1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Ketiva 150 mg/ml solution for injection for cattle, pigs and horses

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:

Ketoprofen 150 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 E1519	15 mg
Arginine	
Citric acid monohydrate (for pH adjustment)	
Water for injection	

Clear, colourless to almost colourless or slightly yellowish or greenish-yellow solution.

3. CLINICAL INFORMATION

3.1 Target species

Cattle, pigs and horses

3.2 Indications for use for each 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.
- Reduction of post-operative pain associated with dehorning in calves.

Pigs:
- Reduction of pyrexia in cases of respiratory disease and Postpartum Dysgalactia 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.

3.3 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 hypersensitivity to the active substance 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.

3.4 Special warnings

Treatment of calves with ketoprofen 10 - 30 minutes before dehorning reduces post-operative pain. Ketoprofen alone will not provide adequate pain relief during the dehorning procedure. To obtain adequate pain relief during dehorning, co-medication with an appropriate local anaesthetic is needed.

3.5 Special precautions for use

Special precautions for safe use in the target species:

Avoid intra-arterial injection. Do not exceed recommended dose and period of treatment.
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 use in any dehydrated, hypovolaemic or hypotensive animals as there is a potential risk of increased renal toxicity.
Animals should have adequate access to drinking water over the course of treatment.
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:

Ketoprofen and benzyl alcohol can cause hypersensitivity reactions. People with known hypersensitivity to ketoprofen or benzyl alcohol should avoid contact with the veterinary medicinal product.
This veterinary medicinal product may be irritant to the skin, eyes and mucous membranes. 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.
This veterinary medicinal product may cause somnolence, dizziness, nausea and vomiting. 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.
NSAIDs, such as ketoprofen, may affect fertility and be harmful for the unborn child. Pregnant and breastfeeding women should administer the veterinary medicinal product with caution.
Wash hands after use.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Cattle, pigs:

Very rare (<1 animal / 10 000 animals treated, including isolated reports):	Injection site necrosis[1]; Digestive tract disorder[2]; Renal disorder.

[1] When injected intramuscularly. Lesions are subclinical, mild and gradually resolve in the days after completion of treatment. Administration in the neck region minimizes the extension and severity of these lesions.
[2] Erosive and ulcerative lesions after repeated administration, gastric intolerance.

Horses:

Very rare (<1 animal / 10 000 animals treated, including isolated reports):	Injection site necrosis[3], Injection site reaction[4]; Digestive tract disorder[5]; Renal disorder.

[3] When injected intramuscularly. Lesions are subclinical, mild and gradually resolve in the days after completion of treatment. Administration in the neck region minimizes the extension and severity of these lesions.
[4] Local reaction resolving after 5 days, after one administration of the veterinary medicinal product at the recommended volume by extravascular route.
[5] Erosive and ulcerative lesions after repeated administration, gastric intolerance.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or its local representative or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

Laboratory studies in rats, mice and rabbits and studies in cattle have not produced any evidence of teratogenic or embryotoxic effects.

Pregnancy:
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 according to the benefit-risk assessment by the responsible veterinarian.

Lactation:
Can be used in cows and sows during lactation.
Do not use in lactating mares.

3.8 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 NSAIDs, corticosteroids, anticoagulants or diuretics concurrently or within 24 hours of administration of the veterinary medicinal 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 veterinary medicinal products used previously.
- Ketoprofen is highly bound to plasma proteins and may compete with other highly bound drugs which can lead to toxic effects.

3.9 Administration routes and dosage

Cattle: intramuscular use (i.m.) or intravenous use (i.v.)
Pigs: intramuscular use (i.m.)
Horses: intravenous use (i.v.)

To ensure a correct dosage, body weight should be determined as accurately as possible. The use of suitably calibrated measuring equipment is recommended.

Cattle:
3 mg of ketoprofen/kg body weight, i.e. 1 ml of the veterinary medicinal product/50 kg body weight/ day, administered via the i.v. or i.m. route, preferably in the neck region.
For the reduction of post-operative pain associated with dehorning in calves, it is recommended to administer the veterinary medicinal product at the same time as the local anaesthetic 10 - 30 minutes before dehorning.
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 veterinary medicinal product/50 kg body weight/day, administered via the i.m. 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 veterinary medicinal product/50 kg body weight/day, administered via the i.v. 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.

The rubber stopper can be punctured a maximum of 25 times. To prevent excessive puncturing of the rubber stopper, when treating a large number of animals with small volumes, use of a dispensing pin is recommended.

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

Overdose with NSAIDs 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 veterinary medicinal 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.

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

Not applicable.

3.12 Withdrawal periods

Meat and offal:
Cattle: 2 days
Pigs: 3 days
Horses: 1 day

Milk:
Cattle: zero hours
Not authorised for use in mares producing milk for human consumption.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QM01AE03

4.2 Pharmacodynamics

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

4.3 Pharmacokinetics

After intramuscular administration of the veterinary medicinal 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 veterinary medicinal product (single dose of 3 mg ketoprofen/kg body weight), the active drug substance is rapidly absorbed, reaching its average Cmax in plasma (mean value: 7.2 μg/ml) between 0.5 and 1 hour (tmax) after initiation of treatment. The fraction of dose absorbed is very high (92.51±10.9%). Following the intravenous administration in cattle, elimination half-life (t1/2) is of 2.1 h. The distribution volume (Vd) of 0.41 L/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 Cmax in plasma (mean value: 16 μg/ml) between 0.25 and 1.5h (tmax) after initiation of the treatment. The fraction of dose absorbed is 84.7±33%. Following the intravenous administration in pigs, elimination half-life (t1/2) 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.

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: 30 months
Shelf life after first opening the immediate packaging: 28 days

5.3 Special precautions for storage

Do not freeze.

5.4 Nature and composition of immediate packaging

Amber glass vial type II, closed with a bromobutyl rubber stopper and aluminium pull off cap or aluminium/plastic flip off cap.

Pack sizes:
Carton box containing one 100 ml vial
Carton box containing ten 100 ml vials

Not all pack sizes may be marketed.

5.5 Special precautions for the disposal of unused veterinary medicinal products 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 THE MARKETING AUTHORISATION HOLDER

VetViva Richter GmbH

7. MARKETING AUTHORISATION NUMBER(S)

VPA23462/019/001

8. DATE OF FIRST AUTHORISATION

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

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

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