

IPAR



**Publicly Available Assessment Report for a
Veterinary Medicinal Product**

Tratol 50 mg/ml oral suspension for pigs, cattle and sheep

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PRODUCT SUMMARY

EU Procedure number	IE/V/0267/001/DC
Name, strength and pharmaceutical form	Tratol 50 mg/ml oral suspension for pigs, cattle and sheep.
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	24 th January 2011
Target species	Pigs (Piglet 3-5 days old). Following extension application IE/V/0267/001/DX/005, the following target species were added: Cattle (calves on dairy farms) Sheep (lambs).
Indication for use	Pigs: For the prevention of clinical signs of coccidiosis caused by <i>Isospora suis</i> . Following extension application IE/V/0267/001/DX/005 the following indications species were added: Cattle: For the prevention of clinical signs of coccidiosis and reduction of oocyst shedding in housed calves replacing cows producing milk for human consumption (dairy cows) on farms with a confirmed history of coccidiosis caused by <i>Eimeria bovis</i> or <i>Eimeria zuernii</i> . Sheep: For the prevention of clinical signs of coccidiosis and reduction of oocyst shedding in lambs on farms with a confirmed history of coccidiosis caused by <i>Eimeria crandallis</i> and <i>Eimeria ovinoidalis</i> .
ATCvet code	QP51AJ01
Concerned Member States	AT, DE, DK, ES, FI, FR, IT, NL, PT, 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 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.

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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 toltrazuril (50 mg/ml) and the excipients sodium benzoate (E211), sodium propionate (E281), propylene glycol, docusate sodium, simeticone emulsion, aluminium magnesium silicate, citric acid monohydrate, xanthan gum and water, purified.

The container/closure system consists of high density polyethylene bottles of 250 ml and 1000 ml with high density polyethylene closures and sealing liners.

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 toltrazuril 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.

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. 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)

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

The test product (Tratol 50 mg/ml oral suspension for pigs) is the same as the reference product Baycox 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).

III.A Safety Testing

Pharmacological Studies

In support of the present application, the applicant has provided the results of a bioequivalence study conducted in piglets 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 (Tratol 50 mg/ml oral suspension for pigs) and the reference product Baycox 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.

Two additional target species were added during procedure IE/V/0267/001/DX/005. The applicant provided the results of two additional *in-vivo* comparative bioavailability studies conducted in calves and lambs.

The bioequivalence study conducted in calves used Baycox Bovis 50 mg/ml oral suspension (Bayer) as reference product. A staggered, single dose, open label, restricted randomised parallel design was used, due to the long terminal elimination half-life (approximately 64 hours according to the SPC of the reference product) of toltrazuril, which would result in an unacceptably long wash out period that would be incompatible with a cross-over study design.

Based upon the data presented, the candidate formulation can be accepted as being bioequivalent to the reference product following single oral administration of 15 mg/kg toltrazuril to calves.

The bioequivalence study conducted in lambs used Baycox Sheep 50 mg/ml oral suspension (Bayer) as reference product. A staggered, single dose, open label, restricted randomised parallel design was used, due to the long terminal elimination half-life (approximately 9 days according to the SPC of the reference product) of toltrazuril, which would result in an unacceptably long wash out period that would be incompatible with a cross-over study design.

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Based upon the data presented, the candidate formulation can be accepted as being bioequivalent to the reference product following single oral administration of 20 mg/kg toltrazuril to lambs.

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 applicant has provided a user safety assessment in line with the relevant guideline which shows that risk to the user in terms of the active substance toltrazuril will be no greater for the candidate formulation than that which already exists for the reference product.

No new risk to the user is expected to arise as a result of exposure to the excipients in the candidate formulation.

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 products are the same in terms of pharmaceutical form,
- The test and reference products 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 an environmental impact assessment for each of the target species (cattle, pigs and sheep).

Phase I

Based upon calculated $PEC_{\text{soil initial}}$ values for each of the three target species, the environmental risk assessment may stop in phase I as the trigger value of 100 $\mu\text{g}/\text{kg}$ has not been exceeded. As additional support for stopping the assessment in phase I, the applicant made reference to the Commission decision relating to referral EMEA/V/A-33/50 (Cevazuril 50 mg/ml oral suspension for piglets) which concluded that no Phase II assessment was necessary for toltrazuril as the $PEC_{\text{soil initial}}$ value was below 100 $\mu\text{g}/\text{kg}$.

Conclusion

Based on the data provided, the ERA can stop at Phase I. The product is not expected to pose an unacceptable risk for the environment when used according to the SPC.

Notwithstanding the above conclusions, the applicant has included similar warnings in respect of the major metabolite of toltrazuril, toltrazuril sulfone (ponazuril) as included in the SPC of the reference product.

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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 an *in vivo* bioequivalence study demonstrating that the test product (Tratol 50 mg/ml oral suspension for pigs) and the reference product Baycox 50 mg/ml oral suspension are bioequivalent.

No residue depletion studies were conducted because bioequivalence with an appropriate reference product has been satisfactorily demonstrated in each of the three target species. Further, given the essential similarity between candidate and reference formulations and the fact that the product is to be orally administered to the same target species using the same dose rates, the withdrawal periods approved for the reference product are considered applicable to the candidate formulation.

MRLs

Toltrazuril and its marker residue toltrazuril sulfone are included in Table I of the Annex to Commission Regulation (EU) No 37/2010 as follows:

	All mammalian food producing species
Muscle	100 µg/kg
Liver	500 µg/kg
Kidney	250 µg/kg
Fat/ skin	150 µg/kg

Withdrawal Periods

Based on the bioequivalence data provided and the essential similarity between candidate and reference formulations, the following withdrawal periods approved for the reference formulation could be accepted as being applicable to the candidate formulation.

Pigs

Meat and offal: 77 days.

Cattle

Meat and offal: 63 days.

Sheep

Meat and offal: 42 days.

The product is not authorised for use in lactating cattle or sheep producing milk for human consumption.

IV. CLINICAL ASSESSMENT

As this is a generic application according to Article 13.1 of Directive 2001/82/EC, as amended and bioequivalence with a reference product has been demonstrated for each of the target species, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

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IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

No specific tolerance studies with the final formulation have been conducted. However, the applicant referred to the limited tolerance data available from the three in-vivo comparative bioavailability studies where it is considered that no product-related adverse events occurred.

This is a generic application (Article 13.1) and bioequivalence with the reference product is claimed. The candidate formulation is qualitatively and quantitatively identical to the reference product (Baycox 50 mg/ml oral suspension) in terms of the active substance (toltrazuril), is qualitatively similar to the reference product in terms of the excipients and is to be administered to the same target species (calves, piglets, lambs) using the same dose rates and route of administration approved for the respective reference products.

In light of the above, the omission of formulation specific tolerance studies was accepted. It is not expected that tolerance to the candidate formulation will differ from that of the reference product in any of the proposed target species. It can be accepted that the candidate formulation will not present an unacceptable risk to the target species when administered in accordance with the recommendations included in the proposed SPC.

Resistance

As the candidate formulation is quantitatively identical to the reference product in terms of the active substance toltrazuril and will be administered to the same target species using the same route of administration at the same dose rate and for the same treatment duration, the potential for resistance development will be the same for the candidate formulation as that which already exists for the reference product.

Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

Laboratory Trials

Field Trials

Given that bioequivalence with an appropriate reference formulation has been demonstrated in each of the target species, no laboratory or field trials were 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.

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Changes:***Safety/Efficacy Changes***

Summary of change (Application number)	Approval date
Addition of cattle (calves on dairy farms) and sheep (lambs) as target species. (IE/V/0267/001/DX/005).	23 rd July 2014.

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