

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

VALEMAS 50 mg/ml solution for injection for cattle, sheep, goats, pigs, dogs and cats.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains:

Active substance:

Enrofloxacin 50 mg
.....

Excipient:

n-Butyl alcohol 30 mg
.....

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, pale yellow to yellow solution.

4. CLINICAL PARTICULARS

4.1. Target species

Cattle (calves), sheep, goats, pigs, dogs and cats.

4.2. Indications for use, specifying the target species

Calves

Treatment of infections of the respiratory tract caused by enrofloxacin susceptible strains of *Pasteurella multocida*, *Mannheimia haemolytica* and *Mycoplasma* spp.

Treatment of infections of the alimentary tract caused by enrofloxacin susceptible strains of *Escherichia coli*.

Treatment of septicaemia caused by enrofloxacin susceptible strains of *Escherichia coli*.

Treatment of acute mycoplasma-associated arthritis due to enrofloxacin susceptible strains of *Mycoplasma bovis*.

Sheep

Treatment of infections of the alimentary tract caused by enrofloxacin susceptible strains of *Escherichia coli*.

Treatment of septicaemia caused by enrofloxacin susceptible strains of *Escherichia coli*.

Treatment of mastitis caused by enrofloxacin susceptible strains of *Staphylococcus aureus* and *Escherichia coli*.

Goats

Treatment of infections of the respiratory tract caused by enrofloxacin susceptible strains of *Pasteurella multocida* and *Mannheimia haemolytica*.

Treatment of infections of the alimentary tract caused by enrofloxacin susceptible strains of *Escherichia coli*.

Treatment of septicaemia caused by enrofloxacin susceptible strains of *Escherichia coli*.

Treatment of mastitis caused by enrofloxacin susceptible strains of *Staphylococcus aureus* and *Escherichia coli*.

Pigs

Treatment of infections of the respiratory tract caused by enrofloxacin susceptible strains of *Pasteurella multocida*, *Mycoplasma* spp. and *Actinobacillus pleuropneumoniae*.

Treatment of infections of the alimentary tract caused by enrofloxacin susceptible strains of *Escherichia coli*.

Treatment of septicaemia caused by enrofloxacin susceptible strains of *Escherichia coli*.

Dogs

Treatment of infections of the alimentary, respiratory and urogenital tracts (including prostatitis, adjunctive antibiotic therapy for pyometra), skin and wound infections, otitis (externa/media) caused by enrofloxacin susceptible strains of *Staphylococcus* spp., *Escherichia coli*, *Pasteurella* spp., *Klebsiella* spp., *Bordetella* spp., *Pseudomonas* spp. and *Proteus* spp.

Cats

Treatment of infections of the alimentary, respiratory and urogenital tracts (as adjunctive antibiotic therapy for pyometra), skin and wound infections, caused by enrofloxacin susceptible strains of, e.g.: *Staphylococcus* spp., *Escherichia coli*, *Pasteurella* spp., *Klebsiella* spp., *Bordetella* spp., *Pseudomonas* spp. and *Proteus* spp.

4.3. Contraindications

Do not use in animals with known hypersensitivity to enrofloxacin or other fluoroquinolones or to any of the excipients.

Do not use in animals that are epileptic or suffer from seizures since enrofloxacin may cause CNS stimulation.

Do not use in young dogs during their growth, i.e. in small breeds of dogs less than 8 months of age, in big breeds of dogs less than 12 months of age, in giant breeds of dogs less than 18 months of age.

Do not use in cats less than 8 weeks of age.

Do not use in growing horses because of possible deleterious damage on articular cartilage.

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 including use deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to enrofloxacin and may decrease the effectiveness of treatment with all fluoroquinolones due to the potential for cross-resistance.

Special caution should be taken when using enrofloxacin in animals with impaired renal function.

Special caution should be taken when using enrofloxacin in cats because higher doses than recommended can cause retinal damage and blindness (see section 4.10).

Degenerative changes of articular cartilage were observed in calves treated orally with 30 mg enrofloxacin/kg body weight during 14 days.

The use of enrofloxacin in growing lambs at the recommended dose for 15 days caused histological changes in the articular cartilage, not associated to clinical signs.

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

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

Valemas may cause skin and eye irritation. Avoid skin and eye contact. Wash any splashes from skin or eyes immediately with water.

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

Care should be taken 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

Wash hands after use.

Other precautions

In countries where feeding of fallen stock to scavenger bird populations is permitted as a conservation measure (see Commission Decision 2003/322/EC), the possible risk to hatching success should be considered before feeding carcasses of livestock recently treated with this product.

4.6. Adverse reactions (frequency and seriousness)

Digestive tract disorders (e.g. diarrhoea) may occur in very rare cases. These signs are generally mild and transient.

Local reactions at injection site

In calves, transient local tissue reactions may occur in very rare cases and may be observed up to 14 days.

In pigs, after intramuscular administration of the product, inflammatory reactions may occur. They may persist up to 28 days after the injection.
In dogs, a moderate and transient local reaction (such as oedema) may occur.

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

Laboratory studies in rats and rabbits have not produced any evidence of teratogenic effects but have shown evidence of foetotoxic effects at maternotoxic doses.

Mammals

The safety of the veterinary medicinal product has not been established during pregnancy and lactation. Use only accordingly to the benefit/risk assessment by the responsible veterinarian.

4.8. Interaction with other medicinal products and other forms of interaction

Do not use enrofloxacin concomitantly with antimicrobial substances acting antagonistically to quinolones (e.g. macrolides, tetracyclines or phenicols).

Do not use concurrently with theophylline as the elimination of theophylline may be delayed.

Care should be taken during the concomitant use of flunixin and enrofloxacin in dogs to avoid adverse drug reactions. The decrease in drug clearances as a result of co-administration of flunixin and enrofloxacin indicates that these substances interact during the elimination phase. Thus, in dogs, the co-administration of enrofloxacin and flunixin increased the AUC and the elimination half-life of flunixin and increased the elimination half-life and reduced the C_{max} of enrofloxacin.

4.9. Amounts to be administered and administration route

Intravenous, subcutaneous or intramuscular use.

Repeated injections should be made at different injection sites.

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

Calves:

5 mg of enrofloxacin/kg bw, corresponding to 1 ml/10 kg bw, once daily for 3-5 days.

Acute mycoplasma-associated arthritis due to enrofloxacin susceptible strains of *Mycoplasma bovis*: 5 mg of enrofloxacin/kg bw, corresponding to 1 ml/10 kg bw, once daily for 5 days.

The product can be administered by slow intravenous or subcutaneous administration. Not more than 10 ml should be administered at one subcutaneous injection site.

Sheep and goats

5 mg of enrofloxacin/kg bw, corresponding to 1 ml/10 kg bw, once daily by subcutaneous injection for 3 days.

Not more than 6 ml should be administered at one subcutaneous injection site.

Pigs:

2.5 mg enrofloxacin/ kg bw corresponding to 0.5 ml/10 kg bw once daily by intramuscular injection for 3 days.

Alimentary tract infection or septicaemia caused by *Escherichia coli*: 5 mg of enrofloxacin/kg bw, corresponding to 1 ml/10 kg bw, once daily by intramuscular injection for 3 days.

In pigs, the injection should be made in the neck at the ear base

Not more than 3 ml should be administered at one intramuscular site.

Dogs and cats:

5 mg enrofloxacin/kg bw corresponding to 1 ml/10 kg bw once daily by subcutaneous injection for up to 5 days.

As the vials should not be broached more than 40 times the user should select the most appropriate vial size according to the target species to be treated.

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

In cases of accidental overdoses digestive tract disorders (e.g. vomiting, diarrhoea) and neurological disorders may occur.

In pigs, no adverse effects were reported after the administration of 5 times the recommended dose.

Cats have been shown to suffer ocular damage after receiving doses of more than 15 mg/kg once daily for 21 consecutive days. Doses of 30 mg/kg given once daily for 21 consecutive days have been shown to cause irreversible ocular damage.

At 50 mg/kg given once daily for 21 consecutive days, blindness can occur.

In dogs, cattle, sheep and goats, overdose has not been documented.

In accidental overdose there is no antidote and treatment should be symptomatic.

4.11. Withdrawal period(s)

Calves:

Following intravenous injection: Meat and offal: 5 days.

Following subcutaneous injection: Meat and offal: 12 days.

Not authorised for use in animals producing milk for human consumption.

Sheep:

Meat and offal: 4 days.

Milk: 72 hours.

Goats:

Meat and offal: 6 days.

Milk: 96 hours.

Pigs:

Meat and offal: 13 days.

5. PHARMACOLOGICAL or IMMUNOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use, fluoroquinolones.
ATCvet 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. Target inhibition is caused by non-covalent binding of fluoroquinolone molecules to these 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. The mode of action of enrofloxacin is bactericidal and bactericidal activity is concentration dependent.

Antibacterial spectrum

Enrofloxacin is active against many Gram-negative bacteria such as *Escherichia coli*, *Klebsiella* spp., *Actinobacillus pleuropneumoniae*, *Mannheimia haemolytica*, *Pasteurella* spp. (e.g. *Pasteurella multocida*), *Bordetella* spp., *Proteus* spp., *Pseudomonas* spp., against Gram-positive bacteria such as *Staphylococcus* spp. (e.g. *Staphylococcus aureus*) and against *Mycoplasma* spp. at the recommended therapeutic doses.

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.

5.2. Pharmacokinetic particulars

Enrofloxacin is rapidly absorbed after parenteral injection. Bioavailability is high (approximately 100% in pig and cattle) with a low to moderate plasma protein binding (approximately 20 to 50%). Enrofloxacin is metabolized to the active substance ciprofloxacin at approximately 40 % in dogs and ruminants, less than 10 % in pigs and cats.

Enrofloxacin and ciprofloxacin distribute well into all target tissues, e.g. lung, kidney, skin, and liver, reaching 2- to 3-fold higher concentrations than in plasma. Parent substance and active metabolite are cleared from the body via urine and faeces.

Accumulation in plasma does not occur following a treatment interval of 24 h.

In milk, most of drug activity consists on ciprofloxacin. Overall drug concentrations peak at 2 hours after treatment showing an approximately 3-fold higher total exposure over the 24 hours dosing interval compared to plasma.

	Dogs	Cats	Pigs	Pigs	Cattle	Calves
Dose rate (mg/kg bw)	5	5	2.5	5.0	5.0	5.0
Route of administration	sc	sc	im	im	iv	sc
T _{max} (h)	0.5	2	2	2	/	1.2
C _{max} (µg/ml)	1.8	1.3	0.7	1.6	/	0.73
AUC (µg·h/ml)	/	/	6.6	15.9	7.11	3.09
Terminal half-life (h)	/	/	13.12	8.10	/	2.34
Elimination half-life (h)	4.4	6.7	7.73	7.73	2.2	/
F (%)	/	/	95.6	/	/	/

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Potassium hydroxide (for pH adjustment)
Hydrochloric acid, dilute (for pH adjustment)
n-Butyl alcohol
Water for injections.

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: 4 years.
Shelf life after first opening the immediate packaging: 28 days.

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

The product is presented in amber Type II glass bottles of 50 ml, 100 ml and 250 ml with chlorobutyl rubber stoppers sealed with a flip-off aluminium cap with a tamper-evident polypropylene seal.
Not all pack sizes may be marketed.

6.6. Special precautions for the disposal of unused veterinary medicinal products or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

FATRO S.p.A.
Via Emilia, 285
Ozzano Emilia - Bologna
Italy

8. MARKETING AUTHORISATION NUMBER

Vm 11557/4003

9. DATE OF FIRST AUTHORISATION

25 May 2019

10. DATE OF REVISION OF THE TEXT

November 2019

11. PROHIBITION OF SALE, SUPPLY AN/OR USE

For animal treatment only.
To be supplied only on veterinary prescription.

A handwritten signature in black ink, consisting of several loops and a long horizontal stroke at the end.

Approved 19 November 2019