1. NAME OF THE VETERINARY MEDICINAL PRODUCT

KETOPROCEN 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)	10 mg
Arginine	
Citric acid *(for pH adjustment)*	
Water for injections	

Clear and colourless to yellowish solution free from visible particles.

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.

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, acetylsalicylic acid or to any of the excipients.
Do not use in animals with evidence of blood dyscrasia or coagulopathy.
Do not use with other non-steroidal anti-inflammatory drugs (NSAIDs) concurrently or within 24 hours of each other.

3.4 Special warnings

None.

3.5 Special precautions for use

Special precautions for safe use in the target species:

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:

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.
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.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Cattle and 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 administrations, gastric intolerance.

Horses:

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Injection site necrosis[1] Injection site reaction[2] Digestive tract disorder[3] 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] Local reaction resolving after 5 days, after one administration of the veterinary medicinal product at the recommended volume by extravascular route.
[3] Erosive and ulcerative lesions after repeated administrations, gastric intolerance.

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

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

Pregnancy:
Laboratory studies in rats, mice and rabbits, and in cattle have not produced any evidence of adverse effects. Can be used during pregnancy in 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 during lactation in cows and sows.
The use is not recommended 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 non-steroidal anti-inflammatory drugs (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

Intravenous or intramuscular use.

Cattle:
3 mg ketoprofen/kg body weight, i.e. 1 ml of the veterinary medicinal 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 ketoprofen/kg body weight, i.e. 1 ml of the veterinary medicinal 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, the treatment may be repeated at 24-hour intervals for a maximum of three treatments. Each injection should be administered at a different site.

Horses:
2.2 mg ketoprofen/kg body weight, i.e. 0.75 ml of the veterinary medicinal 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 usually sufficient. A second administration of ketoprofen requires a clinical re-examination.

To ensure a correct dosage, body weight should be determined as accurately as possible

For multiple vial entry, an aspirating needle or multi-dose syringe is recommended to avoid excessive broaching of the stopper.

The cap may be safely punctured up to 30 times.

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

Overdose with non-steroidal anti-inflammatory drugs can lead to gastro-intestinal 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 mas 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

Cattle:
Meat and offal: 2 days
Milk: zero hours

Horses:
Meat and offal: 1 day
Not authorised for use in animals producing milk for human consumption.

Pigs:
Meat and offal: 3 days

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 anti-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 glucuronide conjugated 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 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±10.9%) Following the intravenous administration in cattle, elimination half-life ($t_{1/2}$) is of 2.1 h. The distribution volume (Vd) of 0.41 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 (t_{max}) after initiation of the treatment. The fraction of dose absorbed is 84.7±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.

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

5.3 Special precautions for storage

Keep the vial in the outer carton in order to protect from light.

5.4 Nature and composition of immediate packaging

Type II amber glass vials, closed with type I bromobutyl stoppers and aluminium flip-off capsules.
Amber polypropylene (PP) vials, closed with type I bromobutyl stoppers and aluminium flip-off capsules.

Package sizes:
- Cardboard box with 1 glass vial of 100 ml
- Cardboard box with 1 glass vial of 250 ml
- Cardboard box with 1 PP vial of 100 ml
- Cardboard box with 1 PP vial of 250 ml

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

CENAVISA, S.L.

7. MARKETING AUTHORISATION NUMBER(S)

VPA23448/002/001

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).