IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Albex Gold 200 mg/ml oral suspension for cattle

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Albex Gold 200 mg/ml oral suspension for cattle
Active substance	Albendazole
Applicant	Chanelle Pharmaceutical Manufacturing Ltd.
Legal basis of application	13(3) hybrid application
Date of authorisation	19th July 2019
Target species	Cattle
Indication for use	For the treatment of benzimidazole susceptible mature and developing immature forms of gastrointestinal roundworms, lungworms, tapeworms and adult liver fluke in cattle. The product is also ovicidal against fluke and roundworm eggs. **Roundworms:** *Ostertagia, Chabertia, Haemonchus, Trichostrongylus, Nematodirus, Oesophagostomum, Bunostomum, Cooperia* and *Strongyloides* spp. It is usually effective against inhibited larvae of *Cooperia* and *Ostertagia* **Lungworms:** *Dictyocaulus viviparus* **Tapeworms:** *Moniezia* spp. **Adult liver fluke**: *Fasciola hepatica*. The product is ovicidal and will kill fluke and roundworm eggs.
ATCvet code	QP52AC11
Concerned Member States	Austria, Belgium, Cyprus, Germany, Greece, France, Netherlands, Poland.

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 200 mg/ml of albendazole as the active substance and the excipients methyl parahydroxybenzoate, propyl parahydroxybenzoate, citric acid monohydrate, sodium citrate, xanthan gum, povidone 90, polysorbate 20, propylene glycol and simethicone emulsion.
The container/closure system consists of 1 L, 2.5 L, 3 L and 5 L white high density polyethylene flexi containers with polypropylene caps. The product is also packaged in 10 L white high density polyethylene containers with high density polyethylene caps.
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 an established substance described in the European Pharmacopoeia. 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)

III.A Safety Testing

Pharmacological Studies

This application was submitted in accordance with Article 13(3) of Directive 2001/82/EC (hybrid application). The reference product cited by the applicant is Valbazen 100 mg/ml Total Spectrum Wormer (Zoetis Ireland Limited).
The applicant has conducted a bioequivalence study in cattle. The results of the study indicated that the 90% confidence intervals for both AUC and C_{max} lie within the narrower limits of 80-125%. It was accepted on the basis of this study, that there were comparable rates and extent of systemic exposure to albendazole-sulphoxide (ABZ-SO) for the test and reference items following oral administration at a dose rate of 10 mg albendazole/kg bodyweight to cattle. For plasma ABZ-SO, the products can be considered bioequivalent with respect to AUC and C_{max}.

As this is a hybrid application according to Article 13(3), and bioequivalence with a reference product has been demonstrated, results of pharmacological studies are not required.

Toxicological Studies
As this is a hybrid application according to Article 13(3), and bioequivalence with a reference product has been demonstrated, results of toxicological studies are not required.
The excipients are commonly used in oral veterinary pharmaceuticals.

User Safety
The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the user safety measures are consistent with the reference product and take into account the potential risk arising from exposure to albendazole and the different excipients.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment
Phase I
A Phase II ERA is required as the Phase I assessment showed that the product is an endoparasiticide for use in animals reared on pasture.
Phase II Tier A
A Phase II Tier A assessment was conducted the results of which are summarised below.

Physico-chemical properties	
Study type	**Result**
Vapour pressure	1.98E-07
Water solubility	25.62 mg/l
Dissociation constants in water pKa	pKa = 6.9
n-Octanol/Water Partition Coefficient logP_{ow}	logP_{ow} = 3.16 at 20 ± 1°C

Environmental fate	
Soil Adsorption/Desorption	Koc =1245
Aerobic and Anaerobic Transformation in Soil	DT_{50} = 10.1 days (20°C)

Effect studies			
Study type	**Endpoint**	**Result**	**Unit**
Algae growth inhibition test/ *Pseudokirchneriella subcapita*	EC_{50}	0.735	mg/l
Daphnia spp. immobilisation	EC_{50}	0.0632	mg/l
Daphnia magna reproduction	NOEC	0.605	µg/l
Fish, acute toxicity/ *Oncorhynchus mykiss*	LC_{50}	0.062	mg/l
Fish, early-life stage toxicity	NOEC	12.8	µg/l
Earthworm/*Eisenia fetida* reproduction	NOEC	2000	µg/kg soil dry weight
Dung fly larvae/*Musca autumnalis*	EC_{50}	>2.65	mg/kg
Dung beetle larvae/*Onthophagus taurus*	EC_{50}	47.1	mg/kg

Risk characterisation
The Predicted Environmental Concentration (PEC) for each compartment was calculated in accordance with guideline requirements.
Using the relevant assessment factors, predicted no effect concentrations (PNECs) were calculated and compared with the PEC values to determine a risk quotient (RQ) for each compartment.
The risk characterisation resulted in risk quotients below 1 which show that the product does not pose a concern for earthworms and algae when used as recommended. In addition, available information indicates that albendazole does not pose a risk to soil microbes or terrestrial plants. However, a potential risk for dung organisms and aquatic organisms exposed via direct and indirect excretion was identified.
Based upon the data provided, an unacceptable risk for the environment could not be excluded and a Tier B assessment was performed.

Phase II Tier B

A Phase II Tier B assessment was conducted.

The risk assessment highlights potential risks for:

- aquatic organisms exposedvia run-off or drainage from the soil,
- daphnids and fish following direct excretion,
- sediment-dwelling organisms in cases of direct excretion, and
- dung dwelling organisms exposed to dung produced by treated pasture animals.

The applicant provided information on the excretion pattern of albendazole as well as the behavioural patterns and compensatory strategies of dung fauna in order to identify factors to mitigate the potential risk to the environment.

The results of the tier B assessment indicate that a risk for the environment cannot be excluded and that appropriate risk mitigation advice is required for this product.

Albendazole is toxic to dung fauna and aquatic organisms. Due to the risk to dung organisms, the product should not be used more than once per year. Treated animals (cattle) should not have access to surface water for 7 days after treatment to avoid adverse effects on aquatic organisms. Faeces containing albendazole excreted onto pasture by treated cattle reduce the abundance of dung fauna feeding organisms which may impact on dung degradation. Albendazole is toxic to aquatic organisms from direct exposure and from drainage and/or run-off of albendazole from the soil. The main metabolite of albendazole, albendazole sulfoxide have been shown to be very persistent. Do not contaminate ponds, waterways or ditches with the product or used containers. Dispose of used containers safely.

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

PBT Assessment

An assessment of the compound in terms of potential for Persistence, Bioaccumulation and Toxicity (PBT) for the environment or whether it may be considered as being very Persistent and very Bioaccumulative (vPvB) was performed.

The log K_{ow} of albendazole was demonstrated to be 3.16.

The compound is not considered to be either PBT or vPvB.

Conclusion

Based on the data provided in the ERA, a risk to the aquatic and terrestrial environment cannot be excluded. Therefore, suitable risk mitigation measures and/or advice were included in the SPC for this product.

III.B Residues Documentation

Residue Studies

No residue depletion studies were conducted because bioequivalence between Albex 200 mg/ml oral suspension and the reference product Valbazen 100 mg/ml Total Spectrum Wormer (Zoetis Ireland Limited) was demonstrated.

MRLs

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

	All ruminants
Muscle	100 µg/kg
Liver	1000 µg/kg
Kidney	500 µg/kg
Fat	100 µg/kg
Milk	100 µg/kg

Withdrawal Periods

The same withdrawal periods approved for the reference product were accepted.

IV. CLINICAL ASSESSMENT

IV.A Pre-Clinical Studies

Pharmacology
The applicant has conducted a bioequivalence study in cattle. The results of the study indicated that the 90% confidence intervals for both total exposure over time (AUC) and peak concentration (C_{max}) lie within the narrower limits of 80-125%. It was accepted on the basis of this study, that there were comparable rates and extent of systemic exposure to albendazole-sulphoxide (ABZ-SO) for the test and reference products following oral administration at a dose rate of 10 mg albendazole/kg bodyweight to cattle. For plasma ABZ-SO, the products can be considered bioequivalent with respect to AUC and C_{max}.

Tolerance in the Target Species of Animals
As this is a hybrid application according to Article 13(3) of Directive 2001/82/EC, and bioequivalence with a reference product has been demonstrated, tolerance studies are not required.
The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance
As this is a hybrid application according to Article 13(3) of Directive 2001/82/EC, and bioequivalence with a reference product has been demonstrated, the resistance profile of the product will be the same as that of the reference product.
Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies
As this is a hybrid application according to Article 13(3) of Directive 2001/82/EC, and bioequivalence with a reference product has been demonstrated, clinical studies are not required. The efficacy claims for this product are equivalent to those of 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.

Changes: None.