Agencia Española de Medicamentos y Productos Sanitarios

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España
(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

DRAFT PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

KETOXYME 100 mg/ml Solution for use in drinking water

MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0213/001/MR
Name, strength and pharmaceutical form	KETOXYME 100 mg/ml Solution for use in drinking water
Applicant	Andersen, S.A. Av. De la Llana, 123 08191 Rubí, Barcelona (Spain)
Active substance(s)	Ketoprofen
ATC Vet code	QM01AE03
Target species	Pigs
Indication for use	Symptomatic treatment for reduction of pyrexia associated with infectious respiratory diseases in pigs in combination with an appropriate anti-infective therapy

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies website (http://www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual Recognition application in accordance with Article 13(a) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition	21/05/2014
Date product first authorised in the Reference Member State (MRP only)	04/02/2013
Concerned Member States for original procedure	BE, CY, HU, IE, NL, PL, PT, SI, UK and HR

I. SCIENTIFIC OVERVIEW

***For public assessment reports for the first authorisation in a range**:*

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 100 mg/ml of ketoprofen as the active substance, benzyl alcohol as preservative and the excipients arginine, citric acid monohydrate and purified water.

The container/closure system comprises 1 litre white HDPE containers coated with fluorinated polymers, provided with white polypropylene caps with screw top and sealed with a three layerseal. 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 at 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.

To demonstrate the suitability of the Ph.Eur monograph to control the active substance from its sources, copies of the current CEPs are provided.

The excipients are the subject of a monograph in the European Pharmacopoeia.

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

Not applicable.

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, demonstrating the stability of the active substance when stored under the approved conditions.

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, after first opening of the immediate packaging and after dilution according to directions.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf-life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf-life after first opening of the immediate packaging: 4 months.
Shelf-life after dilution according to directions: 24 hours

This veterinary medicinal product does not require any special storage conditions.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL)

This is an application in accordance to Article 13a, well established veterinary use. The safety and residue documentation is supported by bibliographic literature.

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data which describe the pharmacological properties

of ketoprofen. The applicant has also conducted a pharmacokinetic study in the target specie.

Ketoprofen is a non-steroidal anti-inflammatory drug belonging to the arylpropionic acid group. Ketoprofen inhibits the biosynthesis of PGE2 and PGF2 alpha without affecting the ratio of PGE2/PGF2 alpha and thromboxanes. This mechanism of action results in its antiinflammatory, anti-pyretic and analgesic activity.

Following oral administration, ketoprofen is readily absorbed and binds strongly to plasma proteins. Bioavailability is high. It is excreted primarily through the kidneys and, to a lesser extent, in the faeces.

Toxicological Studies

The applicant has provided bibliographical data which show a low acute oral toxicity. Clinical signs reported were those usually observed with other NSAID. Gastrointestinal damage and bleeding are the major side effects described for ketoprofen.
It is showed that Ketoprofen have no mutagenic and carcinogenic potential.

- Single Dose Toxicity
  LD_{50} ranged from 30 to 480 mg/kg bw (rats)
  LD_{50}= 500 mg/kg bw (mice, rabbits and dogs)

- Repeated Dose Toxicity
  NOEL= 6 mg/mg bw (1-month study, rat feeding study)
  NOEL= 2 mg/kg bw (1-month oral study, rats)
  NOEL= 2 mg/kg bw (1-month oral study, dogs)
  NOEL= 4.5 mg/kg bw (6-month oral study, baboons)

- Reproductive Toxicity, including Teratogenicity:
  $NOEL_{embriotoxicity}$ = 2 mg/kg bw/day (rabbits) $NOEL_{fertility}$ = 3 mg/kg bw/day.

Observations in Humans

The applicant has provided bibliographical information which shows that the most common side effects of ketoprofen in human involve the gastrointestinal tract.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the product does not pose an unacceptable risk for user.
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. The assessment concluded that the product does not pose an unacceptable risk for the environment.
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. The withdrawal period was based on bibliographic studies and on a pharmacokinetic study conducted in pigs using the final formulation.

MRLs

Ketoprofen is included in Table 1 of Annex of council Regulation (UE) 37/2010. No MRL is required for this active substance.

Withdrawal Periods

Based on the data provided above, a withdrawal period of 2 days for meat in pigs is justified.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

The applicant has provided bibliographical data describing the pharmacodynamic and pharmacokinetic data of ketoprofen. Also, a pharmacokinetic study has been runned in pigs to show the main pharmacokinetic parameters.

Tolerance in the Target Species of Animals

The applicant has conducted a controlled 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 by oral route on 3 or 9 occasions.

Parameters evaluated were clinical observations, clinical examinations, feed intake, water consumption, weighing, haematology, biochemistry, and macroscopic observations together histopathology at necropsy.

Adverse effects consisting of gastric ulcers were seen in two thirds of the treated animals.

These ulcers generally recovered three days after cessation of dosing

Post marketing information has also been provided which shows that after 2 years marketing the product in Spain, no safety issues have risen. This confirms its safety margin.

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

IV.B Clinical Studies

Laboratory Trials

The applicant has conducted a dose determination study to demonstrate ketoprofen efficacy in treatment of *E. coli* induced endotoxemia in pigs and to determine the lowest and most efficient dose reducing the fever after oral dosing.

This study shows that the recommended dose (3 mg/kg, 3 days) is the lowest and most efficient dose reducing the fever after oral dosing.

Field Trials

The applicant has conducted a GCP field study which shows that Ketoprofen 10 % oral solution has a positive effect during treatment of respiratory disease, reducing pyrexia associated with infectious respiratory diseases in pigs in combination with an appropriate anti-infective therapy.

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 veterinary Heads of Agencies website (www.hma.eu).

This section 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.

None