ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

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UNITED KINGDOM

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Reproval 50mg/ml Solution for Injection (Carprofen) for Dogs and Cats

PuAR correct as of 20/12/2018 when RMS was transferred to ES.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0328/001/MR
Name, strength and pharmaceutical form	Reproval 50mg/ml Solution for Injection (Carprofen) for Dogs and Cats
Applicant	Norbrook Laboratories Limited
Active substance(s)	Carprofen
ATC Vetcode	QM01 AE91
Target species	Dogs and Cats
Indication for use	In the dog it is indicated for the control of post-operative pain and inflammation following orthopaedic and soft tissue (including intra-ocular) surgery. In the cat it is indicated for the control of post operative pain following ovariohysterectomy and soft tissue surgery.

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	In accordance with Article 13a of Directive 2001/82/EC as amended by Directive 2004/28/EC
Date of completion of the original mutual recognition procedure	19 March 2009
Date product first authorised in the Reference Member State (MRP only)	02 August 2007
Concerned Member States for original procedure	Austria Denmark Finland France Germany Italy Netherlands Spain sweden

I. SCIENTIFIC OVERVIEW

Carprofen, the active ingredient of Reproval 50mg/ml Solution for Injection (Carprofen) for Dogs and Cats belongs to the group of drugs known as non-steroidal anti-inflammatory drugs (NSAIDs), which are used to control pain and inflammation in various disease conditions. It is a derivative of proprionic acid. Reproval 50mg/ml Solution for Injection (Carprofen) for Dogs and Cats is intended to be used in dogs for the control of post-operative pain and inflammation following orthopaedic and soft tissue (including intra-ocular) surgery. In the cat, it is indicated for the control of post operative pain following ovariohysterectomy and soft tissue surgery.

The application has been submitted in accordance with Article 13a of Directive 2001/82/EC as amended by Directive 2004/28/EC, i.e. well established veterinary use.

The recommended dose in dogs is 4 mg carprofen per kilogram bodyweight (1ml/12.5kg) administered by intravenous or subcutaneous injection, best given pre-operatively, either at the time of premedication or induction of anaesthesia. In cats, the recommended dosage is 4 mg carprofen per kilogram (0.24ml/3kg) bodyweight as a single dose by intravenous injection, best given pre-operatively at least 30 minutes before the time of anaesthesia.

II. QUALITY ASPECTS

A. Composition

Reproval 50mg/ml Solution for Injection (Carprofen) for Dogs and Cats contains the active substance carprofen 50 mg. The product also contains the following excipients; benzyl alcohol, sodium formaldehyde sulphoxylate, L-arginine, poloxamer Type 188 (lutrol F68), and water for injections.
The container/closure system is an amber glass (Type 1) vial sealed with a bromobutyl bung and aluminium seal. The particulars of the containers and controls performed are provided and conform to the regulation.

All the ingredients, including the active substance, have been used in injectable products previously authorised at similar concentrations.

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.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The manufacture and control of the active ingredient has been provided. The data supporting the manufacture was submitted as a drug master file. These data were submitted before the monograph for Carprofen was published in Ph. Eur. 6.2. The company specification did take account of the limits for related substances proposed in the monograph in Pharmeuropa. The applicant has also confirmed that the quality of the carprofen comply with all of the requirements of the monograph in Ph. Eur. 6.2.

Apart from sodium formaldehyde sulphoxylate, which is monographed in the USNF, the other materials are monographed in the Ph.Eur. and comply with that standard. The sodium formaldehyde sulphoxylate is currently authorised in the UK as an anti-oxidant, and the quality standard reference is USP. Therefore, it is considered acceptable.

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

There are no intermediate products.

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.

G. Stability

Active substance
The stability of carprofen has been assessed during consideration of a different application. Reference is made to that application in the assessment of this product.

Finished Product
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.

In-Use
In-use stability testing has been carried out adequately to justify a 28 day in-use shelf life.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Special precautions for storage:
Do not store above 25°C. Do not refrigerate or freeze. Protect from light.

Shelf life:
Shelf-life of the veterinary medicinal product as packaged for sale: 2 years
Shelf-life after first opening the immediate packaging: 28 days

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

There have been many publications on carprofen describing its actions and pharmacokinetics in laboratory animals and in the target species. The applicant has made a comprehensive literature search and has submitted a large number of published papers.

Toxicological Studies

Single Dose Toxicity

The applicant has submitted 4 references to published literature of studies conducted in laboratory species. Published studies were conducted over 20 years ago and report a range of LD_{50} values between 100-500 mg/kg in 3 different laboratory species and show a relatively wide margin of safety between acute lethal dose and pharmacologically effective doses.
In addition, the applicant commissioned 2 recent studies in 2002, which were Acute Dose Fixed-Dose Method Studies and were conducted in compliance with GLP and in accordance with OECD protocols. The published literature and studies demonstrate that the acute toxicity of carprofen is acceptable.

Repeated Dose Toxicity:

The applicant has submitted 19 references to published literature of repeat dose toxicity. The studies were conducted between 1974 and 2000 but the majority were in the late 1990's, in dogs and rats. In the studies conducted in dogs carprofen was administered orally and varied from 5 days to 1 year in duration and doses were in the range of 1-30mg/kg with one study dosing 80mg/kg. Adverse effects were observed mostly at the higher doses.

In addition, the applicant commissioned a 90 day repeat dosing study in 2002, in compliance with GLP and in accordance with OECD protocols. The study submitted has reported an NOEL of 2mg/kg/day and the study is satisfactory.

Reproductive Toxicity, including Teratogenicity:

References were provided for studies conducted on rats (male and female) and rats (female) for the duration of 21 days. The studies investigate the fertility and general reproductive performance in one generation over a period starting 14 days prior to mating, through pregnancy and to the end of the lactation phase. Adverse effects were reported mainly at the mid and high doses, but these were considered to be due to maternal toxicity and there were no significant differences in the percentage of animals pregnant, the number of implantations, or the litter size. No abnormalities were recorded at birth. As carprofen has a well-established use and the product is not for use in pregnant or lactating animals of the target species, the data submitted are considered adequate.

Mutagenicity

The applicant has submitted 2 references to published literature and the CVMP MRL Summary Report and has also conducted a gene mutation study using the Ames Test. This study was conducted in 2002 in compliance with GLP and in accordance with OECD guidelines. The published literature reported that in a number of studies on gene mutation in bacterial cells and repair and reversion tests to detect DNA damage, carprofen was not mutagenic. The CVMP MRL Summary report noted that all the tests had given negative results. The study conducted by the applicant also reports no mutagenic activity and it is therefore concluded that carprofen is not mutagenic.

Carcinogenicity

The applicant has submitted published references on carcinogenicity.
The published literature reports that no evidence of carcinogenic potential was reported in a 6 month oral study in rats administered doses of 200mg/kg/day and a 2 year study also in rats administered 10mg/kg/day reported that carprofen was not carcinogenic. The CVMP MRL Summary report also refers to an 80-week oral study in mice in which no evidence of carcinogenic potential was reported. These data were considered satisfactory to establish an MRL and therefore these data are considered satisfactory.

Observations in Humans

The applicant has submitted 7 references to published literature on observations in humans.

Carprofen was used in human medicine for over 10 years at doses of 150-600mg/day, but has been withdrawn from the market on commercial grounds. The literature reports adverse effects on the gastrointestinal tract, a common effect of NSAIDs although it appears that carprofen is less irritant than other NSAIDs. These gastrointestinal effects are usually mild and reversible but in some cases peptic ulcers and gastrointestinal bleeding has been reported. Reports indicate that carprofen may cause photosensitisation in humans although its incidence is not known; photosensitisation has been observed with other NSAIDs and is a known effect.

Microbiological Studies

Data has not been provided on microbiological studies and, this has been justified because the product does not have any anti-microbial properties.

Special studies

The applicant has submitted 5 references to published literature on special studies. Effects on the nervous system and renal system in dogs and laboratory animals were investigated and it was observed that there were no significant effects. Experimental studies indicated that carprofen may cause phototoxicity although photoallergy has also been proposed.

User Safety

The applicant has submitted several references to published literature of effects observed in humans and has submitted an updated user risk assessment addressing the different routes of exposure and justifying the current user warnings. The main routes of exposure are from accidental contact with skin and eyes during administration or by accidental self-injection. The product is a prescription only medicine and therefore accidental exposure to children is not expected.

In the event of contact with skin, the product could cause irritation but if the area is washed immediately with water, such a reaction is unlikely. The user is advised to immediately wash off any product that comes into contact with skin and is also advised to wash hands after use. Contact with eyes is less likely to occur but such contact is not considered to present a hazard because NSAIDs are used in eye drops for humans prophylactically before ocular surgery. Therefore the very small amount of product that could come into contact with the eye would be unlikely to cause any significant effects.

In the event of accidental self injection, it is unlikely that the entire contents of the syringe would be injected. Assuming a worse case, a syringe containing 50 mls equates to 500 mg of carprofen which would give a dose of 8.33mg/kg for a 60kg adult. Carprofen was used as a human medicine at doses of 150-600mg/day, therefore if a full syringe was accidentally injected, this would not exceed the human dose. However, there is a warning to avoid accidental injection because of the risk of such an event occurring.

The following user warnings are in the SPC and product literature:
Care should be taken when handling the product to avoid accidental self-injection and skin contact.
If skin contact occurs wash any product from the skin immediately.
Wash hands after use.

Ecotoxicity

The applicant provided a first phase environmental risk assessment, which was carried out in accordance with VICH Phase I guidance. The warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV CLINICAL ASSESSMENT (EFFICACY)

Pharmacodynamics

The dossier included a series of published articles describing the chemical processes that lead to the development of inflammation in response to damage to cells in the body, as may happen in the case of lung in young cattle affected by pneumonia. The damaged cells release a substance called arachidonic acid which may be converted into various other substances, such as the prostaglandins, which in turn cause an inflammatory response. These conversions are catalysed by various enzymes, one of which is called cyclo-oxygenase 2 (COX-2). It is thought that carprofen may exert its anti-inflammatory effect by inhibiting this enzyme so that the chain of reactions which leads to inflammation is broken. However, this may be only part of the mode of action; other actions, still to be elucidated, may also occur.

Another member of the cyclo-oxygenase family, COX-1, is involved in normal cellular processes and it may be that carprofen's low level of inhibition on this enzyme is the reason why it has fewer adverse effects on the gastro-intestinal system than some other NSAIDs.

Most of the anti-inflammatory action of carprofen seems to derive from the S-enantiomer.

Pharmacokinetics

Numerous published papers describing studies in various species have shown that carprofen is rapidly absorbed into the bloodstream and readily penetrates and accumulates in acute inflammatory exudate. It is removed from the bloodstream quite slowly and this is responsible for its long duration of action. It is not distributed from the blood to normal tissues to any great extent but it may be metabolised in the liver by the addition of substances called glucuronides, and from here it may be excreted via the bile and faeces.

A comparative pharmacokinetic study was conducted in dogs to study plasma concentration of total carprofen and the individual enantiomers following subcutaneous administration of Carprofen Small Animal Injection and Rimadyl Small Animal Injection. In the study, a total of 16 Beagle dogs were recruited (8 males, 8 females) and randomly allocated to one of two groups. The animals were assigned in such a way as to eliminate weight and sex bias. The plasma concentrations of carprofen and its individual enantiomers were determined from blood samples taken at regular intervals up to 72.0 hours after administration. The samples were examined using a validated HPLC assay. It was concluded that the concentration of carprofen and the enantiomers were all below the limit of quantification prior to the administration of the test articles in both periods of the study (0.1 µg/ml and 0.5 µg/ml, respectively).

Tolerance in the Target Species of Animals

The applicant conducted a target species safety study in dogs following administration of the confirmed final formulation subcutaneously (a proposed route of administration) on two occasions (longer than proposed duration of treatment) at 1X and 3X the proposed dose rate. The study used the product vehicle as a placebo (negative) control. The study was conducted according to GLP.
In the study, a total of 16 Beagle dogs (8 females and 8 males) were used. They were randomly assigned to 3 groups (based on their weights to provide a similar mean weight in each group and an equal number of each sex). The animals were assessed up to 336 hours after the administration of the product. This assessment involved clinical observations, haematology, coagulation profiles, body weight and faecal analysis.

It was concluded that Reproval 50mg/ml Solution for Injection (Carprofen) for Dogs and Cats is well tolerated at the recommended dose rate and also at three times the recommended dose rate. This shows that the product has a good margin of safety.

IV.B Clinical Studies

A broad review of the current literature was submitted in support of the efficacy of carprofen. The clinical documentation consists of published references. In view of the demonstration of bioequivalence between Carprofen Small Animal Injection and Rimadyl® Small Animal Injection only published data generated using Rimadyl® or Zenecarp® (the previous trade name of Rimadyl®) is considered to directly support the application.

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)