ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Ketodolor 100 mg/ml Solution for Injection for Horses, Cattle, Pigs

PuAR correct as of 25/03/2019 when RMS was transferred to IE.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0464/001/DC
Name, strength and pharmaceutical form	Ketodolor 100 mg/ml Solution for Injection for Horses, Cattle, Pigs
Applicant	Le Vet B.V. Wilgenweg 7 Oudewater 3421 TV Netherlands
Active substance(s)	Ketoprofen
ATC Vetcode	QM01AE03
Target species	Horses, cattle and pigs
Indication for use	<u>Horses:</u> Alleviation of inflammation and pain associated with musculoskeletal disorders. Alleviation of visceral pain associated with colic. <u>Cattle:</u> Alleviation of pain (e.g. from pressure trauma) resulting from parturient paresis; Reduction of the pyrexia and distress associated with bacterial respiratory disease when used in conjunction with antimicrobial therapy as appropriate; Improvement of the recovery rate in acute clinical mastitis, including acute endotoxin mastitis, caused by gram negative micro-organisms, in conjunction with antimicrobial therapy; Alleviation of pain associated with udder oedema following calving. Reduction of pain associated with lameness. <u>Pigs:</u> Reducing the pyrexia and respiratory rate associated with bacterial or viral respiratory disease when used in conjunction with antimicrobial therapy as appropriate. Supportive treatment of Mastitis Metritis

	Agalactia Syndrome in sows, in conjunction with antimicrobial therapy as appropriate.

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	Generic application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	27th June 2013
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Austria, Norway, Belgium, Italy, Poland, Spain, Portugal, Finland, Lithuania, Romania, Czech Republic, France, Luxembourg, Sweden, Hungary, Latvia, Denmark, Ireland, Malta, Slovakia, Iceland, Estonia

I. SCIENTIFIC OVERVIEW

Ketodolor Solution for Injection has been developed as a generic of Ketofen 10% Solution for Injection. Bioequivalence with the reference product is claimed. The active substance, ketoprofen, is a non-steroidal anti-inflammatory drug (NSAID) which can be used to control inflammation, pain and pyrexia.

Ketodolor is indicated for use in horses, cattle and pigs to treat a number of conditions including reduction of pyrexia and distress associated with respiratory diseases in cattle and pigs, as well as alleviating pain and inflammation in horses with musculoskeletal disorders. The product is contraindicated in animals that are hypersensitive to ketoprofen and animals that suffer from cardiac, hepatic or renal disease, or in animals where there may be gastro-intestinal ulceration and bleeding. The product should also not be used in animals that have shown previous hypersensitivity to any of the excipients. In addition the product should not be used in conjunction with other NSAIDs.

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[1].

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 benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains ketoprofen as active substance and the excipients benzyl alcohol (E1519), L-arginine, citric acid monohydrate and water for injections.

The container/closure system consists of amber type II glass vials filled with either 50 ml or 100 ml of product and sealed with red chlorobutyl stoppers and aluminium caps. 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.

[1] SPC – Summary of product characteristics

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. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post-authorisation. The product is manufactured firstly by heating the water and mixing the excipients and active substance until they dissolve. Once the solution is cooled and the pH adjusted, water is added until the final weight is reached and further mixing is performed. Once the solution is prepared it can be held before filtration and filling of the pre-sterilised vials and then sterilised by heating.

C. Control of Starting Materials

The active substance is ketoprofen, an established active substance described in the European Pharmacopoeia (Ph. Eur). Certificates of suitability have been provided from the two manufacturers of the active substance. 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.

All excipients comply with their respective Ph. Eur monographs. Certificates of analysis were received from each manufacturer, and testing of the excipients is performed on receipt.

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. The tests include identification and assay of the active substance and excipients, identification of impurities, pH, appearance and sterility.

Satisfactory validation data for the analytical methods have been provided.
Batch analytical data from the proposed production sites 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. A retest period of 30 months has been established for one manufacturer of the active substance and a retest period of 5 years is supported for the other manufacturer.

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. A shelf life of 3 years has been established for the finished product as packaged for sale.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

- Shelf life of the finished product as packaged for sale: 3 years.
- Shelf life after first opening the immediate packaging: 28 days.
- Do not refrigerate or freeze.
- Keep the vial in the outer carton in order to protect from light.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

As this is a generic application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed because of the nature of the product, results of pharmacological studies are not required.

Toxicological Studies

As this is a generic application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed because of the nature of the product, results of toxicological studies are not required.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the risk of exposure is very low, with the main route identified as accidental injection.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

- In case of accidental self-injection seek medical advice and show the package leaflet or the label to the physician.
- People with known hypersensitivity to the active substance and/or benzyl alcohol should avoid contact with the product.
- Avoid splashes on the skin and eyes. Wash the affected area thoroughly with water should this occur. If irritation persists seek medical advice.
- Wash hands after use.

Ecotoxicity

The applicant provided a Phase I environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that as the product will only be used to treat individual animals there will be limited exposure to the environment. Therefore 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

As this is a generic application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed because of the nature of the product, results of residue studies are not required.

Withdrawal Periods

Cattle:
Meat and offal: following intravenous administration – 1 day
following intramuscular administration – 4 days
Milk: zero hours

Pigs:
Meat and offal: 4 days

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

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

As this is a generic application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed because of the nature of the product, results of pharmacological studies are not required.

Tolerance in the Target Species of Animals

As this is a generic application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed because of the nature of the product, results of target species tolerance studies are not required.

IV.B Clinical Studies

Laboratory Trials

As this is a generic application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed because of the nature of the product, results of laboratory trials are not required.

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 benefit/risk 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)