IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Otoxolan ear drops, suspension for dogs

PRODUCT SUMMARY

EU Procedure Number	IE/V/0438/001 (formerly UK/V/0604/001)
Name, Strength, Pharmaceutical Form	Otoxolan ear drops, suspension for dogs
Active Substances(s)	Marbofloxacin,Clotrimazole ,Dexamethasone acetate
Applicant	KRKA, d.d., Novo mesto Šmarješka cesta 6, 8501 Novo mesto Slovenia
Legal Basis of Application	Generic application (Article 13(1) of Directive No 2001/82/EC)
Target Species	Dogs
Indication For Use	Treatment of otitis externa of both bacterial and fungal origin respectively due to bacteria sensitive to marbofloxacin, and fungi especially Malassezia pachydermatis sensitive to clotrimazole. The product should be used based on susceptibility testing.
ATC Code	QS02CA06
Date of completion of the original decentralised procedure	19 October 2016
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States	Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, France, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, The Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain. UK added via change of RMS

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

This was a generic application submitted in accordance with Article 13 (1) of Directive 2001/82/EC (as amended). The reference product is Aurizon Ear Drop Suspension which has been authorised in the UK since 2001. The proposed product had the same pharmaceutical form, contains the same active substances, in the same quantities, and the same excipients in similar quantities, as the reference product. Data were provided which demonstrated that the minor differences in formulation between the test and reference products are not likely to impact on the rate or extent of availability of the active substances at the site of action or local tolerance
Otoxolan ear drops are indicated for the treatment of otitis externa of both bacterial and fungal origin respectively due to bacteria sensitive to marbofloxacin, and fungi especially *Malassezia pachydermatis* sensitive to clotrimazole.
The product should be used based on susceptibility testing.
The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto the market. It has been shown that the product can be safely used in the target species, any reactions observed are indicated in the SPC.[1] 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 [2] 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.

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

II. QUALITY ASPECTS

II.A. Composition
The product contains marbofloxacin 3.0mg, clotrimazole 10 mg, dexamethasone acetate 1.0 mg (equivalent to 0.9 mg dexamethasone) and the excipients triglycerides medium-chain, propyl gallate (E310), sorbitan oleate and silica, hydrophobic colloidal.

The container/closure system consists of an LDPE bottle with an LDPE dropper and HDPE screw cap, and a thermoplastic elastomer dropper with cap. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the 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.

II.B. Description of the Manufacturing Method
The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of a simple mixing and filling process.

The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post-authorisation

II.C. Control of Starting Materials
The active substances are marbofloxacin, clotrimazole and dexamethasone acetate, established substances described in the European Pharmacopoeia. The active substances are manufactured in accordance with the principles of good manufacturing practice.

The active substance specifications are considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with the specifications have been provided.

The data provided for the active substances are comprehensive. Clotrimazole and dexamethasone are supplied in accordance with certificates of suitability (CEPs). Marbofloxacin is supplied against a satisfactory active substance master file (ASMF).

All the excipients are controlled against their respective Ph. Eur. Monographs.

II.C.4. Substances of Biological Origin
There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process
Not applicable.

II.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 sites have been provided demonstrating compliance with the specification. Control tests on the finished product include appearance, density, identification and assay of the active substances and microbial quality.

II.F. Stability
The active substance is fully tested to ensure compliance with its specification immediately prior to its use in manufacture of the product. 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. Batches were stored under VICH conditions of 25°C/60% RH, 30°C/65% and 40°C/75% RH for a variety of time periods, and the results are reflected in the established shelf-life data information provided in the SPC.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 18 months.
Shelf life after first opening the immediate packaging: 3 months.
Do not store above 30 °C.
Keep the bottles in the outer carton in order to protect from light.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13 (1), and data were provided which demonstrated that the proposed product was qualitatively identical to the reference product, results of pharmacological and toxicological tests are not required. Warnings and precautions as listed on the product literature are in line with those of the reference product and are adequate to ensure safety of the product to users and the environment.

III.A Safety Documentation

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that the product should have similar user warnings as the reference product.

These are:

- Wash hands carefully after applying the product.
- Avoid contact with eyes. If splashed in the eye, rinse with large amounts of clean water.
- If skin or eye symptoms persist, or the product is accidentally swallowed, seek medical attention and show the package insert to the physician.
- People with known hypersensitivity (allergy) to (fluoro)quinolones, (cortico)steroids or antifungals and to other ingredients in the product should take care to avoid contact with the product during administration.

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

Environmental Safety

An environmental risk assessment was carried out in accordance with VICH[1] and CVMP[2] guidelines.

Phase I:

The ERA stops at question 3 of the VICH Phase I decision tree, the product will only be used in non-food animals and as a result environmental exposure will be low. A Phase II ERA was not required.

[1] Guideline on Environmental Impact Assessments (EIAS) for Veterinary Medicinal Products – Phase I. CVMP/VICH/592/98-FINAL
[2] Revised Guideline on Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL 38. EMEA/CVMP/ERA/418282/2005-Rev.

IV. CLINICAL ASSESSMENT

This is a generic application according to Article 13 (1); however bioequivalence can only be demonstrated for systemically acting products. Therefore, data were provided comparing the test product composition and physicochemical characteristics with those of the reference product in order to justify omission of preclinical and clinical tolerance and efficacy studies; this approach has been proposed in CVMP guidance documents for locally acting products and is considered acceptable.
The efficacy claims for this product are equivalent to those of the reference product.

IV.I. Pre-Clinical Studies

Pharmacology

The applicant has conducted studies to show that the proposed product is qualitatively identical to the reference product and that there is no impact on bioavailability.

Resistance

The bibliography provided suggests that susceptibility breakpoints have been determined as ≤ 1 µg/ml for sensitive, 2 µg/ml for intermediate and ≥ 4 µg/ml for resistant bacterial strains. Marbofloxacin is not active against anaerobes. Resistance to fluoroquinolones occurs by chromosomal mutation with three mechanisms: decrease of the bacterial wall permeability, expression of efflux pump or mutation of enzymes responsible for molecule binding.

Adequate warnings and precautions appear on the product literature.

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 of the product is favourable.