofloxacin per kg body weight to lactating cows, peak plasma concentrations of approx. 23 mg/L are reached immediately. The overall drug exposure in plasma is 4.4 mg*h/L. Enrofloxacin is excreted from the body at a half-life of 0.9 h. Approximately 50% of parent compound are metabolized to ciprofloxacin with peak plasma concentrations of 1.2 mg/L reached at 0.2 h. Elimination half-life is at a mean of 2.1 h.

In milk mainly the metabolite ciprofloxacin accounts for antibacterial activity (approx. 90%). Ciprofloxacin reaches peak milk concentrations of 4 mg/L within 2 hr after intravenous dosing. Total exposure in milk over 24 hours is approx. 21 mg*h/L. Ciprofloxacin is excreted from milk at a half-life of 2.4 h. Peak concentrations of 1.2 mg enrofloxacin per liter are reached in milk within 0.5 hours with an total enrofloxacin exposure in milk of approx. 2.2 mg*h/L. Enrofloxacin is excreted from milk at 0.9 h.

Pig:

After intramuscular administration of 7.5 mg/kg body weight to pigs a mean peak serum concentration of 1.46 mg/L was achieved within 4 hours. The overall drug exposure over 24 hours was 20.9 mg*h/L. The drug was excreted from the central compartment at a terminal half-life of 13.1 h. With peak concentrations less than 0.06 mg/L mean serum concentrations of ciprofloxacin were very low.

Enrofloxacin has a high volume of distribution. The concentrations in the tissues and organs mostly significantly exceed serum levels. Organs in which high concentrations can be expected include the lungs, liver, kidneys, gut and muscle tissue. Enrofloxacin is excreted renally.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Arginine
n-Butanol
Benzyl alcohol (E 1519)
Water for injection

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 in glass vials: 3 years
Shelf life of the veterinary medicinal product as packaged for sale in polypropylene vials: 2 years
Shelf life after first opening the immediate packaging: 28 days

6.4. Special precautions for storage

Do not freeze.
Keep the container in the outer carton.

6.5 Nature and composition of immediate packaging

Amber glass type II vials, with bromobutyl stopper and aluminium cap with FLIP-OFF seal.
Amber polypropylene vials, with bromobutyl stopper and aluminium cap with FLIP-OFF seal.

Pack sizes:

- Box with 1 vial of 100 ml
- Box with 1 vial of 250 ml
- Box with 10 vials of 100 ml
- Box with 10 vials of 250 ml

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 AUTHORISATION HOLDER

CENAVISA, S.L.
Camí Pedra Estela s/n
43205 Reus (SPAIN)

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT

PROHIBITION OF SALE, SUPPLY AND/OR USE

Dispensing conditions: To be supplied only on veterinary prescription.

Administration conditions: Administration by a veterinarian surgeon (in case of intravenous route) or under their direct responsibility.