IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Urilin 40 mg/ml syrup for dogs

PRODUCT SUMMARY

EU Procedure Number	IE/V/0510/001 (formerly UK/V/0357/001)
Name, Strength, Pharmaceutical Form	Urilin 40 mg/ml syrup for dogs
Active Substances(s)	Phenylpropanolamine
Applicant	Dechra Regulatory B.V., Handelsweg 25, 5531 AE Bladel, Netherlands
Legal Basis of Application	Generic application (Article 13(1) of Directive No 2001/82/EC)
Target Species	Dogs
Indication For Use	For the treatment of urinary incontinence associated with acquired urethral sphincter incompetence in the bitch only. The efficacy of phenylpropanolamine has only been demonstrated in ovariohysterectomised bitches.
ATC Code	QG04BX91
Date of completion of the original mutual recognition procedure	28 April 2010
Date product first authorised in the Reference Member State	28 January 2005 (UK) 03 September 2010 (IE)
Concerned Member States for original procedure	Austria Belgium Bulgaria Czech Republic Denmark Finland France Germany Greece Hungary Ireland (now RMS) Italy Luxembourg Netherlands Poland Portugal Slovakia Spain Sweden UK added via RMS change

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

Urilin 40 mg/ml Syrup for dogs is authorised for the treatment of urinary incontinence associated with acquired urethral sphincter incompetence in the bitch only. The efficacy of phenylpropanolamine has only been demonstrated in ovariohysterectomised bitches. The dosage rate of phenylpropanolamine is 0.8 mg/kg body weight (equivalent to 1 mg/kg phenylpropanolamine HCL) three times daily in the feed, corresponding to 0.1 ml Urilin syrup/5 kg body weight three times daily. One drop for every 2.34 kg body weight three times daily in feed.

The application was made in accordance with article 13(1) of Directive 2001/82/EC, as amended by Directive 2004/28/EC i.e. application for a generic product. Bioequivalence is claimed with the reference product, Propalin Syrup, which was first marketed in the UK in 1993. Urilin Syrup has been authorised in the UK since January 2005.

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 possible reactions are indicated in the SPC. The product is safe for the user, the consumer of foodstuffs from treated animals 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 phenylpropanolamine hydrochloride as an active substance and sodium methyl parahydroxybenzoate (E219), sodium propyl parahydroxybenzoate (E217), maltitol liquid, saccharin sodium, citric acid monohydrate (E330) and purified water as excipients.

The product is supplied in 50 ml or 100 ml amber type III glass bottles containing 45 ml or 100 ml of syrup, with a low density polyethylene dropper and a polypropylene child resistant screw cap.

The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation is justified.

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 supporting data for phenylpropanolamine hydrochloride have been provided in the form of a Drug Master File. It is considered that the manufacturing process is adequately controlled and the active substance specification has been suitably justified.

There are six excipients used in the formulation and each has been used previously in veterinary medicines. Sodium methyl parahydroxybenzoate (E219), sodium propyl parahydroxybenzoate (E217), maltitol liquid, saccharin sodium, citric acid monohydrate (E330) and purified water have monographs in the Ph. Eur. and each comply with the requirements of the current edition of the Ph. Eur.

D. 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. A declaration states that no starting materials present a risk with regard to TSEs.

E. Control on intermediate products

The manufactured product may be stored in its container for up to 5 days. A bulk intermediate specification is provided and consists of identity tests for the active substance, chloride, the preservatives, pH and specific gravity. The test methods are the same as for the finished product.

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.

G. Stability

Stability data on the active substance have been provided. Based on the data provided, a retest interval of five years was justified.

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 3 years.

The in-use shelf life of 3 months is justified.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Do not store above 25°C.
Keep the container in the outer carton.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

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.

Mutagenecity

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 this section 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, data on this section are not required.

User Safety

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

Phenylpropanolamine hydrochloride is toxic when overdoses are ingested. Adverse effects may include dizziness, headache, nausea, insomnia or restlessness, and increased blood pressure. High overdose may be fatal, especially in children.

In the event of accidental skin contact, wash the contaminated area with soap and water. Wash hands after use of the product.
In the event of accidental eye contact, rinse the eye with clean water for about 15 minutes and seek medical advice.
To avoid accidental ingestion the product must be used and kept out of the reach and sight of children.
Always replace the cap firmly after use to ensure that the child resistant closure operates correctly.
In the event of accidental ingestion, seek immediate medical attention showing the doctor the package leaflet.

Ecotoxicity

The applicant has provided a first phase environmental risk assessment in compliance with the relevant guideline.
The assessment ended at Phase I as the product will only be used in dogs on an individual basis 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

Pharmacology

Pharmacodynamics
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 this section are not required.

Pharmacokinetics:
A study was conducted to demonstrate bioequivalence between Urilin 40 mg/ml syrup for dogs and the reference product. The study was carried out to the standards of GLP[1]. Bioequivalence was established using ANOVA[2], and a calculation of 90% confidence intervals for AUC and C_{max}[3]. Confidence intervals calculated from C_{max} and AUC[4] were within the stipulated range of 80-125%, bioequivalence was therefore established.

Tolerance in the Target Species of Animals

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 this section are not required.

Resistance

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 this section are not required. The applicant has submitted PSUR data over the four year period which indicated the safety profile of Urilin syrup in field use.

IV.B Clinical 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 this section are not required.
[1] Good Laboratory Practice
[2] Analysis of variance
[3] Maximum concentration
[4] Area under the curve

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