ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey KT15 3LS

(Reference Member State)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Carprogesic 100 mg Tablets for Dogs

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0319/001/DC
Name, strength and pharmaceutical form	Carprogesic 100 mg Tablets for dogs
Applicant	Norbrook Laboratories Limited
Active substance(s)	Carprofen
ATC Vetcode	QM01AE91
Target species	Dogs
Indication for use	Reduction of inflammation and pain caused by musculoskeletal 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	Application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	05 August 2009
Concerned Member States for original procedure	Austria Belgium France Germany Greece Ireland Italy Luxembourg Netherlands Portugal Spain

I. SCIENTIFIC OVERVIEW

Carprofen, the active ingredient of Carprogesic 100 mg Tablets for Dogs, 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 propionic acid. The product is authorised to be used in dogs in the reduction of inflammation and pain caused by musculoskeletal disorders and degenerative joint disease and as a follow up to parenteral analgesia in the management of post operative pain.

The chemical composition of carprofen is such that the atoms in each molecule may be arranged in two different forms, known as R and S enantiomers[1]. In these tablets, carprofen is in the form of a mixture of these two forms and this mixture is known as a racemate.

[1] Enantiomers, when present in a symmetric environment, have identical chemical and physical properties except for their ability to rotate plane-polarized light by equal amounts but in opposite directions.

The recommended dose is 4 mg carprofen per kg bodyweight per day given as a single daily dose or in two equally divided doses. The daily dose may be reduced, subject to clinical response.

These products are 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[2]. 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 benefit/risk analysis is in favour of granting marketing authorisations.

II. QUALITY ASPECTS

A. Composition

The products contain the active ingredient carprofen and excipients tartrazine, microcrystalline cellulose, lactose monohydrate, crosscarmellose sodium, povidone K30, sodium laurilsulphate and magnesium stearate.

The product is supplied in either polypropylene snap secure tubs containing 14, 30 or 100 tablets, sealed with a white low density polyethylene snap secure cap or aluminium-aluminium strips of 10 tablets in cartons containg 10, 20, 30, 50, 60, 70, 100, 140, 180, 200, 250, 280, 300, 500 or 1000 tablets. The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the formulations 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.

Process validation data on the product have been presented in accordance with the relevant European guidelines. The studies conducted demonstrate that the tablets can be produced to a consistent and appropriate quality.

C. Control of Starting Materials

The active substance carprofen is well established and supporting data have been provided to demonstrate compliance with the European Pharmocopoeia monograph. It is considered that the manufacturing process is adequately controlled and the active substance specification has been suitably justified.

All the excipients except Tartrazine (E102) are the subject of monographs in the European Pharmacopoeia and are provided to that standard. In the absence of a Pharmacopoeial monograph, the applicant has developed their own specification for Tartrazine (E102). The specification controls appearance, identification by infrared, loss on drying, pH, bulk density,

[2] SPC – Summary of Product Characteristics.

dye content, free dye content, lead, arsenic, heavy metals and particle size. A certificate of analysis is presented for one batch demonstrating compliance with this specification.

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

Scientific data 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

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. These include appropriate parameters, including appearance, amount of carprofen and any degradation products, hardness, friability, water content, dissolution characteristics, uniformity of mass and microbial quality. 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. The shelf-life of the veterinary medicinal product as packaged for sale is 2 years.

H. Genetically Modified Organisms

Not applicable

J. Other Information

Special Precautions for Storage:
Do not store above 25ºC.
Store in a dry place.
Protect from light.

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.

III. SAFETY ASSESSMENT

III.A Safety Testing

Pharmacological Studies

Since the application is made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of being a generic of a reference medicinal product, data on pharmacodynamics and pharmacokinetics are not required.

Toxicological Studies

Since the application is made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of being a generic of a reference medicinal product, data on toxicology are not required.

Other Studies

Since the application is made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of being a generic of a reference medicinal product, the applicant has not submitted any data for this section.

User Safety

The following operator warnings are included in the SPC and product literature:
In the event of accidental ingestion of the tablets, seek medical advice and show the doctor the package leaflet. Wash hands after handling the product.

Ecotoxicity

The applicant provided a phase I environmental risk assessment in compliance with the relevant guidelines. The Phase I assessment has demonstrated that use of the product will not result in extensive exposure of the environment and the assessment can end at Phase I.

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)

Pre-Clinical Studies

The preclinical documentation consists of published references, a bioequivalence study and a target species tolerance study.

Pharmacology

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 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.

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 carprogesic tablets were compared with a product that is already authorised, in terms of how much of the active ingredient, 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 dogs. 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 applicant submitted a study commissioned in accordance with Good Laboratory Practice to investigate whether the product was well-tolerated in dogs.

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 carprogesic tablets are well-tolerated by dogs even if accidentally overdosed. The product has a good margin of safety.

Resistance

Not applicable

Clinical Studies

A series of published documents was presented, in which the efficacy of carprofen containg product was investigated in various circumstances. 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 was 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 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)