IPAR

Publicly Available Assessment Report for a Veterinary Medicinal Product

Toltarox 50 mg/ml Oral Suspension for Cattle

PRODUCT SUMMARY

EU Procedure number	IE/V/0247/002/DC
Name, strength and pharmaceutical form	Toltarox 50 mg/ml Oral Suspension for Cattle
Active substance(s)	Toltrazuril
Applicant	KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia
Legal basis of application	Generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of completion of procedure	26th September 2013
Target species	Cattle
Indication for use	For the prevention of clinical signs of coccidiosis and reduction of coccidia shedding in housed calves replacing cows producing milk for human consumption (dairy cows) on farms with a confirmed history of coccidiosis caused by *Eimeria bovis* or *Eimeria zuernii*.
ATCvet code	QP51AJ01
Concerned Member States	RO, SI

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 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 benefit/risk analysis is in favour of granting a marketing authorisation.

II QUALITY ASPECTS

A. Qualitative and Quantitative Particulars

The product contains 50 mg/ml toltrazuril and the excipients propylene glycol, docusate sodium, simethicone emulsion, aluminium magnesium silicate, citric acid monohydrate, xanthan gum, sodium propionate, sodium benzoate and purified water.

The container/closure system is a HDPE bottle with HDPE closure and LDPE sealing liner.

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 on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is toltrazuril an established active substance. 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.

G. Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The application is made in accordance with Article 13(1) of Council Directive 2001/82/EC (as amended), a generic application.

The test product (Toltrazuril 50 mg/ml oral suspension) is the same as the reference product Baycox Bovis 50 mg/ml

oral suspension (Bayer Animal Health) in terms of qualitative and quantitative composition of the active substance (toltrazuril) and has the same pharmaceutical form (oral suspension).

In support of the present application, the applicant has provided the results of a bioequivalence study conducted in calves comparing the pharmacokinetic profile of toltrazuril (and toltrazuril sulfone) following administration of the test product with that following administration of the reference product.

Quantification of toltrazuril (toltrazuril sulfone) in test samples was by validated HPLC method. Pharmacokinetic parameters of toltrazuril and its metabolite toltrazuril sulfone were calculated for each animal.

The results of the study indicated that the 90% confidence intervals for the pivotal pharmacokinetic parameters (AUC_{tot} and C_{max}) fell within the pre-defined limits. In this case, all were within the narrow limits of 80 -125%. Based on the data provided, it can be accepted that the test product (Toltrazuril 50 mg/ml oral suspension) and the reference product Baycox Bovis 50 mg/ml oral suspension are bioequivalent. Consequently, the omission of the results of safety and residue tests or of pre-clinical and clinical trials may be accepted.

Toxicological Studies

The application is made in accordance with Article 13(1) of Council Directive 2001/82/EC (as amended), a generic application. Data on toxicological studies have not been provided.

User Safety

The risk management measures that the applicant proposes are in line with those accepted for the reference product:

“Wash any splashes from skin or eyes immediately with water.”

Given that:

- The test and reference product are the same in terms of pharmaceutical form,
- The test and reference product are the same in terms of quantitative and qualitative composition of active substance,
- The excipients used in the test product are common in oral dose formulations and are considered safe at the concentrations included in this formulation (Indeed, the qualitative composition of the test product in terms of excipients is very similar to that of the reference product),
- The proposed use of the test product is the same as the authorised use for the reference product (same target species, same dose and treatment regimen), and
- The user safety statements proposed for inclusion in the SPC reflect those agreed for the reference product,

It is accepted that the test product will not present any greater risk to the user than the minimal risk posed by the reference product. The proposed user safety statement is considered appropriate.

Environmental Risk Assessment

The Applicant has provided a Phase I assessment for the product demonstrating that a PEC value below the trigger value of 100 µg/kg was obtained (EMEA/CVMP/ERA/418282/2005-Rev.1). Therefore, in accordance with relevant guidance, the ERA can end at Phase I with no further assessment required.

Warnings and precautions as listed on the product literature are adequate to mitigate the risk to the environment when the product is used as directed.

III.B Residues Documentation

Residue Studies

The application is made in accordance with Article 13(1) of Directive 2001/82/EC, as amended (a generic application). The Applicant has conducted two *in vivo* bioequivalence studies demonstrating that the test product (Toltrazuril 50

mg/ml oral suspension) and the reference product Baycox Bovis 50 mg/ml oral suspension are bioequivalent.

No residue studies conducted.

MRLs

The MRL for Toltrazuril, as appears in Annex I of Council regulation (EEC) No. 2377/90, is as follows:

	ALL MAMMALIAN FOOD PRODUCING SPECIES
Muscle	100 µg/kg
Liver	500 µg/kg
Kidney	250 µg/kg
Fat / skin	150 µg/kg
Milk	-

Withdrawal Periods

The Applicant has demonstrated that the product is bioequivalent to the reference product Baycox Bovis 50 mg/ml oral suspension. As the test product is bioequivalent to the reference product it is accepted that there will be no difference between the products with respect to depletion of residues of toltrazuril sulfone. Therefore, the cattle meat withdrawal period of 63 days can be applied to the test product. The product is not permitted for use in lactating animals producing milk for human consumption.

IV CLINICAL ASSESSMENT (EFFICACY)

The application is made in accordance with Article 13(1) of Council Directive 2001/82/EC (as amended), a generic application. The Applicant has conducted an *in vivo* bioequivalence study demonstrating that the test product (Toltrazuril 50 mg/ml oral suspension) and the reference product Baycox Bovis 50 mg/ml oral suspension are bioequivalent. As such, it can be assumed that the efficacy profile will be comparable to that of the reference product.

The conditions of use of the product (target species, indication and posology) are the same as those authorised for the reference product.

Tolerance data specific to Toltrazuril 50 mg/ml oral suspension have not been presented. However, it is accepted that the test product will not present any greater risk to the target animal than the minimal risk posed by 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

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.