Medicines Evaluation Board
Graadt van Roggenweg 500 | 3531 AH Utrecht
The Netherlands

REFERENCE MEMBER STATE: THE NETHERLANDS

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

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

created: November 2023

PRODUCT SUMMARY

EU procedure number	NL/V/0271/001/DC
Name, strength and pharmaceutical form	Dozuril CT 25 mg/ml solution for use in drinking water
Applicant	Dopharma Research B.V. Zalmweg 24 4941 VX Raamsdonksveer The Netherlands
Active substance(s)	Toltrazuril
ATC vetcode	QP51BC01
Target species	Chickens (pullets and breeders), turkeys
Indication for use	Treatment of coccidiosis caused by infections with various species of *Eimeria*: Chickens: *E. acervulina*, *E. brunetti*, *E. maxima*, *E. mitis*, *E. necatrix*, *E. tenella*. Turkeys: *E. adenoides* and *E. meleagrimitis*.

PRODUCT INFORMATION

The Summary of Product Characteristics (SPC), the labelling and package leaflet for this veterinary medicinal product (VMP) is available in the Union Product Database (UPD).

SUMMARY OF ASSESSMENT

Legal basis of original application*	Generic application in accordance with Article Article 13(1) of the Directive 2001/82/EC, as amended.
Reference product (RP)	BAYCOX 2,5%, oplossing voor orale toediening
Marketing authorisation holder	Bayer B.V.
Marketing authorisation number	REG NL 9857
Date of authorisation	08 May 2006
Reference to proprietary data of an additional VMP linked to the reference product	BAYCOX 25 mg/ml solution of use in drinking water for chickens and turkeys
Marketing authorisation holder	Bayer Animal Health GmbH
Marketing authorisation number EU procedure number	REG NL 113710 AT/V/0012/001/DC
Part of the dossier referred to	Part 3B Residues
Date of completion of the original decentralised procedure	18 December 2019
Concerned Member States for original procedure	DE, FR, IT, PL
Concerned Member States for subsequent recognition procedure	Not applicable.

*Please be aware that certain parts of the dossier may be varied and consequently be subject to protection of technical documentation – for these and other changes of referenceability to parts of the dossier, please see chapter POST-AUTHORISATION PROCEDURES

1. SCIENTIFIC OVERVIEW

The veterinary medicinal product (VMP) is produced and controlled using validated methods and tests, which ensure the consistency of the VMP released on the market.

It has been shown that the VMP can be safely used in the target species.

The VMP 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 VMP was demonstrated according to the claims made in the SPC.

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

2. QUALITY DOCUMENTATION (physicochemical, biological or microbiological information)

A. Product description

The product contains toltrazuril 25 mg/ ml and the excipients trolamine and polyethylene glycol 300 (macrogol 300).

The product is supplied in two different multi-dose, airtight and tamper-proof containers: either a white 1000 mL HDPE bottle or a white 5000 mL HDPE jerrycan.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Description of the manufacturing method

The product is manufactured fully in accordance with the principles of good manufacturing practice at licensed manufacturing sites.

Process validation data on the product have been presented on 3 production batches in accordance with the relevant European guidelines.

C. Production and control of starting materials

The active substance is toltrazuril, an established active substance not 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 have been provided.

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

D. Control tests carried out on isolated intermediates during the manufacturing process

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 tests

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.

The shelf life, in-use shelf life and shelf life of the medicated solutions are based on the studies provided in the dossier.

3. SAFETY DOCUMENTATION (safety and residues tests)

As this is a generic application according to Article 13(1) of the Directive 2001/82/EC, as amended and bioequivalence with a reference VMP has been demonstrated, results of pharmacological and toxicological tests are not required.

The pharmacological and toxicological aspects of this VMP are identical to the reference VMP.

Warnings and precautions as listed on the product literature are the same as those of the reference VMP and are adequate to ensure safety of the product to users / the environment / consumers.

A. Safety tests

Pharmacological studies

As this is a generic application according to Article 13(1) of the Directive 2001/82/EC, as amended and bioequivalence with a reference VMP has been demonstrated, results of pharmacological tests are not required.

Toxicological studies

As this is a generic application according to Article 13(1) of the Directive 2001/82/EC, as amended and bioequivalence with a reference VMP has been demonstrated, results of toxicological tests are not required.

Observations in humans

Skin, eye or mucous membrane irritation may occur as a result of the excipients. Macrogols may cause stinging when used topically. There is a risk of hypersensitivity reactions to toltrazuril and/or macrogol 300.

User safety

The applicant has provided a user safety assessment in compliance with the relevant guideline, which shows that there are risks of skin, eye or mucous membrane irritation, hypersensitivity reactions and possible risks for the unborn child.

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

Environmental Risk Assessment

A Phase I environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines. The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the initial predicted environmental concentration in soil (PEC_{soil}, stabled = 27.5 µg/kg for replacement layers, 7.82 µg/kg for broiler breeders and 61.9 µg/kg for turkeys) is less than 100 µg/kg.

For broilers, the PEC_{soil} trigger of 100 µg/kg was exceeded, meaning that a Phase II assessment was deemed necessary. Target species broilers was withdrawn from the application and therefore no Phase II assessment was required.

B. Residues documentation

Residue tests

No residue depletion studies were conducted because bioequivalence with a reference product has been demonstrated on the grounds that the product is to be orally administered to chickens and turkeys as a solution and contains the same active substance in the same concentration as Baycox 25 mg/ml (REG NL 113710, marketing authorisation holder: Bayer B.V.). Minor differences in excipients do not affect gastrointestinal transit, absorption, solubility or *in vivo* stability of the active substance. The proposed formulation for Dozuril CT can be considered as being essentially similar to that of Baycox 25 mg/ml. Therefore the withdrawal periods mentioned in Baycox 25 mg/ml REG NL 113710 also apply for Dozuril CT.

Maximum Residue Limits

Toltrazuril is included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 as follows:

Pharmacologically active Substance	Marker residue	Animal Species	MRL	Target Tissues	Other Provisions *(according to Article 14(7) of Regulation (EC) No 470/2009)*	Therapeutic Classification
Toltrazuril	Toltrazuril sulfone	All mammalian food producing species	100 µg/kg 150 µg/kg 500 µg/kg 250 µg/kg	Muscle Fat Liver Kidney	For porcine species the fat MRL relates to 'skin and fat in natural proportions'. Not for use in animals from which milk is produced for human consumption. Not for use in animals from which eggs are produced for human consumption.	Antiparasitic agents/Agents acting against protozoa
		Poultry	100 µg/kg 200 µg/kg 600 µg/kg 400 µg/kg	Muscle Skin and fat Liver Kidney		

Withdrawal Periods

Based on the data provided above, a withdrawal period of 16 days for meat and offal in chickens and turkeys are justified.

4. EFFICACY DOCUMENTATION (preclinical studies and clinical trials)

As this is a generic application according to Article 13(1) of Directive 2001/82/EC as amended and bioequivalence with a reference VMP has been demonstrated, efficacy studies are not required. The efficacy claims for this VMP are equivalent to those of the reference VMP.

A. Pre-Clinical Studies

No pre-clinical studies were performed.

Bioequivalence with the reference product has been demonstrated on the grounds that the product is to be orally administered as a solution and contains the same active substances in the same concentration and similar excipients as the reference product. A comparative study of the physicochemical characteristics of both products was performed, showing that both products have comparable physicochemical properties. The proposed formulation for Dozuril CT can be considered essentially similar to that of the reference product.

B. Clinical trials

No clinical trials were performed.

5. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the VMP 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 VMP for humans and the environment is acceptable.

POST-AUTHORISATION PROCEDURES

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the VMP. The current SPC is available in the Union Product Database (UPD).

This section contains information on changes, which have been made after the original procedure.

Summary of change (Application number)	**Approval date**
• Change of the invented name of the product in France (NL/V/0271/001/IB/001)	8 August 2020
• Change in a manufacturing site performing production of the end product, batch control/testing, primary packaging, secondary packaging, batch release. • Increase up to 10-fold compared to the originally approved batch size • Change in shape or dimensions of the container or closure (immediate packaging) (NL/V/0271/IB/002/G)	11 March 2021
• One-off alignment of the product information to QRD template version 9.0 • Implementation of referral C(2002) 8153 (NL/V/xxxx/A/070)	13 April 2023