College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
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The Netherlands

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Dozuril 25 mg/ml solution for use in drinking water for chickens

RMS transfer from FR (FR/V/0233/001/DC) to NL (NL/V/0216/001) on 22 June 2016

First created FR: July 2012

Updated NL: October 2020

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0216/001
Name, strength and pharmaceutical form	Dozuril 25 mg/ml solution for use in drinking water for chickens
Applicant	Dopharma Research B.V. Zalmweg 24 4941 VX Raamsdonksveer The Netherlands
Active substance(s)	Toltrazuril
ATC Vetcode	QP51AJ01
Target species	Chickens (pullets and breeders)
Indication for use	Treatment of coccidiosis in pullets and broiler breeders.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicines Agencies website (http://www.HMA.eu) and on the Medicine Evaluation Board – Veterinary Medicinal Products Unit website (https://www.diergeneesmiddeleninformatiebank.nl/nl).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	25 April 2012
Date product first authorised in the Reference Member State (MRP only)	N/A
Concerned Member States for original procedure	BE – BG – DE – DK - EE – EL – HU – IE - LT – LV – NL - PL – RO

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

Dozuril is authorized by means of a generic application. The reference product is BAYCOX 2.5% ORAL SOLUTION, marketed by BAYER SANTE, which has been authorized in France since 27 September 1989.

II. QUALITY ASPECTS

A. Composition

The product contains 25 mg/ml toltrazuril as the active substance and the excipients trolamine and macrogol 300.

The container/closure system is a high-density polyethylene bottle with high-density polyethylene screw cap and removable polyethylene sealing disk. The particulars of the containers and controls performed are provided and conform to the regulation.
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 toltrazuril, an established substance which is not described in the European/British Veterinary 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.

D. 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.

E. Control on intermediate products

Not applicable.

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.

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.

G. 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.

An in-use shelf-life after first opening and an in-use shelf-life after dilution as detailed on the SPC have been supported by appropriate data.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

Based on information provided in support of this application, it is accepted that the test product is bioequivalent to the reference product BAYCOX 2,5%, marketed by BAYER SANTE.
As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, results of pharmacological tests are not required.

The pharmacological aspects of this product are identical to the reference product.

Toxicological Studies

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, results of toxicological tests are not required.

The toxicological aspects of this product are identical to the reference product.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline.

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

Ecotoxicity

The applicant has provided a phase I and a phase II in the environmental risk assessment for Toltrazuril and the metabolite Toltrazuril sulfone in compliance with the relevant guideline. The results did not support a safe use for the environment for broilers. Thus, the marketing authorization was only approved for pullets and breeders.
If used according to the SPC, the product should not raise concerns for the environment.

III.B Residues documentation

Residue Studies

No residue depletion studies were conducted since the tested product is bioequivalent to the reference product and the product is administered via oral route.

MRLs

a. active substances

The active substance, toltrazuril, is included in table 1 of the MRL regulation 37/2010, as follows:

Marker residue	Animal Species	MRL	Target Tissues	Other Provisions	Therapeutic Classification	Regulation
Toltrazuril sulfone	All mammalia	100 µg/kg 150 µg/kg	Muscle Fat	For porcine species the fat MRL relates to “skin	Antiparasitic agents/	37/2010 of

	n food producing species	500 µg/kg 250 µg/kg	Liver Kidney	and fat in natural proportions". Not for use in animals from which milk or eggs are produced for human consumption.	Agents acting against protozoa	22.12.2009
	Poultry	100 µg/kg 200 µg/kg 600 µg/kg 400 µg/kg	Muscle Skin + fat Liver Kidney			

b. excipients

The MRL status of excipients of the product dozuril 25 mg/ml oral solution for poultry is indicated in the following table.

Excipient	MRL status
triethanolamine	Out of scope
Polyethylene glycol 300	No MRL required

Withdrawal Periods

The tested product will be applied identical withdrawal periods than the reference product that is:
Meat and offal: 16 days.
Not permitted for use in laying birds producing eggs for human consumption.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

The applicant has not provided tolerance study which is acceptable because:

- the tested product and the reference product are bioequivalent,
- the excipients of the tested product are deemed unproblematic as regards tolerance.

The tolerance aspects of this product are identical to the reference product.

IV.B Clinical Studies

As this is a generic application according to Article 13, 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.

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 risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

MODULE 4

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 Heads of Veterinary Medicines Agencies website (www.HMA.eu).

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.

Summary of change	**Section updated**	**Approval date**
Change in batch size Addition of 5 litre pack size (FR/V/0233/IB/001/G)	N/A SPC	18 September 2013
RMS transfer from FR (FR/V/0233/001/DC) to NL (NL/V/0216/001)	Module 1	22 June 2016
Renewal (NL/V/0216/001/R/001)	N/A	30 May 2017
Change in batch size Addition of a secondary packaging site Addition of a batch release site (NL/V/0216/IA/001/G)	N/A N/A SPC	10 November 2019
Replacement of a manufacturing site Change of the batch size Change in shape or dimensions of the containers Tightening of specification. (NL/V/0216/IB/004/G)	N/A	11 March 2021
ASMF update NL/V/0216/001/II/002	N/A	23 July 2021
Align the product information with QRD 9.0 (NL/V/xxxx/A/070)	SPC	13 April 2023