SHORT WITHDRAWAL PERIOD:

CATTLE: Meat & Offal: IV: 1 Day, IM: 2 Days, Milk: 0 Hours

PIGS: Meat & Offal: 2 Days

Ketoprofen 100 mg/ml solution for injection for cattle, horses and pigs
Pharmacodynamics

The non-steroidal anti-inflammatory agent (NSAID) Ketoprofen has a pronounced analgesic, antipyretic and anti-inflammatory action.

Ketoprofen acts by inhibition of the synthesis of inflammation mediators such as bradykinin, tromboxane and prostaglandins.\textsuperscript{5,6,7,8,9}

Ketoprofen compared to other NSAIDs

- **Antipyretic effect:**
  - 3 x indomethacin
  - 12.5 x phenylbutazone

- **Anti-inflammatory potential:**
  - 20 x ibuprofen
  - 80 x phenylbutazone
  - 160 x aspirin

- **Analgesic effect:**
  - 20-70 x aspirin

Pharmacokinetics

KELAPROFEN is quickly absorbed following intramuscular administration reaching maximal plasma concentrations in cattle within 25 minutes and in pigs 34 minutes after injection.\textsuperscript{12,13}

Kelaprofen 100 mg/ml solution for injection for cattle, horses and pigs

An inflammation is a natural reaction of the body to tissue damage or external stimuli, intended to remove the harmful agent and to restore the damage caused.

**General tolerance**

- **HORSE:** following 5-times normal dose for 15 days no hematological, clinical and biochemical effects\textsuperscript{11}
- **CATTLE:** following 5-times normal dose for 5 days no signs of general intolerance\textsuperscript{7}
- **PIGS:** following 3-times normal dose for 3 days no significant side effects\textsuperscript{23}

**Local tolerance**

Absence of pain reactions and relevant tissue damage following intramuscular injection of the recommended dose in cattle.\textsuperscript{12}

**Bioequivalence**

KELAPROFEN 100 mg/ml proved to be bioequivalent in horses, cattle and pigs with the reference veterinary medicine containing ketoprofen.\textsuperscript{1,19}

Figure 1. Inhibition of synthesis of inflammation mediators in calves following IV administration of ketoprofen (3 mg/kg), flunixin (2.2 mg/kg) and tolfenamic acid (2 mg/kg).\textsuperscript{6}

Figure 2. Mean plasma concentrations of ketoprofen in cattle following intramuscular injection of KELAPROFEN 100 mg/ml and the reference veterinary medicine containing ketoprofen at a dose of 3 mg/kg body weight.\textsuperscript{1}
Efficacy in horses

Following a 5-day treatment significant improvement is shown in pain at palpation and manipulation, oedema, skin temperature and lameness score.

In colic treatment excellent clinical improvement of pain, pulse frequency, breathing frequency and sweating is shown one hour after treatment.

Efficacy in pigs

Ketoprofen efficiently lowers fever and limits detrimental effects of the infection on feed intake. Due to its anti-inflammatory effect at the level of the respiratory tract, respiration becomes more efficacious and frequency lower.

In the treatment of M.M.A., 72 hours following administration of ketoprofen in conjunction with an antibiotic, 68% of sows made a recovery.

Efficacy in cattle

An increased response to an antibiotic treatment in respiratory infections is clearly demonstrated with less lung lesions when ketoprofen is also administered.

In Gram-negative clinical mastitis a combined ketoprofen and antibiotic therapy clearly restores premastitis daily milk production volume in 92 to 94% of treated cows, compared to 64 to 82% of control animals.

Ketoprofen also demonstrated efficacy in treatment of udder oedema, colic and musculoskeletal affections.

References

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16. SHIPGEL N.Y., Research in veterinary science, 1994, 56, 62-68
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20. ANONYMOUS – EMEA/CVMP/016/00-corr-Final

Posology, administration and withdrawal period

<table>
<thead>
<tr>
<th></th>
<th>PIGS</th>
<th>CATTLE</th>
<th>HORSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADMINISTRATION</td>
<td>Deep IM</td>
<td>IV or deep IM</td>
<td>IV</td>
</tr>
<tr>
<td>POSOLOGY</td>
<td>1 ml Kelaprofen per 33 kg BW</td>
<td>1 ml Kelaprofen per 33 kg BW</td>
<td>1 ml Kelaprofen per 45 kg BW</td>
</tr>
<tr>
<td>DURATION of TREATMENT</td>
<td>Once</td>
<td>Once daily for 3 days</td>
<td>musculoskeletal conditions: 3 to 5 consecutive days. colic: may be repeated when colic returns.</td>
</tr>
<tr>
<td>WITHDRAWAL PERIOD</td>
<td>Meat: 2 days</td>
<td>Meat: IV 1 day – IM 2 days Milk: 0 hours</td>
<td>Meat: 1 day Not to be used in lactating animals when milk is intended for human consumption.</td>
</tr>
</tbody>
</table>

KETAPROFEN 100 mg/ml

- bioequivalent with the reference veterinary medicinal product containing ketoprofen
- very short withdrawal times

Ketoprofen

- penetrates fast and reaches high therapeutic concentrations at site of inflammation
- very well tolerated
- outstanding antipyretic, analgesic and anti-inflammatory properties and is indicated in numerous conditions
1. NAME OF THE VETERINARY MEDICAL PRODUCT
Kalaprofen 100 mg/mL solution for injection for cattle, horses and pigs.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Per ml
Active substance: Ketoprofen 100mg
Excipients: Benzyl alcohol (E1519) 10mg
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection. Clear, colourless or yellowish solution.

4. CLINICAL PARTICULARS
4.1 Target species
Horses, cattle, pigs.

4.2 Indications for use, specifying the target species
Horse:
- the alleviation of inflammation and pain associated with musculoskeletal disorders;
- the alleviation of visceral pain associated with colic.
Cattle:
- the supportive treatment of parturient pain associated with calving;
- reducing the pyrexia and distress associated with bacterial respiratory disease when used in conjunction with antimicrobial therapy as appropriate;
- improving the recovery rate in acute clinical mastitis, including acute endotoxin mastitis, caused by gram negative micro-organisms, in conjunction with antimicrobial therapy;
- reducing edema of the udder associated with calving.
Pigs:
- reducing the pyrexia and respiratory rate associated with bacterial or viral respiratory disease when used in conjunction with antimicrobial therapy as appropriate;
- the supportive treatment of Mastitis Metritis Agalactica Syndrome in sows, in conjunction with antimicrobial therapy as appropriate.

4.3 Contra-indications
Do not use in animals with known hypersensitivity to the active substances or to any of the excipients.
Do not administer other non-steroidal anti-inflammatory drugs (NSAIDs) concurrently or within 24 hours of each other, corticosteroids, diuretics and anticoagulants.
Do not use in animals suffering from cardiac, hepatic or renal disease, where there is the possibility of gastro-intestinal ulceration or bleeding, or where there is evidence of blood dyscrasia.

4.4 Special warnings for each target species
None.

4.5 Special precautions for use
Special precautions for use in animals
The use of ketoprofen is not recommended in foals under the age of 15 days. Use in any animal less than 6 weeks of age or in aged animals may involve additional risk.
If such use cannot be avoided animals may require a reduced dosage and careful management.
Avoid use in any dehydrated, hypovolaemic or hypotensive animals as there is a potential risk of increased renal toxicity.
Avoid intra-articular injection.
Do not exceed the stated dose or duration of treatment.
Special precautions to be taken by the person administering the medicinal product to the animals:
People with known hypersensitivity to the active substance and/benzyl alcohol should avoid contact with this product
In case of accidental self injection, seek medical advice and provide the package leaflet or label to the physician.
Wash hands after use.
Avoid splashes on the skin and eyes. Wash affected area thoroughly with water should this occur. If irritation persists seek medical advice.

4.6 Adverse reactions (frequency and seriousness)
In common with all NSAIDs, due to their action of inhibition of prostaglandin synthesis, there can be the possibility in certain individuals of gastric or renal intolerance. Allergic reactions may occur very rarely.

4.7 Use during pregnancy, lactation or lay
The safety of Ketoprofen has not been investigated in pregnant laboratory animals (rats, mice and rabbits) or cattle. Ketoprofen showed no teratogenic or embryotoxic effects. Ketoprofen may be given to pregnant and lactating cattle. As the safety of ketoprofen has not been assessed in pregnant sows, the product should be used in these cases only according to the benefit/risk assessment by the responsible veterinarian. Do not use in pregnant mares.

4.8 Interaction with other medicinal products and other forms of interaction
Do not administer with other non-steroidal anti-inflammatory drugs (NSAIDs) concurrently or within 24 hours of each other, corticosteroids, diuretics and anticoagulants.
Some NSAIDs may be highly bound to plasma proteins and compete with other highly bound drugs which can lead to toxic effects.
Concurrent administration with nephrotoxic drugs should be avoided.

4.9 Amounts to be administered and administration route
Use of a draw off needle is recommended when treating large groups of animals. Do not breach the container more than 33 times.

Horse: Intravenous administration
For use in musculo-skeletal conditions: 2.2 mg ketoprofen/kg i.e. 1ml of product per 45 kg body weight, administered by intravenous injection once daily for up to 3 to 5 days.
For use in equine colic: 2.2 mg/kg (1 ml/45 kg) body weight, given by intravenous injection for immediate effect. A second injection may be given if colic recurs.

Cattle: Intravenous or intramuscular administration.
3 mg ketoprofen/kg body weight, i.e. 1ml of product per 33 kg body weight, administered by intravenous or deep intramuscular injection once daily for up to 3 days.
Pigs: Intramuscular administration.
3 mg ketoprofen/kg body weight, i.e. 1ml of product per 33 kg body weight, administered once by deep intramuscular injection.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary
No clinical signs were observed when ketoprofen was administered to horses at 5 times the recommended dose for 15 days, to cattle at 5 times the recommended dose for 5 days, or to pigs at 3 times the recommended dose for 3 days.

4.11 Withdrawal periods
Cattle: Meat and offal:
- IV: 1 day
- IM: 2 days
Milk: zero hours.
Horses: Meat and offal: 1 day.
Milk: Not authorised for use in lactating animals producing milk for human consumption.
Pigs: Meat and offal: 2 days.

5. PHARMACOLOGICAL PROPERTIES
Pharmacotherapeutic group: Anti-inflammatory, antirheumatic products, non-steroids; propionic acid derivatives.
ATC Vet Code: G01AE03

5.1 Pharmacodynamic properties
Ketoprofen is a derivative of phenylpropionic acid, and belongs to the non steroidal anti-inflammatory group of drugs. Like all such substances, its principal pharmacological actions are anti-inflammatory, analgesic and anti pyretic. The mechanism of action is related to the ability of ketoprofen to interfere with the synthesis of prostaglandins from precursors such as arachidonic acid.

5.2 Pharmacokinetic properties
Ketoprofen is rapidly absorbed. The maximum plasma concentration is reached in less than an hour after parenteral administration. The bioavailability is about 80 to 95%. Ketoprofen binds strongly to plasma proteins (about 95%), allowing its accumulation in the exudate at the site of inflammation.
This action is longer than what should be expected from the plasma half-life that varies between one and four hours depending on the species. Ketoprofen enters the synovial fluid and remains there at higher levels than in plasma, with a half-life two to three times higher than in plasma.
Ketoprofen is metabolized in the liver and 90 percent is excreted in the urine and is complete after 18 hours.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
L-Arginine
Benzyl Alcohol (E1519)
Citric Acid Monohydrate (for pH adjustment)
Water for Injection

6.2 Incompatibilities
In the absence of compatibility studies, this product should not be mixed with other substances in the same syringe.

6.3 Shelf-life
Shelf-life of the veterinary medicinal product as packaged for sale: 30 months. Shelf-life after first opening of the immediate packaging: 28 days.

6.4 Special precautions for storage
Do not refrigerate or freeze.
Protect from light.

6.5 Nature and composition of immediate packaging
Nature of the container:
Amber glass vials type II of 50, 100 and 250 ml, closed with bromobutyl rubber stoppers and aluminium caps, packed in an outer carton.
Clinical containers of 6, 10 and 12 units of 50 ml, 100 ml and 250 ml. Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products, if appropriate
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
KELA N.V.
St. Lanaartseweg 48
2320 Hoogstraten
BELGIUM

8. MARKETING AUTHORISATION NUMBER
Vm 061264000

9. DATE OF FIRST AUTHORISATION
27 February 2012.

10. DATE OF REVISION OF THE TEXT
February 2012.