# IPAR

# Publicly Available Assessment Report for a Veterinary Medicinal Product

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

## PRODUCT SUMMARY

| | |
|---|---|
| EU Procedure number | IE/V/0333/001/DC |
| Name, strength and pharmaceutical form | Tolracol 50 mg/ml oral suspension for pigs, cattle and sheep. |
| Active substance(s) | Toltrazuril |
| Marketing Authorisation Holder | KRKA, d.d., Novo mesto<br>Šmarješka cesta 6<br>8501 Novo mesto<br>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 | 23rd July 2014 |
| Target species | Pigs (Piglet 3 - 5 days old).<br>Cattle (calves on dairy farms).<br>Sheep (lambs). |
| Indication for use | Pigs:<br>For the prevention of clinical signs of coccidiosis in neonatal piglets (3 – 5 days) on farms with a confirmed history of coccidiosis caused by *Isospora suis*.<br><br>Cattle:<br>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 *Eimeria bovis* or *Eimeria zuernii*.<br><br>Sheep:<br>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 *Eimeria crandallis* and *Eimeria ovinoidalis*. |
| ATCvet code | QP51AJ01 |
| Concerned Member States | DE, BE, NL, UK, PT, FR, ES, IT |

## 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.

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) as the active substance and the excipients propylene glycol, docusate sodium, simethicone emulsion, aluminium magnesium silicate, citric acid monohydrate, xanthan gum, sodium propionate, sodium benzoate and purified water.
The container/closure system consists of HDPE containers (250 ml and 1000 ml) with HDPE closures and LDPE 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 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)

As this is a generic application according to Article 13.1 and bioequivalence with a reference product has been demonstrated, results of safety tests are not required. The reference formulation cited by the applicant in this application is Baycox 50 mg/ml oral suspension (Bayer Ltd – VPA 10021/044/001). Bioequivalence of the candidate formulation with the reference formulation in each of the three proposed target species was satisfactorily demonstrated.

The pharmaco-toxicological aspects of this product are considered to be identical to the reference product.

Warnings and precautions as listed on the product literature are in line with those of the reference product and other similar products currently authorised and are considered adequate to ensure safety of the product to users, the environment and consumers.

### *III.A Safety Testing*

#### *Pharmacological Studies*

The applicant has provided the results of three *in-vivo* comparative bioavailability studies conducted in each of the target species (piglets, calves, lambs).

The bioequivalence study conducted in piglets used Baycox 5% oral suspension as reference product. A staged, single dose, open label, non-randomised parallel design was used, due to the long terminal elimination half-life (approximately 3 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.

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 4 day old piglets.

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.

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.

#### *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 proposed risk mitigation advice to wash splashes from the skin or eyes immediately with water is identical to that approved for the reference product and is considered sufficient to ensure safety to users of the product.

***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 $PEC_{soil\ initial}$ values for each of the three target species, the environmental risk assessment may stop in phase I as the trigger value of 100 µg/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 $PEC_{soil\ initial}$ value was below 100 µg/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.

## *III.B Residues Documentation*

***Residue Studies***

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 |
| Milk | - |

***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 (EFFICACY)

***IV.A. Pre-Clinical Studies***

***Tolerance in the Target Species***

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.

**Changes:**
None.