Veterinary Medicines Directorate

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Veterinary Medicines Directorate
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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Chanox Multi 50 mg/ml oral suspension for Piglets, Calves and Lambs
Chanox vet 50 mg/ml Oral Suspension for Piglets, Calves and Lambs (Finland, Norway, Sweden)
Cenzuril 50 mg/ml Oral Suspension for Piglets, Calves and Lambs (Spain)

Date Created: November 2017

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0654/001/MR
Name, strength and pharmaceutical form	Chanox Multi 50 mg/ml oral suspension for Piglets, Calves and Lambs
Applicant	Chanelle Pharmaceuticals Manufacturing Ltd. Loughrea Co. Galway Ireland
Active substance(s)	Toltrazuril
ATC Vetcode	QP51AJ01
Target species	Pig (piglets), Calves (on dairy farms). For environmental reasons: Do not use in calves weighing more than 80 kg bodyweight. Do not use in fattening units such as veal or beef calves. Sheep (lambs)
Indication for use	Piglets: For the prevention of clinical signs of coccidiosis in neonatal piglets on farms with a confirmed history of coccidiosis caused by *Cystoisospora suis*. Calves: 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*. Lambs: For the prevention of clinical signs of coccidiosis and reduction of coccidia shedding in lambs on farms with a confirmed history of coccidiosis caused by *Eimeria crandallis* and *Eimeria ovinoidalis*.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

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 conclusion of the mutual recognition procedure	18th October 2017
Date product first authorised in the Reference Member State (MRP only)	13th March 2017
Concerned Member States for original procedure	Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Italy, The Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Spain, Sweden

I. SCIENTIFIC OVERVIEW

This was a generic application for Chanox Multi 50 mg/ml Oral Suspension for Piglets, Calves and Lambs. The reference product is Baycox 50 mg/ml Oral Suspension for Piglets, Calves and Lambs, authorised in the UK since August 2009. Baycox 50 mg/ml belongs to the same global marketing authorisation as Baycox 25% w/v Oral Solution, authorised in the UK since February 2004.

The product is indicated for use in piglets, for the prevention of clinical signs of coccidiosis in neonatal piglets on farms with a confirmed history of coccidiosis caused by *Cystoisospora suis.* In Calves, the product is indicated 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*. In lambs, the product is indicated for the prevention of clinical signs of coccidiosis and reduction of coccidia shedding on farms with a confirmed history of coccidiosis caused by *Eimeria crandallis* and *Eimeria ovinoidalis*.

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, the

[1] SPC – Summary of product Characteristics.

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 [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.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains 50 mg/ml toltrazuril and the excipients sodium benzoate (E211), sodium propionate (E281), citric acid monohydrate (for pH adjustment), sodium hydroxide (for pH adjustment), xanthan gum, aluminium magnesium silicate, sodium laurilsulfate, propylene glycol, simethicone emulsion and purified water.

The container/closure system consists of high density polyethylene bottles containing 100 or 250 ml with a high density polyethylene screw cap closure, and high density polyethylene flexi-pack bottles containing 1 L and 5 L with a polypropylene screw cap closure.

The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the formulation and the presence of preservatives 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 of the ingredients into bottles, with appropriate quality control.

II.C. Control of Starting Materials

The active substance is toltrazuril, an established active substance, which is not described in a Pharmacopoeia, but for which there are active substance manufacturer's specifications. 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. Certificates of Analysis were provided.

[2] Efficacy – The production of a desired or intended result.

All excipients are monographed within the European Pharmacopoeia (Ph. Eur). All packaging complies with either Ph. Eur monographs or Commission Directive 10/2011.

II.C.4. Substances of Biological Origin

Declarations have been provided, and 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. No materials of animal origin are contained in the product. The HDPE bottles contain fatty acids of animal origin and completed European Directorate for the Quality of Medicines tables were provided for the product as a whole.

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 those for: identification of the active substance and the preservatives, resuspendability, pH, viscosity, microbiological quality, particle size and uniformity of fill.

II.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. The retest period for the active substance is 2 years. Stability studies were performed on 3 batches of active substance, stored in suitable containers for long term testing at 25°C±2°C/60% RH ±5% RH for 36 months and accelerated conditions at 40°C±2°C/75% RH ±5% RH for 6 months. The results support the retest period and storage conditions. Appropriate post-approval testing was instigated. Suitable stability data were obtained for the finished product.

G. Other Information

Shelf-life of the veterinary medicinal product as packaged for sale: 4 years

Shelf life after first opening the immediate packaging: 1 year.

This veterinary medicinal product does not require any special storage conditions.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

As this was an application for a generic product, toxicological and pharmacological data were not required, provided bioequivalence of the proposed product to the reference product could be demonstrated. A user risk assessment (URA) and environmental risk assessment (ERA) were provided. The proposed and reference product were the same with regard to active substance. The dispersal and suspending excipients differed, with docusate sodium and bentonite, present in the reference product and magnesium aluminium silicate and sodium lauryl sulfate, (commonly used in veterinary medicines), in the proposed product.

User Safety

A user risk assessment was provided in compliance with the relevant guideline. The user warnings are the same as those of the reference product. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. The warnings were revised in order to bring them up to date with more recent developments. The following applicant's user recommendations are appropriate:

- People with known hypersensitivity to toltrazuril, or any of the excipients, should avoid contact with the veterinary medicinal product.
- This product can cause skin and eye irritation.
- Avoid skin and eye contact with the product.
- In case of accidental exposure to the skin or eyes, wash the affected area thoroughly with plenty of water.
- If irritation persists, seek medical advice and show the package leaflet or the label to the physician.
- Do not eat, drink or smoke whilst using the product.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

The ERA concludes in Phase I at Question 17 of the decision tree on the basis that the PEC_{soil} value calculated for each category of target animal species is

below the threshold value (100 µg/kg). The same disposal advice and environmental warnings as agreed for the reference product have been

proposed for the test product and are supported. The product is not expected to pose a risk for the environment when used in accordance with the recommendations included in the SPC.

III.B.2 Residues documentation

Residue Studies

No residue depletion studies were conducted because as the proposed product was bioequivalent to the reference product, no additional data were required for this section.

MRLs

Toltrazuril is listed in Table 1 of the Annex of Commission Regulation (EU) No. 37/2010 in accordance with the following table. (Marker residue toltrazuril sulfone)

MRLs are listed below:

	All mammalian food-producing species	Other provisions	Therapeutic classification
Muscle	100 µg/kg	Not for use in animals from which milk is produced for human consumption	Antiparasitic agents/ Agents acting against protozoa
Liver	500 µg/kg		
Kidney	250 µg/kg		
Fat	150 µg/kg		

Withdrawal Periods

Piglets

Meat and offal: 77 days

Calves

Meat and offal: 63 days

Not authorised for use in animals producing milk for human consumption.

Lambs

Meat and offal: 42 days

Not authorised for use in animals producing milk for human consumption.

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics

Due to the legal basis of the application, and because bioequivalence with the reference product has been demonstrated, no pharmacodynamic studies were required. Pharmacodynamic data as shown in the SPC are as follows:

Toltrazuril is a triazinon derivative. It acts against coccidia of the genus *Cystoisospora* and *Eimeria*. It is acting against all intracellular development stages of coccidia of the merogony (asexual multiplication) and gamogony (sexual phase). All stages are destroyed, thus the mode of action is coccidiocidal.

Pharmacokinetics

The applicant has provided bibliographical data pharmacokinetic properties of the active substance, in addition to 3 bioequivalence studies, one on each of the target species.

Bioequivalence study on the 50 mg/ml reference and proposed toltrazuril products in calves

This was a single dose, two group, parallel design study conducted to GLP[3] in calves. Animals were divided into 2 treatment groups and 3 sampling groups, (3 test periods). Forty-eight calves were divided into roughly 3 equal groups. Animals were administered a single oral dose of 3 ml/10 kg bodyweight (15 mg/kg) to the root of the tongue. Examinations and blood sampling were performed at suitable time-points. Pharmacokinetic parameters were measured and statistical analysis performed on results. The 90% confidence limits for the $AUC_{0\text{-}t}$[4] and C_{max}[5] treatment effect ratios of the test and reference products entirely fell within the pre-set acceptance bounds of 80 - 125% and 70 - 143%, respectively. Therefore, it could be confirmed that the products were bioequivalent.

[3] GLP – Good laboratory Practice.
[4] $AUC_{0\text{-}t}$ – Area under the curve.
[5] C_{max} – maximum concentration.

Bioequivalence study on the 50 mg/ml reference and proposed toltrazuril products in lambs

This was a single dose, two group, parallel design study conducted to GLP[6] in calves. Animals were divided into 2 treatment groups and 3 sampling groups, (3 test periods). Forty-eight lambs were divided into roughly 3 equal groups. Animals were administered a single oral dose of 0.4 ml/kg bodyweight (20 mg/kg) to the root of the tongue. Examinations and blood sampling were performed at suitable time-points. Pharmacokinetic parameters were measured and statistical analysis performed on results. The 90% confidence limits for the AUC_{0-t} and C_{max} treatment effect ratios of the test and reference products entirely fell within the pre-set acceptance bounds of 80 - 125% and 70 - 143%, respectively. Therefore, it could be confirmed that the products were bioequivalent.

Bioequivalence study on the 50 mg/ml reference and proposed toltrazuril products in piglets

This was a single dose, two group, parallel design study conducted to GLP in calves. Forty-eight pigs were divided into 2 treatment groups. Animals were administered a single oral dose of 0.4 ml/kg bodyweight (20 mg/kg) to the root of the tongue. Examinations and blood sampling were performed at suitable time-points. Pharmacokinetic parameters were measured and statistical analysis performed on results. The 90% confidence limits for the AUC0-t and Cmax treatment effect ratios of the test and reference products entirely fell within the pre-set acceptance bounds of 80 - 125% and 70 - 143%, respectively. Therefore, it could be confirmed that the products were bioequivalent.

Tolerance in the Target Species

Tolerance studies were not required because the proposed and reference products were shown to be bioequivalent.

Resistance

No legal obligation required the submission of resistance data. Adequate warnings and precautions appear on the product literature:

As with any antiparasiticide frequent and repeated use of antiprotozoals from the same class may lead to the development of resistance. It is recommended to treat all animals in a pen.

IV.II. Clinical Documentation

Due to the legal basis of the application, no data were required for this section.

[6] GLP – Good laboratory Practice.

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(s) is favourable.

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 Product Information Database of the Veterinary Medicines Directorate website.

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The post-authorisation assessment (PAA) 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.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

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