IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Bovicox 50 mg/ml oral suspension for cattle and sheep

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Bovicox 50 mg/ml oral suspension for cattle and sheep
Active substance(s)	Toltrazuril
Marketing Authorisation Holder	J&M Veterinary Services Limited Loughrask Ballyvaughan Co. Clare Ireland
Legal basis of application	Generic application submitted in accordance with Article 13.1 of Directive 2001/82/EC as amended.
Date of authorisation	20th September 2013
Target species	Cattle (calves: dairy calves, beef suckler, bull beef). Sheep (lambs).
Indication for use	Cattle: For the prevention of clinical signs of coccidiosis and reduction of oocyst shedding in calves on farms with a confirmed history of coccidiosis caused by *Eimeria bovis* or *Eimeriazuernii*. 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 *Eimeria crandallis* and *Eimeria ovinoidalis*.
ATCvet code	QP51BC01

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 and the excipients sodium benzoate (E211), sodium propionate (E281), propylene glycol, docusate sodium, simethicone emulsion, aluminium magnesium silicate, citric acid monohydrate, xanthan gum and water, purified. The container/closure system is a HDPE bottle with HDPE closure and LDPE sealing liner.

The choice of the formulation and presence of preservatives is justified.

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 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.

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.

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)

III.A Safety Testing

Pharmacological Studies

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

The test product (Bovicox 50 mg/ml oral suspension for cattle and sheep) is the same as the reference products Baycox Bovis 50 mg/ml oral suspension and Baycox Sheep 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).

The applicant has provided the results of two bioequivalence studies, one conducted in calves, the other in lambs 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 both studies 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 (Bovicox 50 mg/ml oral suspension for cattle and sheep) and the reference products Baycox Bovis 50 mg/ml oral suspension and Baycox Sheep 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.

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 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.'

As a precaution the statement 'People with known hypersensitivity to any of the ingredients should avoid contact with the veterinary medicinal product.' was also included.

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 products,

It is accepted that the test product will not present any greater risk to the user than the minimal risk posed by the reference products. The proposed user safety statement is considered appropriate.

Environmental Risk Assessment

The Applicant has provided a Phase I assessment for the product demonstrating that a PEC value below the trigger value of 100 microgram/kg was obtained (EMEA/CVMP/ERA/418282/2005-Rev.1). Therefore, in accordance with relevant guidance, the ERA can end at Phase I with no further assessment required. Warnings and precautions as listed on the product literature are adequate to mitigate the risk to the environment when the product is used as directed.

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 two *in vivo* bioequivalence studies demonstrating that the test product (Bovicox 50 mg/ml oral suspension for cattle and sheep) and the reference products Baycox Bovis 50 mg/ml oral suspension and Baycox Sheep 50 mg/ml oral suspension are bioequivalent.

No residue studies conducted.

MRLs

The MRL for Toltrazuril, as appears in Table 1 of Commission Regulation (EU) No 37/2010, is as follows:

Pharmacologically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Toltrazuril	Toltrazuril sulfone	All mammalian food producing species	100 microgram/kg 150 microgram/kg 500 microgram/kg 250 microgram/kg	Muscle Fat Liver Kidney	Not for use in animals from which eggs are produced for human consumption

Withdrawal Periods

The Applicant has demonstrated that the product is bioequivalent to the reference products Baycox Bovis 50 mg/ml oral suspension and Baycox Sheep 50 mg/ml oral suspension. As the test product is bioequivalent to the reference products it is accepted that there will be no difference between the products with respect to depletion of residues of toltrazuril sulfone. Therefore, the cattle meat withdrawal period of 63 days and sheep meat withdrawal period of 42 days can be applied to the test product. The product is not permitted for use in lactating animals producing milk for human consumption.

IV. CLINICAL ASSESSMENT

The application is made in accordance with Article 13(1) of Council Directive 2001/82/EC (as amended), a generic application. The Applicant has conducted two *in vivo* bioequivalence studies demonstrating that the test product (Bovicox 50 mg/ml oral suspension for cattle and sheep) and the reference products Baycox Bovis 50 mg/ml oral suspension and Baycox Sheep 50 mg/ml oral suspension are bioequivalent. As such, it can be assumed that the efficacy profile will be comparable to that of the reference products.

The conditions of use of the product (target species, indication and posology) are the same as those authorised for the reference products.

Indications for use, specifying the target species

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 *Eimeria bovis* or *Eimeria zuernii*.

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 *Eimeria crandallis* and *Eimeria ovinoidalis*.

Amounts to be administered and administration route

Cattle:
Each animal: a single oral dose of 15 mg toltrazuril/kg body weight (i.e. 3.0 ml of the product/10 kg bw.).
For the treatment of a group of animals of the same breed and same or similar age, the dosing should be done according to the heaviest animal of this group.

Sheep:
Each animal: a single oral dose of 20 mg toltrazuril/kg body weight (i.e. 0.4 ml of the product/kg bw.).
If animals are to be treated collectively rather than individually, they should be grouped according to their body weight and dosed accordingly, in order to avoid under- or over-dosing.

The ready-to-use oral suspension must be shaken before use.
To ensure administration of a correct dose, body weight should be determined as accurately as possible.
To obtain maximum benefit, animals should be treated before the expected onset of clinical signs, i.e. in the prepatent period. Treatment during an outbreak will be of limited value for the individual animal, because of damage to the small intestine having already occurred.

Tolerance data specific to Bovicox 50 mg/ml oral suspension for cattle and sheephave not been presented. However, it is accepted that the test product will not present any greater risk to the target animal than the minimal risk posed by the reference product.

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.

Safety/efficacy changes

Summary of change	Approval date
Addition of Sheep to an existing authorisation	20 September 2013