

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

DANIDOL 150 mg/ml solution for injection for cattle, pigs and horses (DE, AT)
EDERAL 150 mg/ml solution for injection for cattle, pigs and horses (only ES)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:

Ketoprofen 150 mg

Excipients:

Benzyl alcohol (E1519) 10 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

A clear colourless to yellowish solution

4. CLINICAL PARTICULARS

4.1. Target species

Cattle, pigs and horses

4.2. Indications for use, specifying the target species

Cattle:

- Reduction of inflammation and pain associated with post-partum, musculoskeletal disorders and lameness.
- Reduction of fever associated with bovine respiratory disease.
- Reduction of inflammation, fever and pain in acute clinical mastitis. in combination with antimicrobial therapy where appropriate.

Pigs:

- Reduction of pyrexia in cases of respiratory disease and Postpartum Dysglactia Syndrome -PDS-(Metritis, Mastitis, Agalactia syndrome) in sows, in combination with antimicrobial therapy, where appropriate.

Horses:

- Reduction of inflammation and pain associated with osteoarticular and musculoskeletal disorders (lameness, laminitis, osteoarthritis, synovitis, tendinitis, etc.).
- Reduction of postoperative pain and inflammation.
- Reduction of visceral pain associated with colic.

4.3. Contraindications

Do not use in animals where there is the possibility of gastro-intestinal ulceration or bleeding, in order not to aggravate their situation.

Do not use in animals suffering from cardiac, hepatic, or renal disease.

Do not use in cases of known hypersensitivity to ketoprofen or acetyl-salicylic acid or to any of the excipients. Do not use in animals with evidence of blood dyscrasia or coagulopathy.

Do not administer other non-steroidal anti-inflammatory drugs (NSAIDs) concurrently or within 24 hours of each other.

4.4. Special warnings for each target species

None

4.5. Special precautions for use

Special precautions for use in animals

Do not exceed the recommended dose. Do not exceed the recommended treatment period.

The use of ketoprofen is not recommended in foals less than one month of age. When administering to animals of less than 6 weeks of age, ponies or in aged animals it is necessary to adjust the dose accurately as well as to perform a close clinical follow-up.

Avoid intra-arterial injection.

Avoid use in any dehydrated, hypovolaemic or hypotensive animals as there is a potential risk of increased renal toxicity'.

Since gastric ulceration is a common finding in PMWS (Post-weaning Multisystemic Wasting Syndrome), the use of ketoprofen in pigs affected by this pathology is not recommended, in order not to aggravate their situation.

In horses, avoid extravascular administration.

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

Avoid contact with the skin, eyes and mucous membranes.

In case of accidental skin, eye or mucous membrane contact, wash the affected area thoroughly with clean running water immediately. Seek medical advice if irritation persists.

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

Wash hands after use.

Hypersensitivity reactions (skin rash, urticaria) could occur. People with known hypersensitivity to the active substance or to any of the excipients should avoid contact with the veterinary medicinal product.

4.6. Adverse reactions (frequency and seriousness)

In very rare cases intramuscular injection of ketoprofen can cause mild, transient, necrotic subclinical muscular lesions that gradually resolve in the days after completion of treatment. Administration in the neck region minimizes the extension and severity of these lesions.

In very rare cases, in horses, transient local reactions, which disappeared after 5 days, were observed after one administration of the product at the recommended volume by extravascular route.

Due to the mechanism of action of ketoprofen, after repeated administrations, erosive and ulcerative lesions of the gastrointestinal tract may occur in very rare cases.

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

- Very common (more than 1 in 10 animals displaying adverse reaction(s) during the course of one treatment).
- Common (more than 1 but less than 10 animals in 100 animals).
- Uncommon (more than 1 but less than 10 animals in 1,000 animals).
- Rare (more than 1 but less than 10 animals in 10,000 animals).
- Very rare (less than 1 animal in 10,000 animals, including isolated reports).

If side effects occur treatment must be stopped and the advice of a veterinarian should be sought.

4.7. Use during pregnancy, lactation or lay

Pregnancy:

Studies in laboratory animals (rats, mice, rabbits) and cattle have not produced any evidence of adverse effects. Can be used in pregnant cows.

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

Lactation:

Can be used in lactating cows and sows.

The use is not recommended in lactating mares.

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

- Concurrent administration of diuretics or potentially nephrotoxic drugs should be avoided since there is an increase of renal disturbances, including renal failure. This is secondary to the diminished blood flow caused by the inhibition of prostaglandins synthesis.

- Do not administer other non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, anticoagulants or diuretics concurrently or within 24 hours of administration of the product since the risk of gastrointestinal ulceration and other adverse reactions may be exacerbated.
- The treatment free period should however take into account the pharmacological properties of the products used previously.
- Ketoprofen is highly bound to plasma proteins and may compete with other highly bound drugs which can lead to toxic effects.

4.9. Amounts to be administered and administration route

Intramuscular or intravenous use.

Cattle:

3 mg ketoprofen/kg body weight, i.e. 1ml of product per 50 kg body weight/ day, administered via the intravenous or intramuscular route, preferably in the neck region.

The duration of treatment is 1-3 days, and should be established according to the severity and duration of symptoms.

Pigs:

3 mg of ketoprofen/kg body weight i.e. 1 ml of the product per 50 kg body weight/ day, administered via the intramuscular route on a single occasion.

Depending on the response observed and based on the benefit-risk analysis by the responsible veterinarian treatment may be repeated at intervals of 24 hours for a maximum of three treatments. Each injection should be given at a different site.

Horses:

2.2 mg of ketoprofen/kg body weight, i.e. 0.75 ml of the product. per 50 kg body weight/ day, administered via the intravenous route. The duration of treatment is 1-5 days, and should be established according to the severity and duration of symptoms.

In the case of colic one injection is normally sufficient. A second administration of ketoprofen requires a clinical re-examination.

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

Overdose with non-steroidal anti-inflammatory drugs can lead to gastrointestinal ulceration, loss of proteins, hepatic and renal impairment.

In tolerance studies performed in pigs, up to 25% of the animals treated at three times the maximum recommended dose (9 mg/kg bw) for three days or at the recommended dose (3 mg/kg bw) for triple the maximum recommended time (9 days) showed erosive and/or ulcerative lesions in both the aglandular (pars oesophagica) and glandular parts of the stomach. Early signs of toxicity include loss of appetite and pasty faeces or diarrhoea.

The intramuscular administration of the product to cattle, at up to 3 times the recommended dose or for 3 times the recommended duration of the treatment (9 days) did not result in clinical signs of intolerance. However, inflammation as

well as necrotic subclinical lesions were detected at the injection site of the treated animals as well as an increase in CPK levels. The histopathological examination showed erosive or ulcerative abomasal lesions related to both dosage regimes.

Horses have been found to tolerate intravenous dosages of ketoprofen up to 5 times the recommended dose for three times the recommended duration (15 days) with no evidence of toxic effects.

If clinical signs of overdose are observed, there is no specific antidote, therefore symptomatic treatment should be initiated.

4.11. Withdrawal period(s)

Cattle:

Meat and offal: 2 days

Milk: zero hours

Horses:

Meat and offal: 1 day

Milk: Not authorised for use in mares producing milk for human consumption

Pigs:

Meat and offal: 3 days

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Anti-inflammatory and Antirheumatic Products, Non-Steroids, Propionic acid derivatives,
ATC vet code: QM01AE03

5.1. Pharmacodynamic properties

Ketoprofen, 2-(phenyl 3-benzoyl) propionic acid is a non-steroidal anti-inflammatory drug belonging to the arylpropionic acid group. The primary mechanism of action for ketoprofen is considered to be inhibition of the cyclooxygenase pathway of arachidonic acid metabolism, leading to decreased production of inflammatory mediators, such as prostaglandins and thromboxanes. This mechanism of action results in its anti-inflammatory, anti-pyretic and analgesic activity. These properties are also attributed to its inhibiting effect on bradykinin and superoxide anions together with its stabilizing action on lysosomal membranes.

The antiinflammatory effect is enhanced by the conversion of the (R)-enantiomer to (S)-enantiomer. It is known that the (S)-enantiomer supports the anti-inflammatory effect of ketoprofen.

5.2. Pharmacokinetic particulars

After intramuscular administration of the product (single dose of 3 mg ketoprofen/kg body weight), ketoprofen is rapidly absorbed, and has a high bioavailability.

Ketoprofen binds extensively to plasma proteins (>90%).

The concentrations of Ketoprofen are more sustained in inflammatory exudates than in plasma. It reaches high concentrations and persists in inflamed tissue, due to the fact that Ketoprofen is a weak acid. Ketoprofen is metabolized in the liver to inactive metabolites and it is excreted mainly in urine (primarily as glucuroconjugated metabolites) and, to a lesser extent, in faeces. Small amounts of ketoprofen can be detected in the milk of treated animals.

In cattle, following the intramuscular administration of the product (single dose of 3 mg ketoprofen/kg body weight), the active drug substance is rapidly absorbed, reaching its average C_{max} in plasma (mean value: 7.2 µg/ml) between 0.5 and 1 hour (t_{max}) after initiation of treatment. The fraction of dose absorbed is very high ($92,51 \pm 10,9\%$)

Following the intravenous administration in cattle, elimination half-life ($t_{1/2}$) is of 2.1 h. The distribution volume (Vd) of 0.41L/kg, and plasma clearance (Cl) of 0.14 L/h/kg.

In pigs, following the intramuscular injection of a single dose of 3 mg/ketoprofen/kg body weight, the active drug substance is rapidly absorbed, reaching its average C_{max} in plasma (mean value: 16 µg/ml) between 0.25 and 1.5h (t_{max}) after initiation of the treatment. The fraction of dose absorbed is $84.7 \pm 33\%$.

Following the intravenous administration in pigs, elimination half-life ($t_{1/2}$) is of 3.6 h. The distribution volume (Vd) of 0.15 L/kg, and plasma clearance (Cl) of 0.03 L/h/kg.

Ketoprofen also shows a low volume of distribution when administered by the intravenous route in equine species.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Benzyl alcohol (E1519)
L-arginine
Citric acid anhydrous *for pH adjustment*
Water for injection

6.2. 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: 5 years
Shelf-life after first opening the immediate packaging: 28 days

6.4. Special precautions for storage

Keep the vial in the outer carton

6.5. Nature and composition of immediate packaging

Nature of the container

Amber type II glass vials of 100 ml and 250 ml, closed with bromobutyl rubber stoppers and flip-off aluminium caps (100 ml) or aluminium caps (250 ml).

Pack sizes

Box with 1, 5 or 10 vials of 100 ml.

Box with 1 or 5 vials of 250 ml.

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

Ecuphar Veterinaria S.L.U.
C/Cerdanya, 10-12 Planta 6º
08173 Sant Cugat del Vallés
Barcelona (España)

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

02/2022

PROHIBITION OF SALE, SUPPLY AND/OR USE

Dispensing conditions:
Veterinary prescription
For animal treatment only

Administration by a veterinary surgeon, or under their direct responsibility

Administration only by a veterinary surgeon, in cases of intravenous administration.