IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Proin 50 mg chewable tablets for dogs

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PRODUCT SUMMARY

EU Procedure number	IE/V/0361/002/DC
Name, strength and pharmaceutical form	PROIN 50 mg chewable tablets for dogs
Active substance(s)	Phenylpropanolamine hydrochloride
Applicant	Pegasus Laboratories Limited 10 McCurtain Hill Clonakilty County Cork Cork P85 K230 Ireland
Legal basis of application	Application in accordance with paragraph 3 of Article 13 of Directive 2001/82/EC as amended.
Date of completion of procedure	22/11/2017
Target species	Dogs
Indication for use	For the management of urinary incontinence associated with urethral sphincter incompetence in the bitch, particularly that associated with ovariohysterectomy.
ATCvet code	QG04BX91
Concerned Member States	BE, DE, FR, IT, NL, ES and UK

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 slight reactions observed are indicated in the SPC along with their expected frequency of occurrence.

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 a marketing authorisation.

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II. QUALITY ASPECTS

A. Qualitative and Quantitative Particulars

PROIN 15 mg chewable tablets for dogs contains 15 mg/tablet phenylpropanolamine hydrochloride (as 12.1 mg/tablet phenylpropanolamine) and the excipients dark brown lake LB506, calcium hydrogen phosphate dihydrate, silica colloidal anhydrous, sorbitol, stearic acid, whey, powdered soy protein concentrate, chicken liver powder, dry liver flavour, dry garlic flavour, garlic powder and brewer's yeast.

PROIN 50 mg chewable tablets for dogs contains 50 mg/tablet phenylpropanolamine hydrochloride (as 40.3 mg/tablet phenylpropanolamine) and the excipients dark brown lake LB506, calcium hydrogen phosphate dihydrate, silica colloidal anhydrous, sorbitol, stearic acid, whey, powdered soy protein concentrate, chicken liver powder, dry liver flavour, dry garlic flavour, garlic powder and brewer's yeast.

The product is presented in white high density polyethylene bottles containing a 5 gram desiccant pack and cotton, sealed with a child resistant, foil lined heat sealed white polypropylene cap.

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 at a licensed manufacturing site.

Process validation data for the manufacturing process has been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is phenylpropanolamine hydrochloride, 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 has been provided.

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

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.

D. Control on Intermediate Products

Not applicable.

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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 has been provided.

Batch analytical data from the proposed production site has been provided demonstrating compliance with the specification.

F. Stability

Stability data on the active substance has 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 has 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 application was submitted in accordance with paragraph 3 of Article 13 of Directive 2001/82/EC – application for a hybrid veterinary medicinal product. The reference product cited in this application is Propalin syrup 50 mg/ml (VPA 10966/009/001;
Vetoquinol UK Limited) which was first authorised in the RMS (Ireland) on 14/07/1993, based upon a full dossier.
Bioequivalence with the reference product has been demonstrated by means of an *-in-vivo* bioequivalence study using the 15 mg tablet strength, with the findings of bioequivalence extrapolated to the 50 mg strength by means of *in-vitro* dissolution study data.

As bioequivalence with the reference product was demonstrated, the extrapolation of toxicity data from the reference to the candidate formulation was accepted.

Warnings and precautions as listed on the product literature are in line with those approved for the reference product but updated to account for the different physical presentation (tablets) compared to the reference product (syrup) and are considered adequate to ensure safety of the product to users and the environment.

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III.A Safety Testing

Pharmacological Studies

An *in-vivo* bioequivalence study was conducted using the 15 mg tablet strength and the reference product. Based on the results of this study, the product was demonstrated to be bioequivalent to the reference product for the parameters $AUC_{0\text{-}LOQ}$ and C_{max} with the ratio of the two treatment means contained within the acceptance limits.

Additional *in-vitro* dissolution study data was provided in order to extrapolate the findings of bioequivalence for the 15 mg tablet strength to the 50 mg tablet strength.

Toxicological Studies

As this application was submitted in accordance with paragraph 3 of Article 13 of Directive 2001/82/EC and bioequivalence with the reference product was demonstrated, no toxicological data was required.

User Safety

The applicant provided a user safety assessment in compliance with the relevant guideline. The immediate packaging was demonstrated to be child resistant.

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

It was accepted that the product will not present an unacceptable risk to the user when handled, administered, stored and disposed of in accordance with the recommendations included in the SPC.

Environmental Risk Assessment

Phase I

The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the product will only be administered to a non-food producing target species (dogs).

It was accepted that the product will not present an unacceptable risk for the environment when handled, administered, stored and disposed of in accordance with the recommendations included in the SPC.

III.B Residues Documentation

No residue data was required because the product is not intended for use in a food-producing target species.

IV. CLINICAL ASSESSMENT

As this is an application for a hybrid veterinary medicinal product submitted in accordance with paragraph 3 of Article 13 of Directive 2001/82/EC and bioequivalence with the reference product has been demonstrated, efficacy studies were not required. The efficacy claims for this product are equivalent to those of the reference product.

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IV.A Pre-Clinical Studies

Pharmacology

As this is an application for a hybrid veterinary medicinal product submitted in accordance with paragraph 3 of Article 13 of Directive 2001/82/EC and bioequivalence with the reference product has been demonstrated, pre-clinical study data was not required.

Tolerance in the Target Species of Animals

Given the physical difference in pharmaceutical form and qualitative and quantitative composition between candidate and reference product formulations, a target animal tolerance study was conducted investigating tolerance to 2, 6 and 10 mg phenylpropanolamine hydrochloride/kg bodyweight administered twice daily over a 26 week period.

Findings from this study suggest that the administration of phenylpropanolamine results in hypertension and that the incidence of hypertension was in general both time- and dose-dependent at all three dose levels. Vomiting/emesis and anorexia were very commonly reported. The SPC suitably communicates these findings and contraindicates use of the product in hypertensive animals or in animals that become hypertensive after initiating therapy.

IV.B Clinical Studies

Field Trials

As this is an application for a hybrid veterinary medicinal product submitted in accordance with paragraph 3 of Article 13 of Directive 2001/82/EC and bioequivalence with the reference product has been demonstrated, clinical studies (including field trials) were not required. The efficacy claims for this product are equivalent to those of the reference product.

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

None.

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