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

Norodyl 100mg Tablets for Dogs

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

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0318/001/DC
Name, strength and pharmaceutical form	Norodyl 100mg 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	Decentralised application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	21/07/2009
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Austria, Belgium, Germany, Denmark, Greece, Spain, Finland, France, Italy, Luxembourg, The Netherlands, Portugal, Sweden

I. SCIENTIFIC OVERVIEW

This application for a Marketing Authorisation for Norodyl 100mg Tablets for Dogs was made in accordance with Article 13 (1) of Directive 2001/82/EC as amended, as a generic product with the UK authorised product Rimadyl 100mg Tablets. The global reference product, Rimadyl 20mg Tablets were formally known as Zenecarp Tablets, which were authorised in 1993. Rimadyl 50mg Tablets, authorised in the UK, were used in an appropriate bioequivalence study.

The tablets are designed for oral administration, at 4mg of carprofen per kg bodyweight per day. Initially, a daily dose of 4mg per day is given as a single dose, or in two equally divided doses. Subject to clinical response, the dose may then be reduced. Duration of treatment is dependent on the clinical response, and long-term treatment should be carried out under regular veterinary supervision. Post-operatively, parenteral and pre-operative treatment with an injectable carprofen product may be followed with Norodyl Tablets at 4mg/kg/day for up to 5 days. The product is not to be used in dogs suffering from cardiac hepatic, or renal disease, where there is a possibility of gastrointestinal ulceration or bleeding. Similarly, the product may not be used in dogs where there is evidence of blood dyscrasia, or hypersensitivity. Not to be used in cats.

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 100mg carprofen per tablet. Excipients are Tartrazine (E102), microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, povidone K30, sodium laurilsulphate and magnesium stearate.

The container systems for Norodyl 100mg tablets are either 14, 30 or 100 tablets in a Snap Secure Tub with a low density white polyethylene Snap Secure Cap, or aluminium-aluminium blister strips of 10 tablets in cartons containing 10, 20, 30, 50, 60, 70, 100, 140, 180, 200, 250, 280, 500 or 1000 tablets. The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the formulation and absence of preservative are 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 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 for which supporting data have been provided in the form of a European Drug Masterfile (EDMF). 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.

Excipients used have all been previously authorised for use in the UK, and all excipients apart from Tartrazine (E102) are monographed in the European Pharmacopoeia. 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, 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.

Any residual solvents are controlled in accordance with VICH guideline GL18, and heavy metals are within acceptable limits. Batch analysis data concerning

13 production scale batches showed that quality standards and compliance with the proposed specification was achieved. The specification for the active substance is appropriate to control the material.

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. 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. Certificates of analysis for two batches of 100mg Norodyl Tablets were provided, these were satisfactory.

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. The shelf life for 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.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

As this is a generic application according to Article 13 (1), and bioequivalence with a reference product has been demonstrated, results of pharmacological and toxicological tests are not required.

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

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.

Observations in Humans

The applicant has provided bibliographical information which shows that there may be irritation from handling the product, but this maybe abrogated by washing the hands. Deliberate ingestion is unlikely to cause a significant hazard.

User Safety

In the event of accidental ingestion of the product, seek medical advice and show the doctor the package leaflet. Wash hands after handling the product.

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

Ecotoxicity

The applicant provided a phase 1 environmental risk assessment in compliance with the relevant guideline which showed that no further assessment was 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.

IV CLINICAL ASSESSMENT (EFFICACY)

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.

IV.A Pre-Clinical Studies

Pharmacology

The applicant has provided bibliographical data describing an overview of the pharmacodynamics of carprofen, referring in particular to its analgesic and antipyretic properties in comparison to other non steroidal anti-inflammatories (NSAIDs).

Information was also provided on the pharmacological effects of carprofen, with regard to the major organ systems, carprofen having an effect as a reversible inhibitor of cyclo-oxygenase, and being a moderately potent inhibitor of phospholipase A_2. Additional data discussed some of the cellular mechanisms of the inflammatory response of carprofen, in comparision with hydrocortisone and ibuprofen.

Results suggested that carprofen inhibits the extent of leucocyte transport, and as leucocytes carry potential inflammatory mediators, any ensuing inflammatory response is muted.

Bibliographic data relating to the absorption, distribution, metabolism and elimination of carprofen were presented, along with a dissolution study on Norodyl 100mg Tablets for Dogs.

Tolerance in the Target Species of Animals

The applicant has conducted a target animal tolerance study using varied and multiple doses in the target species. A placebo was used as a control. In all groups, all doses were administered (if applicable), by the oral route, twice a day for up to 15 days. Parameters evaluated were urea, creatinine, ALT, ALP, total protein albumin and bilirubin. Blood cells were also analysed, including any occult blood occurring in faecal samples.

Adverse effects seen were minimal, and the product literature accurately reflects the type and incidence of adverse effects which might be expected.

IV.B Clinical Studies

No data was required for this section, as reference was made to previous data submitted for Carprogesic 20mg and 50mg tablets. Bibliographic data submitted included details of dose titrations, observations of the therapeutic use of carprofen in degenerative joint disease and osteoarthritis, and pre-operative administration for post-operative analgesia.

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.

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