ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

**United Kingdom**
**Veterinary Medicines Directorate**
**Woodham Lane**
**New Haw**
**Addlestone**
**KT15 3LS**

**DECENTRALISED**
**(Reference Member State)**

**DECENTRALISED PROCEDURE**

# PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

## KetoProPig 100 mg/ml Oral Solution for use in drinking water for Pigs

**PuAR correct as of 04/09/2018 when RMS was transferred to ES.**
**Please contact the RMS for future updates.**

# MODULE 1

## PRODUCT SUMMARY

| | |
|---|---|
| EU Procedure number | UK/V/0239/001/DC |
| Name, strength and pharmaceutical form | KetoProPig 100 mg/ml Oral Solution for use in drinking water for Pigs |
| Applicant | Labiana Life Sciences S.A.U.<br>C/Venus 26<br>Can Parellada Industrial<br>Terrassa<br>08228 Barcelona<br>Spain |
| Active substance | Ketoprofen |
| ATC Vetcode | QM01AE03 |
| Target species | Pigs |
| Indication for use | Symptomatic treatment for reduction of pyrexia in cases of acute infectious respiratory disease in fattening pigs in combination with an appropriate anti-infective therapy. |

# MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

# MODULE 3

## PUBLIC ASSESSMENT REPORT

| | |
|---|---|
| Legal basis of original application | Decentralised application in accordance with Article 13a of Directive 2001/82/EC as amended. |
| Date of completion of the original decentralised procedure | 29 April 2008 |
| Date product first authorised in the Reference Member State (MRP only) | n/a |
| Concerned Member States for original procedure | Austria<br>Belgium<br>Czech Republic<br>Denmark<br>France<br>Germany<br>Hungary<br>Italy<br>The Netherlands<br>Poland<br>Portugal<br>Spain |

# I. SCIENTIFIC OVERVIEW

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released on the market. It has been shown that the product can be safely used in the target species; the slight reactions observed are indicated in the SPC. The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy of the product was demonstrated according to the claims made in the SPC. The overall risk/benefit analysis is in favour of granting a marketing authorisation.

# II. QUALITY ASPECTS

## *A. Composition*

The product contains the active substance ketoprofen and excipients: arginine, benzyl alcohol, citric acid monohydrate and purified water.

The container/closure system comprises 1 litre white high density polyethylene containers coated with fluorinated polymers, provided with white polypropylene caps with screw top and sealed with a three layer-seal. Each container is provided with a polypropylene cup measuring device graduated from 10 up to 75 ml. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and presence of preservative are justified.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

## *B. Method of Preparation of the Product*

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

## *C. Control of Starting Materials*

The active substance is ketoprofen an established active substance described in the European Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

Each excipient is the subject of a monograph in the European Pharmacopoeia, which appropriately forms the raw material specification. Copies of both the supplier's and the finished product manufacturer's batch analysis data have been submitted for each ingredient. All results are satisfactory.

## *D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies*

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

## *E. Control on intermediate products*

There are no intermediate products.

## *F. Control Tests on the Finished Product*

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product.
Satisfactory validation data for the analytical methods have been provided.
Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

## *G. Stability*

Stability data on the active substance have been provided in accordance with applicable European guidelines. The Certificate of Suitability indicates a retest interval of 5 years for material packed in double polyethylene bags within a cardboard outer.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions. Appropriate in-use stability data on the finished product have also been provided.

## *H. Genetically Modified Organisms*

Not applicable.

## *J. Other Information*

Shelf-life

- Shelf-life of the veterinary medicinal product as packaged for sale: 36 months
- Shelf-life after first opening the immediate packaging: 4 months
- Shelf-life after dilution: 24 hours

Special precautions for storage

This veterinary medicinal product does not require any special storage conditions

# III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

## *III.A Safety Testing*

The applicant submitted published literature and book references as well as company sponsored studies to support the application.

### *Pharmacological Studies*

**Pharmacodynamics**

The applicant has provided bibliographical data which show the mode of action of ketoprofen. Ketoprofen, 2-(phenyl 3benzoyl) propionic acid, is a nonsteroidal anti-inflammatory drug belonging to the arylpropionic acid group. It contains a chiral centre and therefore exists as R (-) and S (+) enantiomeric[1] forms. It has been shown that, *in vivo*, these compounds undergo uni-directional sterospecific metabolic chiral inversion from the inactive R form to the pharmacologically active S form. Ketoprofen inhibits the biosynthesis of PGE2 and PGF2 alpha without affecting the ratio of PGE2/PGF2 alpha and thromboxanes. Although it is a cyclooxygenase inhibitor, ketoprofen is said to stabilize lysosomal membranes and antagonizes the actions of bradykinin. Ketoprofen possesses anti-inflammatory, analgesic and antipyretic activity.

**Pharmacokinetics**

A number of references have been provided relating to pharmacokinetics and absorption, metabolism and excretion. Oral bioavailability of NSAIDs[2] is generally good with bioavailability ranging from 50% to 100%. It has been shown that concomitant administration of food and other drugs may have a minor effect on the onset or rate of absorption. It was also reported that food only reduces the rate but not the extent of absorption. Bioavailability does not seem to be impaired by food. After oral administration of the racemic mixture, absorption is non-enantioselective. Pharmacokinetic studies in the rat, dog and monkey have shown that gastrointestinal absorption of ketoprofen is rapid and almost complete with maximal plasma concentration achieved within 0.25 to 2 hours after oral administration. Administration of multiple doses yields absorption characteristics which are similar to those seen following single doses.

After absorption, ketoprofen binds extensively to plasma proteins, mainly albumin , proving that this union is enantioselective. Mean distribution volume was 223.2 ml/kg. The predominant metabolic route is by glucoconjugation, forming the corresponding ketoprofen metabolites (50%-80% of the parent drug), which are rapidly excreted through urine. Liver is the main organ involved in the elimination of the drug. Mean elimination lifetime value was 2.1 hours and MRT 3.1 hours.

[1] Enantiomers, when present in a symmetric environment, have identical chemical and physical properties except for their ability to rotate plane-polarized light by equal amounts but in opposite directions. A mixture of equal parts of an optically active isomer.
[2] NSAIDs – Non-steroidal anti-inflammatory drugs

## *Toxicological Studies*

### Single Dose Toxicity

The applicant has provided bibliographical data in the acute toxicity of ketoprofen in various species by different routes. Gastrointestinal damage and bleeding are the major side effects of NSAIDs. A lethal dose ($LD_{50}$) when administered orally in rats was reported to be 100 $LD_{50}$ (mg/kg), this being over 30 times the recommended daily dose of 3 mg of ketoprofen/kg bodyweight.

Repeated Dose Toxicity

A number of studies were reported on the repeated dose toxicity of ketoprofen Species included rats, mice, dogs and baboons

| Species | Route | Dose used (mg/kg) | Toxic effects |
|---|---|---|---|
| Rat | Oral | 300 (30 days continuously) | Changes in spleen & testicular weight |
| Rat | Oral | 1080 (26 weeks intermittently) | Death |
| Rat | Rectal | 300 (30 days continuously) | Pigmented/nucleated red blood cells, weight loss or decreased weight gain, death |
| Mouse | Oral | 900 (5 days intermittently) | Death |
| Dog | Oral | 1092 (13 weeks intermittently) | Ulceration or bleeding from duodenum, weight loss or decreased weight gain, death |
| Rat | Oral (feed) | 6 mg/kg/day | NOEL |
| | Oral | 2 mg/kg/day | NOEL |
| Dog | Oral | 2 mg/kg/day | NOEL |
| Baboons | Oral | 4.5 mg/kg/day | NOEL |

**Reproductive Toxicity, including Teratogenicity:**

The applicant has provided references from literature relating to the effect of ketoprofen on reproduction. In fertility studies, in rats, effects of ketoprofen on male and female reproduction functions were observed with a NOEL[3] of 3 mg/kg/day.

There was a significant increase in the number of blastocyst pre-implantation deaths observed in rats which were administered 10 mg ketoprofen/kg compared to the other NSAIDs (indomethacin, ibuprofen and aspirin).

**Embryotoxicity/foetotoxicity (inc. teratogenicity)**

The applicant has provided bibliographic data relating to the effect of ketoprofen on reproduction. It was shown that after oral administration, no embryotoxic or teratogenic effects could be seen in rats and mice. However, in rats, ketoprofen was maternotoxic at 9 mg/kg bw/day. In rabbits, ketoprofen was maternotoxic for doses higher than 2 mg/kg bw/day after oral administration. The NOEL for embryotoxicity was 2 mg/kg bw/day.

[3] NOEL = No observed effect level

Ketoprofen did not show any embryotoxic or teratogenic effects in mice, rats and rabbits which were given doses of 3 – 12 mg/kg orally during the period of organogenesis.

**Mutagenicity**
The applicant has provided references from literature relating to the mutagenicity of ketoprofen. Ketoprofen and its metabolite did not show mutagenic activity.

Results from an assay in bone marrow of mice showed ketoprofen to be weakly genotoxic. However, cytogenetic[4] investigations using *in vivo* human lymphocytes did not reveal any genetic effects during a treatment period of two weeks.

**Carcinogenicity**
The applicant provided reference to carcinogenicity studies. These were carried out in mice (4, 8, 16 or 32 mg of ketoprofen for 105 consecutive weeks) and on rats (3, 4.5 and 7 mg of ketoprofen for 91 weeks followed by a 13-week observation period) and showed no treatment-related effects on the incidence or distribution of spontaneous tumours in the animals.

Ketoprofen did, however, show a significant inhibition of the occurrence of tumors of the large intestine. The ability of NSAIDs to reduce the risk of developing colorectal cancer in humans was also reported.

***Other Studies***
The applicant provided reference to other studies. These data confirmed the phototoxic effects of ketoprofen, the hepatotoxic effect of NSAIDs on the liver and the inhibition of ketoprofen on platelet aggregation.

***Observations in Humans***
The applicant has provided data which show that the most common side effects of ketoprofen involve the gastrointestinal (GI) tract. These side effects are generally mild and less frequent than those treated with aspirin, and the effects are reduced when taken with food, milk or antacids. Ketoprofen can cause fluid retention and increased plasma concentration of creatinine but these are more common in patients receiving diuretics or those over 60.

Ketoprofen co-administration with aspirin was investigated in men after administration of both drugs orally. Ketoprofen did not alter salicylate[5] absorption and disposition, concurrent administration of aspirin decreased ketoprofen protein binding and increased its plasma clearance. Salicylate also appeared to reduce metabolic ketoprofen conversion to conjugates and non conjugate metabolites.

There were no reports on the teratogenicity of ketoprofen in humans. Doses of 200 mg/day for 3 to 8 days to pregnant women did not cause any adverse effects to the mothers or their offspring.

[4] Cytogenetics is a branch of genetics that is concerned with the study of chromosomes and cell division.
[5] Metabolite of aspirin

### *Microbiological Studies*

The applicant has provided data showing that as well as its anti-inflammatory properties, ketoprofen also exhibited antibacterial (against gram positive) and antifungal activity *in vitro*.

**Studies on Metabolites, Impurities, Other Substances and Formulation.**

The product contains citric acid, benzyl alcohol, arginine base and water. All these ingredients are well established and have been used in veterinary medicine for a long time. The safety of these substances was assessed by the CVMP and they have all been entered in Annex II of Regulation 2377/90.

### *User Safety*

The applicant has provided a user safety assessment in compliance with the relevant guideline addresses all the major routes of exposure. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

### *Ecotoxicity*

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

## *III.B Residues documentation*

### *Residue Studies*

No residue depletion studies were conducted because ketoprofen is entered in Annex II of Regulation 2377/90 which indicates that no maximum residue level need be applied.

### *MRLs*

Ketoprofen is listed in Annex II of Council Regulation 2377/90. MRLs are listed below:

| Pharmacologically active substance(s) | Animal species | MRLs (µg/kg) | Target tissues | Annex entry |
|---|---|---|---|---|
| Ketoprofen | Porcine | - | All | Annex II (1742/1996) |
| Arginine | All species | - | - | Annex II (1931/1999) |
| Benzyl alcohol | All species | - | - | Annex II (1442/1995) |
| Citric acid | All species | - | - | Annex II (2034/1996) |
| Purified water | All species | - | - | Out of scope |

The CVMP, during its evaluation of the MRL application, concluded that no MRL was necessary for ketoprofen. The CVMP also stated that consumer intake was approximately 30% of the pharmacological ADI after 24 hours.

### *Withdrawal Periods*

Given the rapid absorption and elimination of ketoprofen in pigs, a withdrawal period of 2 days for meat in is justified. Consumer safety aspects are, therefore, considered to be satisfactory.

## IV CLINICAL ASSESSMENT (EFFICACY)

### *IV.A Pre-Clinical Studies*

### *Pharmacology*

**Pharmacodynamics**

Ketoprofen is a non-steroidal anti-inflammatory drug and is a central and peripheral analgesic, anti-inflammatory agent and is an antipyretic. Its major action is to inhibit cyclo-oxygenase leading to reduced synthesis of prostaglandins and related compounds which underlies the principal therapeutic and toxic effects.

The applicant submitted a number of literature references to support the pharmacodynamics of ketoprofen. It is well known that ketoprofen has a chiral[6] centre with two enantiomeric forms, R(-) and S(+) which differ in their pharmacodynamic and pharmacokinetic properties. The S(+) enantiomer is a more potent inhibitor of cyclo-oxygenase. KetoProPig contains a racemic mixture (50:50). Ketoprofen also has a number of COX independent beneficial actions.

The references submitted support the effects of ketoprofen as an effective analgesic, anti-inflammatory and antipyretic agent. The information in the SPC is satisfactory.

**Pharmacokinetics**

The applicant has submitted published references and a pharmacokinetic study which demonstrate that ketoprofen is rapidly absorbed after oral administration, is highly bioavailable, and the maximum concentration in plasma is achieved after approximately 1-2 hours. The simultaneous ingestion of food seems to affect the rate of absorption but not the extent.

Adequate dose determination and proof that the oral solution is efficacious have been provided. The information provided on the SPC is satisfactory.

### *Tolerance in the Target Species of Animals*

The applicant has provided a target animal tolerance study using multiples of the recommended dose in the target species. A placebo was used as a control. All doses were administered orally for three days. Parameters evaluated included feed and water intake, body weight, haematology and biochemistry and necropsy.

Adverse effects included gastric ulcers in approximately a total of 70% of treated pigs. However this finding did not appear to be related to the dose rates or dose durations studied in this trial. By three days after the last day of dosing, the

[6] is a property of asymmetry important in several branches of science.

gastric ulcers were generally recovered (with some scarring) or in the process of recovery.

There were no statistical significant differences between treated groups in feed intake; there was an inter-animal variability and feed intake appeared to be more related to the severity of gastric ulceration. Water intake and body weight changes were not related to the dose rate or dose duration.

Statistically significant changes related to treatment were found in neutrophil counts and in serum concentrations of glucose, albumin, total protein, alkaline phosphatase, aspartate aminotransferase, sodium and calcium. However, there was no consistent pattern within the study and were considered to be either an artefact or related to the presence of gastric ulceration and its associated inflammation.

The product literature accurately reflects the type and incidence of adverse effects which might be expected.

## *IV.B Clinical Studies*

### *Laboratory Trials*

The applicant conducted a dose determination study to demonstrate efficacy of ketoprofen in the treatment of *E.coli* induced endotoxemia in pigs and to determine the lowest dose reducing fever after oral dosing. Doses of 0.5x, 1x and 2x the proposed dose rate were used. The effects of treatment were compared to an untreated control group. Both groups drank the proposed dose rate of 3mg/kg over the 10 hours of the study. Rectal temperatures reached a maximum at approximately 4 hours, and then decreased to normal in the untreated control group, however, treatment with 3mg/kg ketoprofen prevented the increase in temperature in the treated groups. Thromboxane levels increased in the untreated control group (indicating that inflammation had not reduced) and treatment with all tested doses of ketoprofen prevented this increase.

This study was not conducted in line with the CVMP Guideline for the conduct of efficacy studies for non-steroidal anti-inflammatory drugs which states that *'Where possible, dose determination studies should incorporate not only the dose itself, but for a given indication, the intended dosing frequency*'. The study submitted only tested the doses for 10 hours over one day rather than the product being administered over the proposed period of 3 days, however, the *E.coli* model used was only efficacious for up to 10 hours. This active substance can be considered to have a well established use in the EU, and the pharmacokinetic study demonstrated that the oral solution has a bioavailability of approximately 93%. Although the submitted dose determination study has some deficiencies, it can be considered satisfactory for this application taking the other data into account. Therefore 3 mg/kg bodyweight is accepted as the efficacious dose. A number of supportive literature references and a company run clinical efficacy study were submitted to support the dose rate and duration of therapy.

***Field Trials***

The field trial was conducted to assess the efficacy of Ketoprofen 10% oral solution in reducing pyrexia and/or inflammation and/or respiratory distress when treating respiratory diseases associated with fever in pigs. Pigs were included into the study based on the clinical diagnosis of respiratory disease. The pigs had a significantly increased rectal temperature in conjunction with clinical signs at the start of the study. The positive control group was administered a placebo and an injectable antimicrobial, Draxxin, and the test group was administered KetoProPig 10% Oral Solution and Draxxin.

In the ketoprofen treated groups, the intake of the test product was close to or slightly more than the proposed dose rate. In both groups, rectal temperature decreased during the first day of treatment, but the decrease was more significant in the group treated with ketoprofen. During the following days, the rectal temperature remained more or less stable in both groups, even after administration of the test product had stopped, but it was lower in the ketoprofen treated group. Clinical signs including respiratory distress improved more quickly in the ketoprofen treated group with a statistically significant difference observed on days 4 and 5. The reduction in plasma thromboxane levels indicated that inflammation was reduced in both groups. The antimicrobial would have contributed to this reduction, however the reduction was greater in the ketoprofen treated group.

This study therefore demonstrated and confirms that administration of KetoProPig 10% Oral Solution at 3 mg/kg bodyweight in the drinking water for 3 days reduces rectal temperature, inflammation and improves clinical signs during bacterial respiratory disease, when administered in conjunction with an appropriate antimicrobial.

## V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

# MODULE 4

## POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)