*[Version 9, 03/2022] corr. 11/2022*

# ANNEX I

# SUMMARY OF PRODUCT CHARACTERISTICS

# 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Labiprofen 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 (E 1519) | 10 mg |
| Arginine | |
| Citric acid monohydrate (for pH adjustment) | |
| Water for injections | |

Clear colourless to slightly yellow solution for injection, 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 in combination with antimicrobial therapy where appropriate.
- 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 cases of gastro-intestinal ulceration or bleeding, in order not to aggravate their situation.
Do not use in cases of 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 cases of blood dyscrasia, coagulopathy or haemorrhagic diathesis. Do not administer 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 accidental self-injection. In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.
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.

Wash hands after use.

Special precautions for the protection of the environment:

Not applicable.

### 3.6. Adverse events

Cattle, pigs

| | |
|---|---|
| Undetermined frequency (cannot be estimated from the available data) | Muscle necrosis[1]<br>Erosive and ulcerative lesions of the gastrointestinal tract[2]<br>Gastric or renal intolerance[3] |

Horse

| | |
|---|---|
| Undetermined frequency (cannot be estimated from the available data) | Muscle necrosis[1]<br>Erosive and ulcerative lesions of the gastrointestinal tract[2]<br>Gastric or renal intolerance[3]<br>Injection site reactions[4] |

1. After intramuscular injection, subclinical, mild and transient, gradually resolving in the days after completion of treatment. Administration in the neck region minimizes the extension and severity of these lesions.

2. After repeated administrations (due to the mechanism of action of ketoprofen).

3. In certain individuals. Due to the action of inhibition of prostaglandins' synthesis (in common with all NSAIDS).

4. Transient. Observed after one administration of the product at the recommended volume by extravascular route. Disappeared after 5 days.

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 also the section 16 of the package leaflet for respective contact details.

## 3.7. Use during pregnancy, lactation or lay

Pregnancy:
Laboratory studies in rats, mice and rabbits, and studies 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 during lactation in 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 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.

## 3.9. Administration routes and dosage

Intramuscular use: cattle, pigs
Intravenous use: cattle, horses

- 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.

### 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 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

To be completed in accordance with national requirements after conclusion of the MRP/DCP/SRP

### 3.12 Withdrawal periods

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

Pig:
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 ant-inflammatory effect of ketoprofen.
The maximum anti-inflammatory effects of ketoprofen occur at 4 hours after a dose and last for 24 hours, illustrating that the anti-inflammatory effects are not related to plasma concentrations in horses.

### 4.3 Pharmacokinetics

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±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 $C_{max}$ 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±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.

In horses Ketoprofen is 92.8% protein bound and it has a moderate Vd of approximately 0.5 L/kg and short plasma elimination half-lives of 1 to 1.5 hours. The active substance is hepatically metabolized by conjugation reactions, with only 25% of a dose eliminated as unchanged in urine.

## 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

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

### 5.4 Nature and composition of immediate packaging

Amber type II glass vials of 50 ml, 100 ml and 250 ml closed with bromobutyl stoppers and aluminium caps.

Package sizes:
Cardboard box containing 1 vial of 50 ml
Cardboard box containing 1 vial of 100 ml
Cardboard box containing 1 vial of 250 ml
Cardboard box containing 12 vials of 50 ml
Cardboard box containing 10 vials of 100 ml
Cardboard box containing 10 vials 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

Labiana Life Sciences, S.A.

## 7. MARKETING AUTHORISATION NUMBER(S)

XXXXXX

## 8. DATE OF FIRST AUTHORISATION

Date of first authorisation: DD/MM/YYYY

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

{MM/YYYY}

## 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).