Agencia Española de Medicamentos y Productos Sanitarios

Parque Empresarial Las Mercedes
Edificio 8
C/Campezo 1,
28022 – Madrid
España
(Reference Member State)

DESCENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

DINALGEN 150 mg/ml
solution for injection for cattle

MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0115/001/DC
Name, strength and pharmaceutical form	Dinalgen 150 mg/ml solution for injection for cattle (all countries except DK and SE) Dinalgen (DK) Dinalgen Vet (SE)
Applicant	Laboratorios Dr. ESTEVE, S.A. Avda. Mare de Déu de Montserrat, 221 08041 – Barcelona SPAIN
Active substance(s)	Ketoprofen
ATC Vet code	QM01AE03
Target species	Cattle
Indication for use	- Reduction of inflammation and pain associated with post-partum musculoskeletal disorders and lameness. - Reduction of fever associated with bovine respiratory disease. - Reduction of inflammation, fever and pain in acute clinical mastitis. in combination with antimicrobial therapy where appropriate.

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	Decentralised application in accordance with Article Article 13(a) of Directive 2001/82/EC as amended. "Well established veterinary use"
Date of completion of the original decentralised procedure	Day 210: 27/01/2010
Date product first authorised in the Reference Member State (MRP only)	-
Concerned Member States for original procedure	RMS: ES CMS: AT, BE, CZ, DK, FI, FR, DE, HU, IE, IT, LT, NL, PL, PT, RO, SK, SE and UK

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 Ketoprofen (150 mg/ml).

The excipients are L-arginine, benzyl alcohol, citric acid, anhydrous and water for injection.

The container is type II amber glass vial, closed with bromobutyl rubber stopper and aluminium cap.

The particulars of the containers and controls performed are provided and conform to the regulation.

The presence of benzyl alcohol as preservative is 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 using conventional manufacturing techniques. A flow chart is enclosed in the dossier. The manufacturing process is detailed.

Process validation data on the product have been presented in accordance with the relevant European guidelines. Analysis certificates of three full-scale batches also support the suitability of the process to obtain a product with a consistent quality.

C. Control of Starting Materials

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

The active substance specifications are considered adequate to control the quality of the material. Certificates of analysis of three batches demonstrating compliance with these specifications have been provided.

The applicant justifies the quality of the raw material with the Certificate of suitability of both of the suppliers.

The excipients L-arginine, benzyl alcohol, citric acid, anhydrous and water for injections comply with their corresponding monograph of European Pharmacopeia. Certificates of analysis for all the excipients are submitted.

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

There are no substances of animal origin 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 finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life (24 months) when stored under the approved conditions.

The claim of a 28 days stability after broaching is based on the demonstration of stability for a batch broached and stored one month at +25°C.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL)

The application of marketing authorisation of a medicine of veterinary use by means Decentralised Procedure is submitted according to the article 13a of Directive 2004/28/EC (amending article 13a of Directive 2001/82/EC). Ketoprofen is considered to have been in "well established veterinary use" within the Community for at least ten years, with recognised efficacy and acceptable level of safety for the proposed indications in the target species (bovine) using the proposed routes of administration (iv, im) and dosage regimen (3mg/kg/d).

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data which show that ketoprofen acts by 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. The antiinflammatory 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 applicant has provided bibliographical data which show that ketoprofen is rapidly absorbed in cattle. 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 and it is excreted

mainly in urine and, to a lesser extent, in faeces. Small amounts of ketoprofen can be detected in the milk of treated animals.

Toxicological Studies

The applicant has provided bibliographical data which shows the acute toxicity of ketoprofen was studied and compared with other anti-inflammatories. Ketoprofen shows a low potential for toxicity in all laboratory species studied in any of the routes of administration and much less than indomethacin. The chronic toxicity of ketoprofen was less than that of indomethacin. Ketoprofen does not affect the reproductive function of either sex and there is no teratogenic activity. Ketoprofen and its metabolite do not show mutagenic activity and ketoprofen does not show carcinogenicity activity.

- Single Dose Toxicity

After intravenous administration, a LD_{50}>350 mg/kg, species: mouse.
a LD_{50}>400 mg/kg, species: guinea pig.
After oral administration, a LD_{50}= 360 mg/kg, species: mouse.
a LD_{50}= 62,4 mg/kg, species: rat.
a LD_{50}= 1300 mg/kg, species: guinea pig.
a LD_{50}= 145 mg/kg, species: rabbit.
a LD_{50}>2000 mg/kg, species: dog.

- Repeated Dose Toxicity

According to Summary Report: NOEL

Species	Rat	Rat	Dog	Baboons
Duration	1 month	1 month	1 month	6 months
Route of administration	Oral	Oral	Oral	Oral

- Reproductive Toxicity, including Teratogenicity:

A study of reproductive toxicity was carried out in mouse and rat. The administration of different doses of ketoprofen in the period prior to and in the early stages of gestation has no effect on the fertility and reproductive function of both sexes.

A study on the pharmacological properties of ketoprofen, including its teratogenicity in rats, mice, rabbits shows that ketoprofen was not teratogenic, however, in the group of rabbits that received the highest dose some slight embryotoxic effect were observed.

- Mutagenicity

The Ames test was carried out in various cell lines (TA97a, TA100 and TA102). No mutagenic effect was observed.
Genotoxicity was also determined *in vivo* using the Sister Chromatid Exchange (SCE)

technique. It was observed to be very mildly genotoxic in this type of cell.

According to Summary Report, the negative results obtained in the following mutagenicity tests: -Ketoprofen: Ames, Test CHO/HGPRT, Chromosome aberration test in CHO, Micronucleus
Test
-RP69400: Ames, Micronucleus Test

Other Studies

The applicant has provided bibliographical data which shows CNS effects, cardiovascular system effects, gastrointestinal tract effects, effects on blood.

Observations in Humans

The applicant has provided bibliographical data which shows the general characteristics of ketoprofen in humans, with regard to pharmacokinetics, pharmacodynamics, toxicity, tolerance, adverse reactions, interactions with other medications, and use in the elderly.

Studies on Metabolites, Impurities, Other Substances and Formulation.

The applicant has provided information regarding impurities which show that these are found in the Pharmacopoeia, and they are all known, and the impurity grade is below the maximum permitted, so there is no problem from a safety point of view.

Excipients are commonly used in injectable solutions and are totally nontoxic and safe.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline on User Safety for Pharmaceutical Veterinary Medical Products EMEA/CVMP/543/03-FINAL.
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 EMEA/CVMP/592/98-FINAL and EMEA/CVMP/ERA/418282/2005-Rev.1 which showed that no further assessment is required. The assessment concluded that environmental safety is justified adequately and Dinalgen 150 mg/ml injectable product that will be used to treat a small number of animals in a herd. No warnings regarding ketoprofen 150 mg/ml injectable solution are therefore 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

The applicant has conducted residue depletion studies which show that the concentrations of ketoprofen and its metabolite (RP69400) in the kidneys, liver and fat of each animal were quantitated, in order to calculate the percent residue with pharmacological activity with respect to the ADI.

The results show that parent drug is present at the injection site 12 h after the last administration, with considerably lower levels at 24h (near the limit of quantitation). No residues of ketoprofen or metabolite were detected 48h or 96h after discontinuation of treatment in animals that received the drug product.

The analytical method used (chromatograph by a UV detector) was fully validated.

MRLs

Ketoprofen is listed in Annex II of Council Regulation No 2377/90.

ANNEXE	Pharmacologically active substances	Marker residue	Animal species	MRLs	Target tissues	Last Regulation	Other provisions	Therapeutic classification
II	Ketoprofen		Bovine			(508/99)		NONSTEROIDAL ANTI-INFLAMMATORY AGENTS

For substances where there is no MRL defined, the reference value for the assessment of injection site residues is usually the ADI.

Withdrawal Periods

Based on the data provided above, a withdrawal period of 2 days for meat in cattle and zero hours for milk are justified.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

The applicant has conducted one study that characterized the pharmacokinetic behaviour of this veterinary medicinal product.

Tolerance in the Target Species of Animals

The applicant has conducted a controlled target animal tolerance study using multiples of the

recommended dose (3 times the recommended dose during the recommended duration of treatment: 9 mg/kg/day for 3 consecutive days) or multiples of the recommended duration of treatment (1 time the recommended dose for 3 times the recommended duration of treatment: 3 mg/kg/day for 9 consecutive days) in the target species. A placebo (saline) was used as a control. All doses were administered by the intramuscular route.

Clinical examinations and haematological and biochemical analyses were carried out to evaluate the general tolerance. Moreover, a histopathological examination was also conducted. Local tolerance at the injection site was also considered.

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.

The applicant conducted other study, regarding local tolerance, following intramuscular administration at therapeutic doses and posology.

It was shown that: *intramuscular injection of ketoprofen can cause mild, necrotic subclinical muscular lesions that gradually resolve in the days after completion of treatment.*

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

IV.B Clinical Studies

Field Trials

The applicant has conducted a field study and provided bibliographical data which support the indications of the veterinary medicinal product:

- *Reduction of inflammation and pain associated with post-partum musculoskeletal disorders and lameness.*
- *Reduction of fever associated with bovine respiratory disease. - Reduction of inflammation, fever and pain in acute clinical mastitis. in combination with antimicrobial therapy where appropriate.*

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