ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

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Veterinary Medicines Directorate
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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Norodyl 20 mg Tablets for Dogs
Norodyl 50 mg Tablets for Dogs

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0242/001/MR UK/V/0242/002/MR
Name, strength and pharmaceutical form	Norodyl 20 mg Tablets for Dogs Norodyl 50 mg Tablets for Dogs
Applicant	Norbrook Laboratories Ltd Station Works Camlough Road Newry Co. Down BT35 6JP
Active substance	Carprofen
ATC Vetcode	QM01AE91
Target species	Dogs
Indication for use	Reduction of inflammation and pain caused by musculo-skeletal disorders and degenerative joint disease. As a follow up to parenteral analgesia in the management of post-operative pain.

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	Mutual recognition application in accordance with Article 13(a) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	23 May 2007
Date product first authorised in the Reference Member State (MRP only)	05 October 2006
Concerned Member States for original procedure	Belgium France Germany Luxembourg

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, 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 the active substance carprofen and excipients microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, povidone K30, sodium laurel sulfate and magnesium stearate.

For both products the tablets may be supplied in aluminium blister strips of 10 tablets, or in polypropylene snap secure tubs sealed with white polyethylene snap secure caps. There are either 100 or 500 tablets in each tub. The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the formulation 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. . All production steps are performed according to pharmaceutical Good Manufacturing Practice, using conventional tabletting techniques. The validation of the process was carried out on three batches of each strength of tablet, and the data provided included information showing that tablets can be divided accurately. The studies conducted demonstrate that the tablets can be produced to a consistent and appropriate quality.

C. Control of Starting Materials

The active substance is carprofen. Supporting data have been provided in the form of an Active Substance Drug Master File (ASMF). It is considered that the manufacturing process is adequately controlled and the active substance specification has been suitably justified.

All the other substances in the tablets comply with the requirements of the relevant European Pharmacopoeial monographs.

The supplier of the polypropylene tubs and polyethylene caps has provided appropriate information on their specification. The PVC material which is used in the contact surface of the aluminium blisters complies with the requirements of the European Pharmacopoeia for such material.

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

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

E. Control on intermediate products

The bulk tablets are stored in polyethylene bags with a closure made by tying it. These bags are stored in either cardboard or plastic drums. The polyethylene bags comply with the requirements of Directive 92/39/EEC concerning plastic materials and articles in contact with food regulations. The bulk tablets are not routinely tested. However, it has been considered that the bulk tablets are not intermediate products as they are packed into their final containers within a month.

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 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 active substance when stored under the approved conditions.

The company provided data on three batches of each strength of tablet after storage in rigid polyethylene containers with snap-on polyethylene lids under standard and accelerated conditions of temperature and humidity. Tests conducted on the tablets stored in this way demonstrated that the product still meets the agreed specification after 3 years.

Samples from three batches of each tablet strength were also tested after storage in blister packs. The data derived from the batches support a shelf-life of 2 years.

H. Genetically Modified Organisms

Not applicable

J. Other Information

A shelf-life of 3 years is justified for tablets supplied in tubs, and 2 years for those supplied in blisters, subject to the following storage warnings.

Do not store above 25°C. Store in a dry place.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

As indicated in part I of this document, carprofen, the active substance in Norodyl 20 and 50 mg Tablets, has a well-established use in veterinary medicine and the safety information submitted by the company therefore includes a review of published literature on the pharmacology and toxicology of carprofen in the treatment of inflammation and pain in dogs.

Pharmacological Studies

Pharmacodynamics

The applicant has made references to published literature and has summarised the references in the dossier. The majority of these references are relevant to target species safety and are reported in detail in Part IV of this discussion.

In summary, carprofen is a NSAID (non-steroidal anti-inflammatory drug) and belongs to the 2-arylpropionate class. Carprofen is a racemate with a single chiral centre and therefore has 2 stereoisomers, the S(+) and R(-) enantiomers. In common with other NSAIDs, carprofen possesses analgesic, anti-inflammatory and antipyretic properties. The mechanism of action is not fully understood but it is regarded as a weak inhibitor of cyclooxygenase, an enzyme in the arachidonic acid cascade.

Pharmacokinetics

The applicant has made references to published literature of pharmacokinetic studies in a range of species including laboratory animals, man and the target species, dogs. These studies report ADME (absorption, distribution, metabolism and elimination) findings for the racemate and in the individual enantiomers demonstrating a marked difference in their pharmacokinetic profile in all species studied.

Absorption after oral and subcutaneous administration is relatively rapid and there is a low volume of distribution with a high degree of plasma protein binding. In all species studies the R(-) enantiomer was predominant and there were species differences in clearance and elimination with the S(+) enantiomer being cleared more rapidly.

The applicant has also submitted a pharmacokinetic study in dogs referred to in Part IV of this discussion.

Toxicological Studies

Single dose toxicity

The applicant has submitted references to published literature of studies conducted in laboratory species. They report a range of values for LD_{50} studies between 100-200 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 has commissioned 2 recent Acute Dose Fixed-Dose Method Studies and were conducted in compliance with Good Laboratory Practice (GLP). The published literature and studies demonstrate that the acute toxicity of carprofen is acceptable.

Repeated dose toxicity
The applicant has submitted references to published literature of repeat dose studies. All of these studies except for one were conducted in dogs in the late 1990's, but it is not known if these were GLP compliant; the other study was much older and conducted in rats and is unlikely to be GLP compliant. In the studies conducted in dogs, carprofen was administered orally and varied from 5 days to 1 year in duration with doses in the range of 1-30 mg/kg and one study dosing 80 mg/kg. Adverse effects were observed mostly at the higher doses. In addition, the applicant has conducted a recent 90 day repeat dose study repeat dosing study in compliance with GLP. The study submitted has reported a No Observed Effect Level (NOEL) of 2 mg/kg/day and the study is satisfactory.

Reproductive Toxicity
The applicant has submitted references to studies to 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 in the young dogs at birth and dead pups were associated with maternal deaths. The studies did not report an NOEL and this cannot be established from the published literature. However, 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.

Embrotoxicity/fetotoxicity (inc. teratogenicity)
Studies submitted also investigated embryo and foetotoxicity as well as teratogenicity. Although a larger number of abnormalities were observed in the control and treated groups, these were not considered to be treatment related and there was no statistically significant differences reported. There were no adverse effects on embryonic and foetal development in spite of some maternal toxicity.

Reference to reproductive studies conducted in a number of laboratory species and no teratogenic or foetotoxic effects were reported although effects considered related to maternal toxicity were observed in some studies. These were considered satisfactory data to establish an MRL and therefore data on multigeneration studies are not considered necessary.

Mutagenicity
Other published literature indicates that carprofen has been tested for mutagenic potential in a range of tests covering relevant end-points, and all tests produced negative results. A study conducted by the applicant also reports no mutagenic activity and it is therefore concluded that carprofen is not mutagenic and the data are satisfactory.

Carcinogenicity
The applicant has submitted published references on carcinogenicity and has not submitted any new study data.

The published literature reports that no evidence of carcinogenic potential was reported in a 6 month oral study in rats administered doses of 200 mg/kg/day and a 2 year study also in rats administered 10 mg/kg/day reported that carprofen was not carcinogenic. Reference is also made to an 80 week oral study in mice in which no evidence of carcinogenic potential was reported.

Other Studies
A lack of adverse effects on the nervous and renal systems of dogs and laboratory animals has also been reported in the published literature. Other reports indicated that carprofen may cause phototoxicity, and photosensitivity has also been suggested.

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

Microbiological Studies
The applicant has not provided any data on microbiological studies and has justified this because the product does not have any anti-microbial properties.

Studies on Metabolites, Impurities, Other Substances and Formulation
The applicant has submitted several references to the metabolism of carprofen. This is not applicable to this section and they are not reviewed in this part of the report. The applicant has not submitted any other data on metabolites, impurities, other substances or on the formulation. Further data were not considered necessary.

User Safety
The applicant has submitted a user risk assessment addressing the different routes of exposure and has proposed user warnings.

The main routes of exposure are skin contact from handling the tablets or accidental ingestion of the tablets by a child. Skin contact is minimal and the

exposure is estimated to be negligible, therefore it is not considered to present a hazard when the product is used as directed. The tablets packaged in blister packs or are dispensed into smaller containers and both of these presentations limit the amount of tablets a young child would have access to. Assuming a worst case, a child would probably only ingest 1 tablet or maybe 2 at the most; carprofen was used as a human medicine at doses of 150-600 mg/day, and therefore such accidental ingestion is not considered to be a hazard.

It is not considered necessary for any special user warnings to be given in the SPC.

Ecotoxicity

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.

Disposal advice is present on both the SPC[1] and product literature as follows:

Any unused product or waste material should be disposed of in accordance with national requirements.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies
Pharmacology

Pharmacodynamics

The company's 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 degenerative joint disease in dogs. 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.

[1] Summary of Product Characteristics

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

Pharmacokinetics
Various published papers 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.

To supplement the published information, the company commissioned a bioequivalence study, i.e. a study in which licensed products Norocarp Tablets were compared with Rimadyl Tablets, in terms of how much of the active substance, carprofen, was absorbed into the bloodstream when the products were given by mouth, as recommended. This study is described below.

The study utilised a well-accepted study design known as a “crossover” design, and involved two groups of 4-year old dogs. The first group received Norocarp Tablets at the maximum recommended starting dose of 4 mg carprofen/kg bodyweight; after a suitable delay to allow all the carprofen to disappear from their systems, they received Rimadyl Tablets, again at the recommended dose. The second group of animals was treated in the same way except that they received Rimadyl Tablets first and Norocarp Tablets second, hence the term “crossover”. Blood samples were collected from the dogs at intervals throughout the study and the amount of carprofen (racemate, R-enantiomer and S-enantiomer) in these samples was measured. When all the measurements had been collected, a graph of the amounts at the different times was produced. From this it was possible to see that the amount of carprofen that had reached the bloodstream was similar for both products. This was confirmed by a statistical analysis of the data.

Tolerance in the Target Species of Animals

The company submitted the report of a study commissioned in accordance with GLP[2] to investigate whether the product was well-tolerated in dogs, using Norocarp Tablets. In this study, dogs received one of the following treatments:

- the recommended maximum starting dose of carprofen (4 mg/kg bodyweight), daily for eight days, then reducing to 2 mg carprofen/kg bodyweight for a further 7 days;
- three times the recommended maximum starting dose of carprofen (12 mg/kg bodyweight), daily for eight days, reducing to 6 mg carprofen/kg bodyweight for a further 7 days; or
- tablets that contained no carprofen, daily for 15 days.

[2] Good Laboratory Practice

The animals were assessed for up to 35 days after the first tablets were given. This assessment involved clinical examination, measurement of heart rate, body temperature and consumption of food and water, as well as an assessment of general activity level, behaviour and appearance of faeces. In addition, blood samples were collected at intervals for blood cell counts, testing of clotting ability and analysis of various enzymes and other blood components.

There were no adverse effects in any of the tests and observations, showing that Norocarp Tablets are well-tolerated by dogs even if accidentally overdosed. Due to Norodyl Tablets having an essential similarity to Norocarp Tablets the above study shows that the product has a good margin of safety.

IV.B Clinical Studies

A series of published documents was presented, in which the efficacy of Rimadyl Tablets was investigated in various circumstances. Rimadyl Tablets are an already licensed product and bioequivalent product to Norodyl Tablets. One study demonstrated that a daily dose greater than 2.2 mg carprofen was required for efficacy. Several studies particularly focused on the use of carprofen in dogs with osteoarthritis. In each case, a significant number of dogs were found to respond favourably to the treatment. Similar results were found when carprofen was given to dogs prior to surgery to reduce postoperative pain in various different procedures, e.g. ovariohysterectomy or orthopaedic surgery. One study showed the efficacy of carprofen as an ocular anti-inflammatory drug.

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 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)