IPAR

Publicly Available Assessment Report for a Veterinary Medicinal Product

Carprofen Flavour KRKA 100mg tablets for dogs

PRODUCT SUMMARY

EU Procedure number	IE/V/0279/003/DC
Name, strength and pharmaceutical form	Carprofen Flavour KRKA 20mg tablets for dogs
Active substance(s)	Carprofen
Applicant	Krka, d.d. Novo mesto, Smarjeska cesta 6, 8501 Novo mesto, Slovenia
Legal basis of application	Article 13(1) of Directive 2001/82/EC, as amended
Date of completion of procedure	21/12/2011
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.
ATCvet code	QM01AE91
Concerned Member States	DK, FI, NO, SE

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.

The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

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 adverse reactions expected to be observed are the same as those included in the SPC of the reference product and are typical of those reactions expected to be observed for non-steroidal anti-inflammatory drugs. It is considered that possible adverse reactions are adequately reflected in the SPC.

The product is considered to be 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 a marketing authorisation.

II QUALITY ASPECTS

A. Qualitative and Quantitative Particulars

The product contains Carprofen 100 mg and excipients lactose monohydrate, maize starch, ferric oxide red (E172), ferric oxide black (E172), povidone K30, sodium starch glycolate (type A), colloidal anhydrous silica, meat flavour

10022, talc and magnesium stearate.

The tablets are presented in a blister (OPA/AL/PVC-AL) with 10 tablets per blister. The outer cartons contain 20, 50, 100 or 500 tablets per box.

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.

C. Control of Starting Materials

The active substance is Carprofen 100 mg, an established substance described in the European Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice.
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.

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.

D. Control on Intermediate Products

Not applicable.

E. 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.

F. 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 product throughout its shelf life when stored under the approved conditions.

G. Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

This is a generic application submitted in accordance with Article 13.1 of Directive 2001/82/EC, as amended. Bioequivalence has been demonstrated with the reference product Rimadyl 100 mg Tablets (VPA 10019/063/003) by

means of an *in-vivo* bioequivalence study and *in-vitro* dissolution studies. The reference product used in the *in-vivo* - bioequivalence study was Rimadyl Compresse 100 mg (Pfizer Italia).

As this is a generic application according to Article 13.1 and bioequivalence with a reference product has been demonstrated, results of safety and residue tests are not required.

The safety aspects of this product considered to be identical to the reference product.

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, the target species (dogs) and the environment.

III.A Safety Testing

Pharmacological Studies

Given the legal basis of the application (a generic application), the applicant was not required to provide the results of pharmacodynamic studies.

The applicant has provided the results of an *in-vivo* bioavailability study conducted using the 100 mg presentation (highest dosage strength) of the test product (Carprofen 100 mg tablet for dogs) and the reference product (Rimadyl Compresse 100 mg (Pfizer Italia)). The results of this study demonstrate that the 100 mg presentation of the test product is bioequivalent to the reference product for the pivotal pharmacokinetic parameters AUC_t, AUC_∞ and C_{max}: for all three pivotal pharmacokinetic parameters, the 90% confidence intervals lie within the narrower limits of 80-125%.

In addition to the *in-vivo* bioequivalence study, the applicant conducted an *in-vitro* dissolution study comparing the dissolution profile of Carprofen 100 mg tablets for dogs with that of the reference product Rimadyl Compresse 100 mg (Pfizer Italia). The dissolution characteristics of the two products were determined in dissolution media at three different pHs. The results of the *in-vitro* dissolution studies demonstrated that the candidate and reference product formulations have similar dissolution profiles.

Given that bioequivalence has been demonstrated between the 100 mg presentations (highest dosage strength) of test and reference products, the applicant also provided the results of *in vitro* studies (dissolution studies) in support of bioequivalence of the lower dosage strengths. The available data indicate a similar dissolution profile for Carprofen flavour 50 mg tablets, Carprofen flavour 20 mg tablets and Carprofen flavour 100 mg tablets.

On this basis, it is accepted that the findings of the *in vivo* study (conducted with the 100 mg tablet) can be extrapolated to the lower dosage strengths and, therefore, bioequivalence for the 20 mg and 50 mg tablet strengths can be assumed.

Toxicological Studies

Given the legal basis of the application (a generic application), the applicant was not required to provide the results of toxicological studies.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the product is not expected to pose a hazard to the user. Proposed user warnings are identical to those approved for other carprofen-containing generic products recently authorised through European procedures.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required and the assessment can be stopped at Phase I on the basis that the product is to be administered only to non-food producing animals. No specific warnings in respect of the environment are

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 13.1, 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

Given the legal basis of the application (a generic application), the applicant was not required to provide the results of pharmacodynamic studies.

The applicant has provided the results of an *in-vivo* bioavailability study conducted using the 100 mg presentation (highest dosage strength) of the test product (Carprofen 100 mg tablet for dogs) and the reference product (Rimadyl Compresse 100 mg (Pfizer Italia)). The results of this study demonstrate that the 100 mg presentation of the test product is bioequivalent to the reference product for the pivotal pharmacokinetic parameters AUC_t, AUC_∞ and C_{max}: for all three pivotal pharmacokinetic parameters, the 90% confidence intervals lie within the narrower limits of 80-125%.

In addition to the *in-vivo* bioequivalence study, the applicant conducted an *in-vitro* dissolution study comparing the dissolution profile of Carprofen 100 mg tablets for dogs with that of the reference product Rimadyl Compresse 100 mg (Pfizer Italia). The dissolution characteristics of the two products were determined in dissolution media at three different pHs. The results of the *in-vitro* dissolution studies demonstrated that the candidate and reference product formulations have similar dissolution profiles.

Given that bioequivalence has been demonstrated between the 100 mg presentations (highest dosage strength) of test and reference products, the applicant has provided the results of *in vitro* studies (dissolution studies) in support of bioequivalence of the lower dosage strengths. The available data indicate a similar dissolution profile for Carprofen flavour 50 mg tablets, Carprofen flavour 20 mg tablets and Carprofen flavour 100 mg tablets.

On this basis, it is accepted that the findings of the *in vivo* study (conducted with the 100 mg tablet) can be extrapolated to the lower dosage strengths and, therefore, bioequivalence for the 20 mg tablet and 50 mg strengths can be assumed.

Tolerance in the Target Species of Animals

Tolerance to the candidate formulation was assessed as part of the *in-vivo* bioequivalence study. No adverse events were reported in animals administered the candidate formulation.

The product literature accurately reflects the type and incidence of adverse effects which might be expected and reflects the information included in the SPC of the reference product.

IV.B Clinical Studies

Laboratory Trials

No data provided. Given the legal basis of the application (a generic application), the applicant was not required to provide the results of laboratory trials.

Field Trials

No data provided. Given the legal basis of the application (a generic application), the applicant was not required to provide the results of laboratory trials.

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.

VI 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 HPRA website.

This section 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.

Changes:
None.