ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Carprieve 20 mg Flavoured Tablets for Dogs
Carprieve 50 mg Flavoured Tablets for Dogs
Carprieve 100 mg Flavoured Tablets for Dogs
(UK, AT, BG, CY, CZ, ET, HU, IE, LV, LT, RO, SK, SL)

Norocarp 20mg Flavoured Tablets for Dogs
Norocarp 50mg Flavoured Tablets for Dogs
Norocarp 100mg Flavoured Tablets for Dogs
(BE, FR, EL, IT, LU, NL, PT, ES)

Norodyl Flavour 20mg Tablets for Dogs
Norodyl Flavour 50mg Tablets for Dogs
Norodyl Flavour 100mg Tablets for Dogs
(DK)

Carprieve 20 mg Chewable Tablets for Dogs
Carprieve 50 mg Chewable Tablets for Dogs
Carprieve 100 mg Chewable Tablets for Dogs
(FI)

Norocarp F 20mg Tablets for Dogs
Norocarp F 50mg Tablets for Dogs
Norocarp F 100mg Tablets for Dogs
(FR)

Paracarp 20mg Flavoured Tablets for Dogs
Paracarp 50mg Flavoured Tablets for Dogs
Paracarp 100mg Flavoured Tablets for Dogs
(DE)

Scanodyl 20mg Flavoured Tablets for Dogs
Scanodyl 50mg Flavoured Tablets for Dogs
Scanodyl 100mg Flavoured Tablets for Dogs
(PL)

Carprieve vet 20 mg Chewable Tablets for Dogs
Carprieve vet 50 mg Chewable Tablets for Dogs
Carprieve vet 100 mg Chewable Tablets for Dogs
(SE)

PuAR correct as of 28/01/2019 when RMS was transferred to IE.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0353/001/DC UK/V/0353/002/DC UK/V/0353/003/DC
Name, strength and pharmaceutical form	Carprieve 20 mg Flavoured Tablets for Dogs Carprieve 50 mg Flavoured Tablets for Dogs Carprieve 100 mg Flavoured Tablets for Dogs (UK, AT, BG, CY, CZ, ET, HU, IE, LV, LT, RO, SK, SL) Please see pages 1 and 2 for all names.
Applicant	Norbrook Laboratories Limited
Active substance(s)	Carprofen
ATC Vetcode	QM01AE91
Target species	Dogs
Indication for use	For analgesia and reduction of chronic inflammation, for example in degenerative joint disease in the dog. The tablets also can be used 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	Applications in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	22 December 2010
Concerned Member States for original procedure	Austria Belgium Bulgaria Cyprus Czech Republic Denmark Estonia Finland France Germany Greece Hungary Ireland Italy Latvia Lithuania Luxembourg The Netherlands Poland Portugal Romania Slovakia Slovenia Spain Sweden

I. SCIENTIFIC OVERVIEW

Carprieve 20 mg flavoured tablets for dogs, Carprieve 50 mg flavoured tablets for dogs and Carprieve 100 mg tablets for dogs contain the active substance carprofen. The products are authorised for use in dogs for analgesia and reduction of chronic inflammation, for example in degenerative joint disease in the dog. These products can also be used in the management of post operative pain. The tablets are administered orally and the dosage rate is 2 to 4 mg carprofen per kg bodyweight. An initial dose of 4 mg carprofen per kg bodyweight per day given as a single daily dose or in two equally divided doses may, subject to clinical response, be reduced after 7 days to 2 mg carprofen/kg bodyweight/day given as a single dose. The products are palatable and willingly consumed by most dogs when offered.

The applications for Carprieve 20 mg, 50 mg and 100 mg flavoured tablets for dogs were submitted in accordance with Article 13(1) of Directive 2001/82/EC, as amended by 2004/28/EC.

The 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 these products can be safely used in the target species and the slight reactions observed are indicated in the SPC[1]. The products are 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 products was demonstrated according to the claims made in the SPC.

II. QUALITY ASPECTS

A. Composition

The products contain the active substance carprofen and excipients lactose monohydrate, sodium lauryl sulphate, spray dried pig liver powder EHT, sucrose, yeast extract (dried), ground wheatgerm, starch pregelatinised, povidone K30, microcrystalline cellulose, guar gum, magnesium stearate and purified water.

The products are supplied in cartons of 20, 25, 100 or 200 tablets presented in aluminium/aluminium strip pack each containing 5 tablets.

The particulars of the containers and the controls performed on them 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.

[1] Summary of Product Characteristics

B. Method of Preparation of the Product

The products are 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 active substance carprofen is an established active substance and supporting data have been provided in the form of an EDMF[2]. It is considered that the manufacturing process is adequately controlled and the active substance specification has been suitably justified.

There are twelve excipients used in the formulation. Lactose monohydrate, sucrose, starch pregelatinised, povidone K30, microcrystalline cellulose, purified water and magnesium stearate have monographs in the European Pharmacopoeia and each complies with the current edition of the Ph. Eur. Sodium lauryl sulphate is the subject of a monograph in the United States Pharmacopoeia.

The applicant provided in-house specifications for spray dried pig liver powder EHT, yeast extract (dried), ground wheatgerm and guar gum. A certificate of analysis was provided for one batch demonstrating compliance with the proposed specification. This is considered acceptable.

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. The satisfactory validation data for the analytical methods have been provided.

[2] European Drug Master File

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 18 months. The shelf-life after first opening the immediate packaging is 24 hours.

H. Genetically Modified Organisms

Not applicable

J. Other Information

Special Precautions for Storage:

- Store in a dry place.
- Protect from light.
- Do not store above 25ºC
- Divided tablets should be stored in the blister pack.
- Due to the palatable nature of the tablets, store in a secure location. Severe adverse reactions may occur if large quantities are ingested. If you suspect your dog has consumed Carprieve 20 mg, 50 mg or 100 mg flavoured tablets above the labelled dose, please contact your veterinarian.

Shelf life:

Shelf life of the veterinary medicinal product as packaged for sale: 18 months.
Shelf-life after first opening the immediate packaging: 24 hours.
Any divided tablet portions remaining after 24 hours should be discarded.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

Pharmacological Studies

Since these generic applications were made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, data on pharmacodynamics and pharmacokinetics were not required.

Toxicological Studies

Since these generic applications were made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, data on toxicology werenot required.

User Safety

The following operator warnings are included in the SPC and product literature:

- In case of accidental ingestion seek medical advice and show the package leaflet or the label to the physician.
- Wash hands after handling product.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline.

The assessment ended at Phase I as the products will only be used in dogs and exposure of the environment is not sufficient to require further assessment. 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)

Pharmacology

Pharmacodynamics

Carprofen is a member of the 2–arylpropionic acid group of non steroidal anti-inflammatory drugs (NSAIDs) and possesses anti-inflammatory, analgesic and antipyretic activity.

Carprofen like most other NSAIDs is an inhibitor of the enzyme cyclo-oxygenase of the arachidonic acid cascade. However the inhibition of prostaglandin synthesis by carprofen is slight in relation to its anti-inflammatory and analgesic potency. At therapeutic doses in the dog, inhibition of the products of cyclo-oxygenase, (prostaglandins and thromboxanes), or lipoxygenase (leukotrienes), has been absent or slight. The precise mode of action of carprofen is not clear.

Pharmacokinetics

The applicant submitted the report of a study conducted in dogs comparing the Carprieve 50 mg tablets against the reference product Rimadyl 50 mg tablet. The applicant then extrapolated the *in-vivo* data to the other tablet strengths, 20 mg and 100 mg, via dissolution studies. The study utilised a well-accepted design known as a "crossover" design, and was conducted to GLP[3] standards. A suitable number of dogs were divided into different groups. The test product was Carprieve palatable tablets containing 50 mg carprofen. The test product was administered to dogs orally at dose levels of 4 mg carprofen per kg body weight. Blood samples were taken before administration of the products, and at a variety of time points subsequently. AUC[4] was used to demonstrate bioequivalence in accordance with the bioequivalence guideline. Confidence intervals calculated from C_{max}[5] and AUC were within the stipulated range of 80-125%, bioequivalence was therefore established.

Tolerance in the Target Species of Animals

The applicant has provided bibliographic data and the report of a study conducted to investigate the target animal safety in dogs following oral administration of a formulation of Carprieve palatable tablets. This was a randomised, blinded, parallel tolerance study designed to investigate three groups of dogs receiving the recommended dose, three times the recommended dose and a negative control via the oral route of administration. All animals were subject to clinical monitoring throughout the study. The study concluded that Carprieve palatable tablets at a nominal dose rate of 4 mg carprofen per kg bodyweight in two equally divided doses for eight consecutive days, followed by a nominal dose rate of 2 mg carprofen per kg bodyweight once daily for a further seven consecutive days, was well tolerated by dogs.

Resistance

Not applicable

[3] Good laboratory practice
[4] Area under the curve
[5] Maximum (or peak) concentration

Clinical Studies

Since these generic applications were made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, data on clinical trials were not required. This is considered acceptable.

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)