



**Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL)
Federal Office of Consumer Protection and Food Safety
Mauerstraße 39-42
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(Germany)**

DECENTRALISED PROCEDURE

**PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY
MEDICINAL PRODUCT**

Carprosol 50 mg/ml solution for injection for cattle

Date: 27 July 2016

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0168/001
Name, strength and pharmaceutical form	Carprosol 50 mg/ml solution for injection
Applicant	CP-Pharma Handelsgesellschaft mbH 31303 Burgdorf Germany
Active substance(s)	Carprofen
ATC Vetcode	QM01AE91
Target species	Cattle
Indication for use	As an adjunct to antimicrobial therapy to reduce clinical signs in acute infectious respiratory disease and in acute mastitis

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicinal Agencies website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original Decentralised procedure	25 January 2012
Date product first authorised in the Reference Member State (MRP only)	n.a.
Concerned Member States for original procedure	HU

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 safety and efficacy aspects of this product are identical to the reference product.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The product contains 50 mg carprofen and the following excipients; ethanol, macrogol 400, poloxamer 188, ethanolamine and water for injection

The product is packed in amber type I glass bottles of 50 ml, fitted with red chlorobutyl rubber stoppers and aluminium caps. The glass vials and stoppers are in conformity with the Ph.Eur. requirements

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.

The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches has been performed. The tests performed during production are described.

C. Control of Starting Materials

The active substance is carprofen, an established active substance described in the European Veterinary 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.

The excipients are in conformity with compendial requirements.

The glass vials and stoppers are in conformity with the Ph.Eur. requirements.

D. Control on intermediate products

Not applicable.

E. 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.

F. 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.

The claim of 28 days stability after broaching has been justified.

G. Other Information

None

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data which show that carprofen acts by inhibition of the enzyme cyclo-oxygenase of the arachidonic acid cascade. However, the inhibition of prostaglandin synthesis by carprofen is slight compared to its anti-inflammatory and analgesic properties. The exact mechanism of action is not clear.

The applicant has also provided bibliographical data which show that following a single subcutaneous dose of 1.4 mg carprofen/kg, the maximum plasma concentration (C_{max}) of 15.4 µg /ml was reached after (T_{max}) 7-19 hours. The highest carprofen concentrations were found in bile and plasma, and more than 98% of the carprofen is bound to plasma proteins. Carprofen was well distributed among the tissues, with the highest concentrations found in kidneys and liver, followed by fat and muscle. Carprofen is metabolised slowly, mainly by ring hydroxylation, hydroxylation at the α-carbon site and by conjugation of the carboxylic acid group with glucuronic acid. The 8-hydroxyl metabolite and unmetabolised carprofen predominate in the faeces. Bile samples contain conjugated carprofen. Carprofen has a plasma elimination half-life of 70 hours and is excreted mainly in the faeces.

Toxicological Studies

The applicant has provided bibliographical data which show that acute toxicity of carprofen is characterized by muscle weakness. No details regarding chronic toxicity were provided. Carprofen has no mutagenicity/ carcinogenicity.>

- Single Dose Toxicity

Subcutaneous LD₅₀ in rats: 190 mg/kg; Intraperitoneal LD₅₀ in rats: 110 mg/kg; Oral LD₅₀ in rats: 74 mg/kg, behavioural signs.

Subcutaneous LD50 in mice: 267 mg/kg; Intraperitoneal LD50 in mice: 165 mg/kg; Oral LD50 in mice: 186 mg/kg.

- Reproductive Toxicity, including Teratogenicity:

Reproductive safety of carprofen has not been established. In rats delayed parturition and increased number of dead pups were observed.

- Mutagenicity:

Tests for mutagenicity were uniformly negative.

- Carcinogenicity:

Studies in mice and rats detected no carcinogenic potential for carprofen.

Other Studies

The applicant has provided bibliographical data which show that carprofen has phototoxic effects. Photosensitization due to carprofen is reported in clinical practice and has been observed in *in vitro* and *in vivo* studies, it involves photosensitization, photoallergic reactions and photohemolysis.

Observations in Humans

The applicant has provided information which show that Carprofen was used in human medicine at dosages of 150 to 600 mg/day and was generally well tolerated. The majority of adverse effects were transient and mild such as gastrointestinal discomfort or pain and nausea. The incidence of side effects in humans is similar to those recorded with aspirin and other NSAIDs. Carprofen is no longer marketed for humans.

User Safety

This is a generic application according to Article 13. The product is considered to be bioequivalent to its reference product. The small difference in quantity in one of the excipients does not affect the user safety of this product. Therefore, the warnings and safety measures as applied for the reference product Rimadyl Cattle 50 mg/ml Solution for injection can be adopted.

The warnings and safety measures as listed in the product literature are adequate to ensure safety of the product to users.

Environmental Risk Assessment

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

This is a generic application according to Article 13. The product is considered to be bioequivalent to its reference product. The small difference in quantity in one of the excipients does not affect the availability of this product after injection. Therefore, the withdrawal periods as applied for the reference product Rimadyl Cattle 50 mg/ml Solution for injection can be adopted.

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

MRLs

Carprofen is included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 as follows:

	Bovine 1	
Muscle	500 µg/kg	
Liver	1000 µg/kg	
Kidney	1000 µg/kg	
Fat / skin	1000 µg/kg	
Milk	No MRL required	

Withdrawal Periods

Based on the data provided above, a withdrawal period of 21 days for meat in cattle and 0 hours for milk are justified.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, tolerance studies are not required.

Bibliographical data has been provided which shows that carprofen was well tolerated by cows when administered intravenously at a daily dose of 0.7 mg/kg for 5 days. The animals continued to feed normally after the injections and milk production remained within normal ranges. Only the plasma cholesterol concentration was slightly raised, the increase being statistically significant. However, they remained within the normal range.

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

IV.B Clinical Studies

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product

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 Heads of Veterinary Medicinal 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.

Date	Procedure no.	Variation code	Change
2016-09-12	DE/V/0168/001/IB/003	B.II.f.1. Change in the shelf-life or storage conditions of the finished product b) Extension of the shelf-life of the finished product 1. As packaged for sale (supported by real time data)	Extension of the shelf-life from 2 to 3 years.