IPAR

Publicly Available Assessment Report for a Veterinary Medicinal Product

Norocarp 50 mg/ml Solution for Injection for Cattle

PRODUCT SUMMARY

EU Procedure number	IE/V/0230/001/MR
Name, strength and pharmaceutical form	Norocarp 50 mg/ml Solution for Injection for Cattle
Active substance(s)	Carprofen
Applicant	Norbrook Laboratories (Ireland) Limited Rossmore Industial Estate Monaghan Ireland
Legal basis of application	Well established use in accordance with Article 13a of Directive 2001/82/EC as amended.
Date of Authorisation	9th September 2005
Date of completion of procedure	27th May 2009
Target species	Cattle
Indication for use	Reduction of pyrexia in acute cases of infectious respiratory disease in cattle, in combination with appropriate anti-infective therapy.
ATCvet code	QM01AE91
Concerned Member States	AT, BE, DE, DK, ES, FI, FR, IT, NL, NO, PT & UK

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.

The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

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; potential treatment related adverse effects are indicated in the SPC.

The product is safe for the user and for the environment, when used as recommended.Suitable warnings and precautions are indicated in the SPC.

The efficacy of the product is adequately supported by the data provided: the claims made in the SPC are justified.
The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

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A.Qualitative and Quantitative Particulars

The product contains 50 mg/ml carprofen in a formulation which also contains polyethylene glycol 600, ethanol (anhydrous), sodium formaldehyde sulphoxylate, polyethylene glycol 4000, L-arginine and water for injection.

The solution for injection is presented in 50 ml multidose amber glass (Type I) vials with bromobutyl bungs and aluminium seals. 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.

The product is manufactured using conventional manufacturing techniques.Process validation for full-scale batches will be performed post-authorisation.

The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C.Control of Starting Materials

The active substance is carprofen, 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.

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.

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.

G.Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

IIISAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

Precise Identification of the Product concerned by the Application

The product is a solution for injection containing 5% w/v carprofen.

III.ASafety Testing

Pharmacological Studies

Pharmacodynamics:

The applicant has provided bibliographical data in support of the pharmacodynamics of the carprofen. *In vitro* studies have shown carprofen to be a cyclo-oxygenase inhibitor.However, the inhibition of prostaglandin synthesis by carprofen is slight in relation to its anti-inflammatory and analgesic potency.The precise mode of action is unclear.
Studies have shown that carprofen has potent antipyretic activity and significantly reduces the inflammatory response in lung tissue in cases of acute, pyrexic infectious disease in cattle.

Pharmacokinetics:

In a pharmacokinetic study using Norocarp Injection for Cattle, following a single subcutaneous dose of 1.4 mg carprofen per kilogram bodyweight the maximum plasma concentration (C_{max}) of 10.4 microgram/ml was reached after (T_{max}) 7.2 hours.

Carprofen is highly bound to plasma proteins.It is well distributed in the tissues with the highest concentrations found in kidney and liver followed by fat and muscle.Elimination is slow.Carprofen is eliminated primarily in the faeces, indicating that the biliary secretion plays an important role.

Toxicological Studies

Toxicity data relating to carprofen have been reviewed by CVMP as part of an application for a maximum residue limit. Based on those data, carprofen has been included in Annex 1 of Council Regulation 2377/90 indicating that the active substance has been approved for use in food-producing species. The Applicant has provided additional bibliography in support of the conclusions of the CVMP MRL assessment report.

The toxicity of the product is well characterised. Carprofen has low toxic potential following single (acute) administration.Based on the acute/repeat dose studies it is evident that the gastrointestinal tract and kidneys are the principle target organs. Indeed, such effects are to be expected for a compound of this class. Of those species in which toxicity studies were conducted, the rat would appear to be most sensitive to the effects of carprofen. For rats, a NOEL of 1 mg/kg bw/day was established based on a 2-year oral toxicity study (EMEA MRL Summary Report).

Carprofen does not exhibit any teratogenic or foetotoxic effects; and, does not show any mutagenic or carcinogenic potential. It is noted that the product is contraindicated for use in pregnant animals.

Other Studies

Carprofen was not a sensitiser in the guinea pig sensitisation test. The compound was classified as non-irritating when applied to either intact or abraded skin of rabbits.

Observations in Humans

Carprofen has been used previously for over 10 years in human medicine at doses of 150 to 600 mg/day. During clinical trials in humans, carprofen was generally well tolerated. The majority of adverse side effects were transient and mild such as gastrointestinal discomfort or pain and nausea. In addition, it is evident that photosensitivity was an occasional reported cutaneous adverse effect associated with carprofen therapy in man.

Studies on Metabolites, Impurities, Other Substances and Formulation

The excipients are either widely used in other pharmaceutical products or generally regarded as non-toxic, such that they are not expected to present any toxicological hazard to the user at the inclusion levels in this product.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the product when used in accordance with label instructions is unlikely to be a hazard to the user.
The following safety statements appear on the SPC:
Carprofen, in common with other NSAIDs, has been shown to exhibit photosensitising potential in laboratory studies.Avoid skin contact with the product.Wash off any splashes immediately.Take care to avoid accidental self-injection.
Keep out of reach of children.

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

Environmental Risk Assessment

Phase I
The applicant has provided a Phase 1 environmental risk assessment in compliance with the relevant guideline which shows that no further assessment is required.

III.BResidues Documentation

Precise Identification of the Product concerned by the Application

The product is a solution for injection containing 5% w/v carprofen.

Residue Studies

The Applicant conducted a confirmatory residue study in cattle for the purposes of determining an appropriate meat withdrawal period following a single subcutaneous administration of Norocarp Injection. In that study, residues of carprofen in all tissues (including injection site) were below the relevant MRLs at the authorised withdrawal period of 21 days.

MRLs

Carprofen is listed in Annex I of Council Regulation 2377/90. The Maximum Residue Limits (MRL) are as follows:

Muscle – 500 µg/kg
Fat, liver and kidney – 1000 µg/kg

Carprofen is listed in Annex II of Council Regulation 2377/90. The Annex II entry applies to milk only.

Withdrawal Periods

Based on the data provided above, a withdrawal period of 21 days for meat is justified.
A milk residue study was not conducted. However, based on the recommendations of the MRL summary report granting an Annex II entry for Carprofen in bovine milk, it can be accepted that the proposed withdrawal period for milk of zero days is justified.

Analytical Methods used

Carprofen is extracted from tissue by solvent extraction with diethyl ether followed by solvent concentration under nitrogen and reconstitution with a series of reagents designed to allow separation of the enantiomers. Final determination is by HPLC with UV detection. Quantification of each enantiomer is conducted individually and is based on measurement of the sample peak responses in comparison to a standard line prepared from spiked plasma of known concentrations of each enantiomer.

Based on validation data provided, it is accepted that the method is sufficiently accurate and precise for the determination of both carprofen enantiomers in bovine muscle, fat, liver and kidney.

IV. CLINICAL ASSESSMENT

IV.APre-Clinical Studies

Pharmacology

See section III.A.2 of this report.

Tolerance in the Target Species of Animals

Two target animal safety studies were conducted with the final formulation. Based on the findings of those studies, it is accepted that product is well tolerated systemically when administered by the intravenous and the subcutaneous route at the recommended treatment dose. When administered by the subcutaneous route, the product may cause mild, transient swelling at the injection site. A statement to this effect has been included in the SPC.
The product literature accurately reflects the type and incidence of adverse effects which might be expected.

IV.B Clinical Studies

Laboratory Trials

The Applicant presented published reports of several field studies that investigated the efficacy of carprofen, when administered in combination with an antibiotic, for the treatment of bovine respiratory disease in cattle.
It is accepted that those data demonstrate that carprofen (+ antibiotic) appears to give added benefit, in terms of reduction of pyrexia, over antibiotic treatment alone. Consequently, the following indication can be accepted: "Norocarp Solution for Injection is indicated as an adjunct to antimicrobial therapy to reduce pyrexia in acute cases of infectious respiratory disease in cattle".

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 users and the environment is acceptable.

VI. 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 HPRA website.

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.

Changes:
None.