IPAR

Publicly Available Assessment Report for a Veterinary Medicinal Product

Baycox Multi 50 mg/ml oral suspension for Cattle, Pigs and Sheep

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PRODUCT SUMMARY

EU Procedure number	IE/V/0360/001/DC
Name, strength and pharmaceutical form	Baycox Multi 50 mg/ml oral suspension for Cattle, Pigs and Sheep
Active substance(s)	Toltrazuril
Applicant	Bayer Animal Health
Legal basis of application	Generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of completion of procedure	21/09/2016
Target species	Cattle (calves: dairy calves, beef suckler, bull beef), Pigs (piglets, 3-5 days old), Sheep (lambs)
Indication for use	Cattle: For the prevention of clinical signs of coccidiosis and reduction of coccidia shedding in calves on farms with a confirmed history of coccidiosis caused by *Eimeria bovis* or *Eimeria zuernii*. Pigs: For the prevention of clinical signs of coccidiosis in neonatal piglets (3 – 5 days old) on farms with a confirmed history of coccidiosis caused by *Cystoisospora suis*. Sheep: 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*.
ATCvet code	QP51AJ01
Concerned Member States	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IS, IT, LT, LU, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK

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

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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, 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 toltrazuril (50 mg/ml) and the excipients sodium benzoate (E211), sodium propionate (E281), docusate sodium, simethicone emulsion, bentonite, citric acid, anhydrous, xanthan gum, propylene glycol and water, purified.

The container/closure system consists of high density polyethylene bottles closed with polypropylene screw caps containing 100, 250 or 1000 ml of product.

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 for the manufacturing process has 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 has 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 has been provided.

Batch analytical data from the proposed production site has been provided demonstrating compliance with the specification.

F.Stability

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.

G.Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

This application was submitted in accordance with Article 13.1 for a generic veterinary medicinal product. The reference product cited by the applicant was Baycox Bovis 50 mg/ml oral suspension (VPA 10021/051/001– Bayer Limited). In addition, the applicant also referred to data in the dossiers of the related products Baycox Sheep, 50 mg/ml oral suspension (10021/058/001) and Baycox 50 mg/ml oral suspension, pig (10021/044/001) which have the same formulation as the reference product.

Given that the candidate formulation is qualitatively and quantitatively identical to the reference product formulation and is manufactured using the same process at the same facilities, it could be accepted that the criteria set out in section 7.1.d of the CVMP bioequivalence guidelines, exempting the requirement for bioequivalence studies, have been met.

It could be accepted that the candidate formulation is bioequivalent to the reference product Baycox Bovis 50 mg/ml oral suspension and the two additional products Baycox Sheep, 50 mg/ml oral suspension and Baycox 50 mg/ml oral suspension, pig (which have the same formulation) without the need to conduct *in-vivo* bioequivalence studies.

Warnings and precautions as listed on the product literature are the same as those of the reference product and are considered adequate to ensure safety of the product to users, the environment and consumers of animals treated with the product.

III.A Safety Testing

Given that bioequivalence between the candidate formulation and the reference product has been satisfactorily demonstrated, pharmacological and toxicological data were not required.

User Safety

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The applicant provided a user safety assessment in compliance with the relevant guideline. It was highlighted that:

- the formulation of the generic product is identical to that of the reference product,

- the generic product will be administered to the same target species, using the sameroute of administration and posology approved for the reference product,

- the tasks and situations that might lead to user exposure are not considered to differ between generic and reference products.

Consequently, it could be concluded that the generic product will not present an unacceptable risk for the user when stored, handled, used and disposed of in accordance with the recommendations proposed for inclusion in the SPC.

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

Environmental Risk Assessment

As required by legislation, the applicant provided an environmental risk assessment.

Phase I

Based upon the data provided, it was accepted that the environmental risk assessment could stop in Phase I for dairy calves because predicted environmental exposure concentrations fall below the trigger value for a Phase II assessment and based upon acceptable reference to relevant aspects of the European Commission's decisions in respect of referrals of other toltrazuril-containing veterinary medicinal products.

Phase II

As part of a post-authorisation variation application, a phase II environmental risk assessment was provided in support of the extension of the indication to beef suckler calves and bull beef calves.

The metabolite toltrazuril sulfone was considered to be the active moiety of concern. All laboratory studies were conducted in accordance with GLP and relevant OECD guidelines.

Physical-chemical properties	
Study type	**Result**
Vapour pressure	$<2.04 \times 10^{-5}$

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Water solubility	1.04 $mg.L^{-1}$
Dissociation constants in water pKa	pKa = 7.15
n-Octanol/Water Partition Coefficient logP_{ow}	logK_{ow} = 2.49

Environmental fate	
Study type	**Result**
Soil Adsorption/Desorption	Koc = 616.5
Aerobic and Anaerobic Transformation in Soil	DT_{50} = 366 days

Effect studies			
Study type	**Endpoint**	**Result**	**Unit**
Algae growth inhibition test/ *Pseudokirchneriella subcapitata*	EC50	15.1	mg/l
Daphnia sp. immobilisation	EC50	23.8	mg/l
Fish, acute toxicity/ *L. macrochirus*	LC50	8.8	mg/l
Soil microorganisms: Nitrogen transformation test (28 days)	% effect	<25%	
Terrestrial Plants, growth test	EC50	0.46	mg/kg
Earthworm/*Eisenia foetida* reproduction	NOEC	>2,000	µg/kg

The DT_{50} value was estimated to be 366 days which exceeds the value of 180 days considered representative of a very persistent substance.

Risk characterisation

Risk quotients (RQs) were calculated for each of the environmental compartments of concern. RQs using tier B endpoints showed no unacceptable risk for the environment when the product will be used in accordance with the recommendations included in the SPC.

Acceptable meta-modelling was used to further refine the predicted exposure of ground water to toltrazuril sulfone and levels were determined to be less than the upper limit of 0.1 µg/L (considered as safe) provided certain risk mitigation measures were taken (as set out in the SPC).

PBT Assessment

The log Kow of toltrazuril sulfone was demonstrated to be <4 and therefore does not meet the criteria to be considered a substance with potential for bioaccumulation.

Conclusion

Based on the data provided in the ERA, a possible risk to the terrestrial environment (growth and emergence of plants) and possible leaching to groundwater by the

metabolite of toltrazuril (ponazuril) might arise if certain risk mitigation measures are not taken. Consequently suitable risk mitigation measures and advice were included in the SPC for this product to ensure safety for the environment, namely:

- manure from treated dairy calves must not be spread onto land without dilution with manure from untreated cows. Manure from treated cdairy alves must be diluted with at least 3 times the weight of manure from mature cows before it can be spread onto land.
- the product should not to be used in dairy calves weighing more than 80 kg bodyweight or in veal calves.
- the product should not be used in beef suckler calves or bull beef calves weighing more than 150 kg bodyweight,
- the product should not be used in bull beef calves less than three months old,- lambs kept throughout the whole life span indoors under an intensive rearing system must not be treated beyond the age of 6 weeks or body weight of more than 20 kg at treatment. Manure from these animals should only be applied to the same piece of land every third year.

III.B Residues Documentation
Residue Studies

No residue depletion studies were conducted because the candidate formulation is qualitatively and quantitatively identical to the reference product formulation and will be administered to the same target species, using the same route of administration and posology approved for the reference product. Consequently, it could be accepted that the rate of depletion of residues following oral administration of this generic product is not expected to differ from that of the reference product.

MRLs

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

Pharmacologically active substance	Marker residue	Animal species	MRL	Target tissues	Other provisions
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.
		Poultry	100 µg/kg 200 µg/kg 600 µg/kg 400 µg/kg	Muscle Skin & fat Liver Kidney	

Withdrawal Periods

The withdrawal periods are the same as those approved for the reference product and the two additional products with the same formulation and to which the applicant also referred.

The proposed withdrawal periods of 63 days, 77 days and 42 days for meat and offal from cattle, pigs and sheep, respectively, are considered adequate to ensure the safety of consumers of products derived from animals administered the product. The product is not permitted for use in lactating animals producing milk for human consumption.

IV. CLINICAL ASSESSMENT

As this is an application for a generic veterinary medicinal product submitted in accordance with Article 13.1 of Directive 2001/82/EC, as amended 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.

IV.APre-Clinical Studies

Tolerance in the Target Species of Animals

This is an application for a generic veterinary medicinal product submitted in accordance with Article 13.1 of Directive 2001/82/EC, as amended and bioequivalence with a reference product has been demonstrated.

The candidate formulation is qualitatively and quantitatively identical to the reference product formulation and is manufactured using the same process at the same facilities. It can therefore be accepted that the candidate formulation is bioequivalent with the reference formulation.

In addition, the candidate formulation is intended to be administered to the same target species, using the same route of administration and dose rate as approved for the reference product and the two additional products to which the applicant also referred.

It could therefore be concluded that target animal tolerance to the candidate formulation is not expected to differ between the generic and reference formulations and consequently, the omission of target animal tolerance data could be accepted for this generic product.

Resistance

This is an application for a generic veterinary medicinal product submitted in accordance with Article 13.1 of Directive 2001/82/EC, as amended and bioequivalence with a reference product has been demonstrated. It could therefore

be concluded that the potential for resistance development will not differ between generic and reference products.

Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

Laboratory Trials

Field Trials

Given that bioequivalence between the candidate formulation and the reference product has been satisfactorily demonstrated, laboratory trial and field trial data were not required.

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:
IE/V/0360/001/II/001 was approved on 27th September 2017. This variation application related to the extension of the indication to beef suckler calves and bull beef calves. Also *Isosporasuis* was updated to *Cystoisospora suis* and the SPC was amended to indicate that toltrazuril sulfone is very persistent (half-life ca. 1 year) in soil.