United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Albex Advance 200 mg/ml Oral Suspension for Cattle

Date Created: August 2017

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Albex Advance 200 mg/ml Oral Suspension for Cattle
Applicant	Chanelle Animal Health Ltd 7 Rodney Street Liverpool L1 9HZ
Active substance	Albendazole 200.0 mg
ATC Vetcode	QP52AC11
Target species	Cattle
Indication for use	The veterinary medicinal product is a broad spectrum multi-purpose anthelmintic for the control of 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 veterinary medicinal product is ovicidal and will kill fluke and roundworm eggs, thus reducing pasture contamination.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Full-Extension application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of conclusion of the procedure	22nd August 2017

I. SCIENTIFIC OVERVIEW

This was an extension application to the marketing authorisation for Albex 10% Oral Suspension, authorised in the UK since 1996, to authorise a new strength of the active substance. Albex 10% Oral Suspension was authorised based on bioequivalence with Valbazen 10% Total Spectrum Wormer authorised in 1993. Valbazen 10% Total Spectrum Wormer was expired in 2008. The applicant provided evidence that the Irish version of Valbazen 10% Total Spectrum Wormer was suitable to be used as a reference product in relevant studies.

Following the principles of the current Directive 2001/82/EC, as amended by 2004/28/EC, since bioequivalence was demonstrated by way of a bioequivalence study, Albex 10% Oral Suspension can be considered as a generic of Valbazen 10% Total Spectrum Wormer. However, as Albex 10% Oral Suspension was authorised prior to 1997 and therefore prior to the existence of the legal basis of a generic product as laid out in Article 13 (1) of the Directive, this extension application is classified as a 'full' application.

The veterinary medicinal product is a broad spectrum multi-purpose anthelmintic for the control of 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.

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, any reactions observed are indicated in the SPC.[1] 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 [2] 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.

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains 200 mg/ml albendazole and the excipients methyl parahydroxybenzoate (E218) 2.0 mg/ml and propyl parahydroxybenzoate 0.2 mg/ml. Additional excipients are citric acid monohydrate, sodium citrate, xantham gum, povidone 90, polysorbate 20, propylene glycol and simethicone emulsion.

The container/closure system consists of 1L, 2.5L, 3L & 5L white HDPE backpack containers with a blue polypropylene cap and an aluminium foil seal.
A 10 L pack is composed of white HDPE container with a white HDPE cap and an aluminium foil seal. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the presence of preservatives are justified. The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of a simple mixing and filling process.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials

The active substance is albendazole, an established active substance described in the European Pharmacopoeia (Ph. Eur). The active substance is manufactured in accordance with the principles of good manufacturing practice and sourced under an acceptable Certificate of Suitability.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

All excipients and packaging are monographed within the Ph. Eur.

II.C.4. Substances of Biological Origin

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.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 have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification. Control tests on the finished product include those for: appearance, identification of active substance and preservatives, resuspendability, pH, viscosity, fill volume, microbiological quality and particle size.

II.F. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. A retest period of 5 years is defined in the Certificate of Suitability. Suitable assay was carried out on the finished product, according to VICH[3] guidelines.

Stability tests were also carried out on the finished product. These assays were for photostability, real-time and forced degradation studies, and in-use studies. Data showed that the product is chemically and physically stable for up to 36 months at 25°C/60%RH and for 6 months at 40°C/75%RH, and supported the proposed shelf life of 3 years

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf life after first opening the immediate packaging: 12 months.

[3] VICH – The International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Due to the nature of the application and as the proposed product was shown to be bioequivalent to the reference product, there was no requirement for toxicological or pharmacological data of the active substance.

User Safety

A user risk assessment was provided in compliance with the relevant guideline. The hazard and tasks and situations that may lead to exposure will be comparable for both Albex Advance 200 mg/ml Oral Suspension and the lower strength (100 mg/ml) reference product. Due to the potential for skin and eye irritation and dermal sensitisation, accidental dermal and eye contact following spillage/splashing have been identified as the exposure routes of most concern. Although the increased strength of Albex Advance poses a two-fold greater exposure over the reference product, use of the same user safety warnings as agreed for the reference product is considered appropriate. The user safety warnings cover the routes of exposure of concern and are considered sufficient to ensure human exposure to the product is kept to a minimum and to mitigate against any potential increased risk to the user. Slight amendments to the user safety warnings were required so as to bring them in line with the ABCD format recommended in the current user safety guidance. The updated user safety warnings are given below.

- This product may cause skin and eye irritation and dermal sensitisation.
- Direct contact with the skin and eyes should be kept to a minimum.
- Personal protective equipment, including impermeable rubber gloves, should be worn when handling the product.
- In case of accidental spillage onto skin, wash the affected area with soap and water.
- In case of accidental eye exposure, flush eye thoroughly with running water.
- If skin or eye irritation persists seek medical advice immediately and show the package leaflet or the label to the physician.
- Wash hands and exposed skin after use.
- Do not smoke, eat or drink while handling the product.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH[4] and CVMP[5] guidelines.

[4] VICH – Veterinary International Conference on Harmonization.
[5] CVMP - Committee for Medicinal Products for Veterinary Use.

Phase I:

The Phase I VICH decision tree was completed. As the product is an endoparasiticide used in pasture animals, and the PEC_{soil} did not exceed 100 µg/ml, a Phase II ERA was required for pasture reared species only. (Questions 15 and 16 of the VICH decision tree).

Phase II Tier A:
A Phase II Tier A data set was provided according to the requirements of the VICH GL 38 and the CVMP guideline in support of the VICH guidelines including studies on physicochemical properties, environmental fate and effects.

Results were mainly obtained from proprietary studies. The active substance albendazole was used in assays.

Physico-chemical properties

Study type	Result	Remarks
Molecular weight	265.3 g/mol	In publishe literature
Water solubility (OECD 105)	25.62 mg/l (20±1ºC and pH7).	Insoluble in water.
Dissociation constants in water pKa	6.9	In published literature
UV-Visible Absorption Spectrum	Principle peak 214 – 294 nm.	In published literature
Melting Point/ Melting Range	208 – 210ºC.	In published literature
Vapour Pressure	1.98 x 10^{-7} Pa.	EPI suite
n-Octanol/Water Partition Coefficient $logP_{ow}$ (OECD 117)	3.61 (Mobile phase: methanol/water 60:40, pH of 6.0 - 6.5. Temperature: 20±1°C)	No significant potential for bioaccumulation and secondary poisoning.

Environmental fate

Study type	Guideline	Result	Remarks
Soil Adsorption/Desorption	OECD 106	Geometric mean K_{oc}: 1230 ml/g (22.5 ± 2.5°C) Arithmetic mean K_{oc}: 1245 ml/g (22.5 ± 2.5°C)	Low to slight mobility in soil

Study type	Guideline	Result	Remarks
Aerobic and anaerobic transformation in soil	OECD 307	Albendazole: DT_{50}: ranging between 0.5 and 19.3 days (4 soils). DT_{90}: ranging between 9.6 and 64.2 days (4 soils). 'M1' metabolite (albendazole-sulfoxide and albendazole-sulfone): DT_{50}: ranging between 110 and 256 days (4 soils). DT_{90}: ranging between 365 and 850 days (4 soils).	Albendazole rapidly dissipated in the four test soils. A low potential for mineralisation was seen. Formation of metabolic fractions in soil was high; four major metabolites could be observed.

Representing a worst case scenario, the geometric mean M1 DT_{50} value (188 days) was used to determine the refined FOCUS PEARL 4.4.4 $PEC_{groundwater}$ and subsequent FOCUS SWASH $PEC_{surface\ water}$ values. The metabolism of albendazole to albendazole sulfoxide and the metabolites demonstrated persistence in soil is communicated in the environmental information section of the SPC and product literature.

Environmental effects

Study type	Endpoint and Result
Algae, Growth Inhibition Test *Pseudokirchneriella subcapitata* (OECD 201)	72 hour EC_{50} growth rate >1 mg/l
Daphnia magna immobilisation (OECD 202)	48 hour EC_{50}: 63.2 µg/l 48 hour NOEC: 29.6 µg/l
Fish, acute toxicity *Oncorynchus mykiss* (OECD 203)	96 hour LC_{50} 0.062 mg/l 96 hour NOEC 0.0194 mg/l
Earthworm *Eisenia foetida* (OECD 220/222)	NOEC Reproduction 2 mg/kg $_{dwt\ soil}$
Dung fly larvae *Musca autumnalis* (OECD 228)	emergence EC_{50} >2.65 mg/kg $_{wwt\ dung}$
Dung beetle larvae *Aphodius constans* (OECD concept paper 122)	emergence EC_{50} 47.1 mg/kg $_{wwt\ dung}$

There was no requirement for toxicity data related to terrestrial plants and soil organisms as the initial PEC_{soil} trigger values were <100 µg/kg. Aquatic organisms were demonstrated to be most sensitive to albendazole, with daphnia and fish being the most sensitive of these.

Exposure assessment (Predicted exposure concentration)

PEC values for soil, dung, groundwater, surface water and sediment were calculated using the equations provided in the CVMP guidelines. The dose and duration of treatment were taken from the proposed SPC of the product. The

calculations correctly included use of the worst case target animal scenario of beef cattle on pasture. The following PEC values were determined.

Outputs	Value	Source
PEC_{soil} (µg/kg)	41.8	CVMP Equation 2[1]
PEC_{dung}(mg/kg wet weight)	253.85	CVMP Equation 8[2]
$PEC_{groundwater}$ (µg/l)	0.473	CVMP Equation 36[3]
Refined $PEC_{groundwater}$ (µg/l)	<0.053	FOCUS PEARL[4]
$PEC_{surface\ water}$ run-off drainage (µg/l)	0.158	CVMP Equation 40[3]
Refined $PEC_{surface\ water}$ run-off drainage (µg/l)	0.60	FOCUS SWASH[4]
$PEC_{surface\ water}$ direct excretion (µg/l)	10.45	CVMP Equation 47[1]
Refined $PEC_{surface\ water}$ direct excretion (µg/l)	1.65	CVMP Equation 50[1]
PEC_{sed} direct excretion (µg/l)	40.60	CVMP Equation 49[1]

1 – One application is expected while the animals are housed. With regard to the pasture scenario, only one application is considered as cumulative concentrations in manure, soil and water are not envisaged based upon the pattern of use (>3 month interval between dosing), subsequent exposure and degradation profile of the compound.
2 – No refinement available based on metabolism and excretion.
3 – Considering albendazole.
4 – Considering both albendazole and the 'M1' metabolite.

As the $PEC_{groundwater}$ value (0.473 µg/l) derived from using the CVMP Equation 36 gave an exposure value above the trigger value of 0.1 µg/l, an unacceptable risk was concluded and further refinement using more specific groundwater modelling (FOCUS-PEARL 4.4.4) was conducted. This modelling predicted concentrations of oxaclozanide and the M1 metabolite to be <0.1 µg/l in groundwater which suggests that there is no risk to groundwater from oxaclozanide.

The initial concentration in surface water, as a result of run-off, was estimated to be 0.158 µg/l which was further refined using FOCUS SWASH modelling, in accordance with the CVMP guideline, giving a maximum value of 0.080 µg/l. The initial concentration in surface water, as a result of defecation and urination by cattle (direct excretion), was estimated as 10.45 µg/l. This estimate was further refined to 1.65 µg/l (beef cattle) based on the partitioning of the compound between water and sediment. $PEC_{sediment}$ was determined in accordance with CVMP Equation 49 as the RQ values for aquatic invertebrates were >1 (see below).

Risk Characterisation (Risk Quotient)

Predicted no effect concentrations (PNECs) were derived by dividing the most sensitive endpoints of the ecotoxicity data by the assessment factors (AFs), according to VICH guidelines. The PNECs were compared with the PEC values for each relevant component to determine the risk quotient (RQ), as follows.

Organism	PEC	PNEC	RQ
Earthworms	41.8 µg/kg (Soil)	200 µg/kg_{dwt}	0.21
Dung fauna	253 850 µg/kg_{wwt}	>26.0 µg/kg_{wwt}	**<9763**
Algae	Surface water *run-off drainage* 0.60 µg/l	10 µg/l	0.008
Daphnia		0.0632 µg/l	**9.49**
Fish		0.062 µg/l	**9.68**
Algae	Surface water *direct excretion* 1.65 µg/l	10 µg/l	0.17
Daphnia		0.0632 µg/l	**26.11**
Fish		0.062 µg/l	**26.61**
Daphnia	Sediment *direct excretion* 40.60 µg/l	4.04 µg/l	**10.05**

Bold indicates unacceptable risk

Based on the calculated risk quotients (RQ), the risk assessment for albendazole and the 'M1' metabolite showed that no unaccepted risk for earthworms and algae is to be expected when the product is used according to the proposed use pattern. As a potential risk for dung organisms and aquatic organisms exposed via direct and indirect excretion was identified in Phase II, Tier A, further assessment of the environmental risk was required.

Following further assessment, based upon information on excretion and metabolism, the risks for dung fauna, aquatic organisms and sediment dwelling organisms could not be fully excluded and, as a result, suitable safety information was added to sections 4.5.iii and 5.3 of the SPC, with equivalent data added to the product literature. Furthermore, the inclusion of a 7 day exclusion period for cattle entering water can be accepted to remove any uncertainty associated with a risk to aquatic organisms and sediment dwellers from direct excretion into surface water.

Agreed environmental safety information is as follows.

SPC Section 4.5.iii 'Other precautions'
Faeces containing albendazole and its main transformation products excreted onto pasture by treated animals may reduce the abundance of dung feeding organisms which may impact on the dung degradation. Treated animals (cattle) should not have access to surface water for 7 days after treatment to avoid adverse effects on aquatic organisms.

SPC Section 5.3 'Environmental properties'
Albendazole is quickly metabolised to albendazole sulfoxide. Albendazole sulfoxide has been shown to be very persistent in soils.

SPC Section 6.6 'Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products'
DANGEROUS to fish and aquatic life. Do not contaminate ponds, waterways or ditches with the product or used containers. Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

III.B.2 Residues documentation

Residue Studies

Due to the legal base of the application there was no requirement for residue depletion study data. As the product is administered orally, the dose regimen is the same and bioequivalence with the reference product has been established, use of the same withdrawal periods as approved for the reference product is considered acceptable.

MRLs

Albendazole is included in Table 1 (Allowed Substances) of the Annex to Commission Regulation (EU) No 37/2010 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin. The marker residue and MRLs for all ruminants are given below.

Marker residue	Target tissues	MRLs (µg/kg)
Sum of albendazole sulphoxide, albendazole sulphone and albendazole 2-amino sulphone expressed as albendazole	Muscle Fat Liver Kidney Milk	100 100 1000 500 100

Withdrawal Periods

Based on the data provided, withdrawal periods cited as follows are justified:

Cattle

Meat and offal: 14 days

Milk: 72 hours

IV. CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Due to the nature of the application, there was no requirement to present pharmacodynamic, target species tolerance or clinical efficacy data. A bioequivalence study was presented in order to show parity between the proposed and reference products.

Pharmacokinetics

A study was conducted assess the bioequivalence of the proposed and reference products. This was a random, two sequence, single dose, two period, cross-over study, with a washout period of 10 days. Twenty-four cattle aged 6-9 months were acclimatised prior to the study, and randomised appropriately into two even groups on day-1. On day 0, each group of animals were treated with a single dose of either the proposed or reference product. Clinical samples were taken at appropriate times after dosing, and measurements of the quantity of albendazole sulphoxide, (the primary albendazole metabolite), were performed. Data analysis was performed using ANOVA, using the parameters ln-transformed AUC[6] (90% confidence limit as defined by a 80-125% confidence interval), and C_{max}[7] (90% confidence limit as defined by 70-143% confidence interval). At the assessment of the results, the products were found to be bioequivalent.

Tolerance in the Target Species

Tolerance studies were not required as bioequivalence between the proposed and reference products was confirmed.

Resistance

A brief literature review was carried out by the applicant. Adequate warnings and precautions appear on the SPC and product literature, and describe the standard CVMP anthelmintic warnings applicable to albendazole.

IV.II. Clinical Documentation

As bioequivalence between the proposed product and reference product were established, there was no requirement for further data in this section.

[6] AUC – Area under the curve.
[7] C_{max} – Maximum concentration of active substance or primary metabolite obtained.

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 of the product is favourable.

MODULE 4

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 Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) 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.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

As the application was refused, there are no post-authorisation assessments.