Annex I

List of the names, pharmaceutical form, strengths of the veterinary medicinal products, animal species, route of administration, marketing authorisation holders in the Member States

Member State EU/EEA	Marketing authorisation holders	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Austria	Zoetis Österreich GmbH Floridsdorfer Hauptstraße 1 A- 1210 Wien Österreich	Valbazen 100 mg/ml-Suspension zum Eingeben für Rinder	Albendazole	100 mg/ml	Oral suspension	Cattle	Oral use
Austria	AniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Albendazol-aniMedica 100 mg/ml Suspension zum Eingeben für Rinder	Albendazole	100 mg/ml	Oral suspension	Cattle	Oral use
Austria	Chanelle Pharmaceuticals Manufacturing Ltd IDA Industrial Estate Dublin Road, Loughrea Co Galway H62 H771 Ireland	Albex Gold 200 mg/ml Oral Suspension for Cattle	Albendazole	200 mg/ml	Oral suspension	Cattle	Oral use
Belgium	Elanco GmbH Heinz-Lohmann-Straβe 4 27472 Cuxhaven Germany	Valbazen 10 %	Albendazole	100 mg/ml	Oral suspension	Cattle	Oral use
Belgium	Chanelle Pharmaceuticals Manufacturing Ltd IDA Industrial Estate Dublin Road, Loughrea Co Galway H62 H771 Ireland	Albex 200 mg/ml oral suspension for cattle	Albendazole	200 mg/ml	Oral suspension	Cattle	Oral use
Bulgaria	Intervet International BV Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Gardal 10%	Albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Bulgaria	Asklep-Pharma Ltd., Lyulin 7, bl. 711A, shop 3, Bulgaria	Albex BG 100 mg/ml oral suspension for cattle and sheep	Albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use

Member State EU/EEA	Marketing authorisation holders	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Croatia	Mount Trade d.o.o., Industrijska cesta 13, 43280 Garešnica Croatia	Albix 100 mg/ml, oralna suspenzija za goveda i ovce	Albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
France	Zoetis France 10 Rue Raymond David 92240 Malakoff France	Valbazen dix	Albendazole	100 mg/ml	Oral suspension	Cattle	Oral use
France	Chanelle Pharmaceuticals Manufacturing Ltd IDA Industrial Estate Dublin Road, Loughrea Co Galway H62 H771 Ireland	Albex Gold 200 mg/ml suspension buvable pour bovins	Albendazole	200 mg/ml	Oral suspension	Cattle	Oral use
Germany	Lilly Deutschland GmbH Abteilung Elanco Animal Health Werner-Reimers-Straße 2-4 61352 Bad Homburg Germany	Valbazen 10%	Albendazole	100 mg/ml	Oral suspension	Cattle	Oral use
Germany	Chanelle Pharmaceuticals Manufacturing Ltd IDA Industrial Estate Dublin Road, Loughrea Co Galway H62 H771 Ireland	Albex Gold 200 mg/ml Oral Suspension for Cattle	Albendazole	200 mg/ml	Oral suspension	Cattle	Oral use
Greece	Provet S.A. 77, Posidonos Avenue 174 55 Alimos, Attiki Greece	Albendazole/Provet, πόσιμο εναιώρημα 10% w/v	Albendazole	100 mg/ml	Oral suspension	Calves, Sheep, Goats	Oral use

Member State EU/EEA	Marketing authorisation holders	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Greece	Chanelle Pharmaceuticals Manufacturing Ltd IDA Industrial Estate Dublin Road, Loughrea Co Galway H62 H771 Ireland	Albex Πόσιμο εναιώρημα 10% w/v/	Albendazole	100 mg/ml	Oral suspension	Cattle, sheep, goats	Oral use
Ireland	Zoetis Belgium S.A. 2nd Floor, Building 10, Cherrywood Business Park, Loughlinstown, Co Dublin, Ireland	Valbazen 100 mg/ml Total Spectrum Wormer	Albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Ireland	Chanelle Pharmaceuticals Manufacturing Ltd IDA Industrial Estate Dublin Road, Loughrea Co Galway H62 H771 Ireland	Albex Gold 200 mg/ml oral suspension for cattle	Albendazole	200 mg/ml	Oral suspension	Cattle	Oral use
Italy	Zoetis Italia S.r.l. Via Andrea Doria 41M 00192 Roma Italy	Valbazen 100 mg/ml sospensione per uso orale per bovini ed ovini	Albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Italy	Fatro S.p.A. Via Emilia, 285 40064 Ozzano dell'Emilia (Bologna) Italy	Sverminator 10, 100 mg/ml, sospensione orale per bovini ed ovini	Albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Italy	Chanelle Pharmaceuticals Manufacturing Ltd IDA Industrial Estate Dublin Road, Loughrea Co Galway H62 H771 Ireland	Albex Gold 200 mg/ml sospensione orale per bovini	Albendazole	200 mg/ml	Oral suspension	Cattle	Oral use

Member State EU/EEA	Marketing authorisation holders	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Luxembourg	Elanco GmbH Heinz-Lohmann-Straβe 4 27472 Cuxhaven Germany	Valbazen 10 %	Albendazole	100 mg/ml	Oral suspension	Cattle	Oral use
Malta	Fatro S.p.A. Via Emilia, 285 40064 Ozzano dell'Emilia (Bologna) Italy	Sverminator 10	Albendazole	100 mg/ml	Oral suspension	Cattle, Sheep	Oral use
Poland	Chanelle Pharmaceuticals Manufacturing Ltd IDA Industrial Estate Dublin Road, Loughrea Co Galway H62 H771 Ireland	Albex Gold 200 mg/ml oral suspension for cattle	Albendazole	200 mg/ml	Oral suspension	Cattle	Oral use
Poland	ZoetisPolska Sp. z.o.o Postępu 17B, 02-676 Warszawa Poland	Valbazen 10%, 10 g/100 ml zawiesina doustna dla bydla i owiec	Albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Poland	C&H Generics Limited c/o Michael McEvoy and Co Seville House New Dock Street H91CKV0 Galway Ireland	Albex 10%	Albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use

Member State EU/EEA	Marketing authorisation holders	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Romania	Crida Pharm S.R.L., Str. Intrarea Vagonetului, Nr.2 Bl 101, Ap. 47, Sector 6, RO-061151 Bucharest, Romania	Cribendazol 10%, 100 mg/ml	Albendazole	100 mg/ml	Oral suspension	Cattle	Oral use
The Netherlands	Chanelle Pharmaceuticals Manufacturing Ltd IDA Industrial Estate Dublin Road, Loughrea Co Galway H62 H771 Ireland	Albex Gold 200 mg/ml, orale suspensie voor runderen	Albendazole	200 mg/ml	Oral suspension	Cattle	Oral use

Annex II

Scientific conclusions and grounds for amendment of the summary of product characteristics

Overall summary of the scientific evaluation of Valbazen 100 mg/ml Total Spectrum Wormer oral suspension and associated names, including its generic/hybrid products (see Annex I)

1. Introduction

Albendazole is a broad-spectrum multi-purpose anthelmintic used for the treatment of gastrointestinal infestations with roundworms, lungworms and tapeworms and adult flukes of *Fasciola hepatica*.

Valbazen and associated names, its generic and hybrid products are oral suspensions which contain 100 mg or 200 mg albendazole per ml. Albendazole as oral suspension is used in cattle most often as single oral use at recommended dosages ranging from 7.5 to 15 mg albendazole per kg body weight.

A 'hybrid' application (due to differences in product strength) was submitted under Article 13(3) of Directive 2001/82/EC for a marketing authorisation under the mutual recognition procedure (IE/V/0637/001/MR) for the veterinary medicinal product 'Albex Gold 200 mg/ml oral suspension for cattle', with Ireland as reference Member State. The reference veterinary medicinal product is Valbazen 100 mg/ml Total Spectrum Wormer oral suspension (hereafter named Valbazen), marketed by Zoetis Belgium S.A. and authorised in Ireland since 1994.

Having reviewed the available residue data for the reference product 'Valbazen' as authorised in Ireland, Germany was unable to confirm that the currently authorised withdrawal periods of 14 days for cattle meat and offal, and 72 hours for cattle milk are safe for the consumer.

In addition, it has been noted that 'Valbazen' is also authorised in other Member States and there were differences between the established withdrawal periods for cattle (milk, meat and offal) across the European Union, i.e. between 5 and 28 days for edible tissues and between 72 to 120 hours for milk. Therefore, Germany considered that it was necessary to refer the matter to the Committee for Medicinal Products for Veterinary Use (CVMP) in the interest of protecting consumer safety in the Union.

Germany requested the CVMP to review all available residue depletion data for Valbazen 100 mg/ml Total Spectrum Wormer oral suspension and associated names, including its generic/hybrid products, and to recommend appropriate withdrawal periods for treated cattle.

2. Discussion of data available

Qualitative and quantitative composition

The provided information for Valbazen 100 mg/ml Total Spectrum Wormer oral suspension, Albex Gold 200 mg/ml oral suspension for cattle, Albex 100 mg/ml oral suspension for cattle, Valbazen 10% as well as Cribendazol 100 mg/ml oral suspension showed that the composition is essentially similar, or bioequivalence has been proven.

Other veterinary medicinal products included within this referral are generic products of Valbazen or have been authorised as 'informed consent' applications with Valbazen as the parent product, and for which bioequivalence is expected since this was demonstrated within the respective marketing authorisation procedures.

Consequently, the CVMP concluded that a common withdrawal period could be applied to the veterinary medicinal products concerned by this referral procedure.

Residue depletion

Residue depletion in cattle meat and offal

Two residue depletion studies conducted in 2002/2003 and 2007 respectively, were made available to the Committee. However, only one Good Laboratory Practice-compliant residue depletion study conducted with Valbazen was considered relevant for this procedure and was used for withdrawal period determination.

Twenty-four male and female beef cattle were allocated to six groups (n=4). The test product (Valbazen) was administered with a commercially available oral drench gun at a target dose level of 15 mg albendazole per kg body weight.

The animal phase of the study is in principle conducted in line with VICH GL48[1], with the exception of the body weight of the animals (138-224 kg, at the start of acclimatisation) which is below the body weight range recommended in the above-mentioned guideline (i.e. ~250 to 400 kg for beef cattle).

The animals were slaughtered at 1, 2, 3, 4, 5 and 7 days after treatment. Tissue samples (liver, kidney, muscle (ca 500 g) and fat (ca 500 g)) were collected and stored below -20°C prior to analysis.

Analysis of the marker residue (albendazole sulphoxide, albendazole sulphone and albendazole 2-aminosulphone) was conducted by high-performance liquid chromatography procedure with fluorescence detection with a limit of quantification (LOQ) of 15 µg/kg for each metabolite, except albendazole sulphoxide in kidney, which had a LOQ of 80 µg/kg. The study was carried out without the addition of an internal standard and with an old analytical method, which might lead to uncertainties in the quantification of the samples.

Residues above the maximum residue limits (MRLs) were measured in all tissues at day 1 and 2. After correction for stability at day 3, only one residue value in liver was above the MRL.

Therefore, liver was considered the determining tissue for withdrawal period calculation. If all values are used, the statistical approach is not applicable because linearity is not given. However, if some data points are excluded (which is in line with the CVMP guideline on determination of withdrawal periods for edible tissues (EMA/CVMP/SWP/735325/2012-Rev.1)[2]), the statistical assumptions are met. Nevertheless, it seems that besides the low body weight of the animals and some deficiencies of the frozen stability data, there are more uncertainties regarding the analytical method which should be considered to correct the measured values and/or apply a sufficient safety factor.

The Committee considered that the uncertainties mentioned above, provided that all residues are proportionally affected by the analytical uncertainties, should be considered for the determination of the withdrawal period.

Therefore, the CVMP concluded that a safety factor of 30% should be applied to the statistically determined 5-day withdrawal period resulting in a withdrawal period of 7 days (based on the statistical determined withdrawal period of 5 days + 30% safety factor).

Residue depletion in cattle milk

Two residue depletion studies conducted in 2002 and 2007, respectively, were made available to the Committee. However, only one Good Laboratory Practice/Quality Assurance-compliant study conducted with Valbazen was considered relevant for this procedure.

Twenty lactating Holstein Friesian cows (with a body weight range of 470–736 kg at the start of acclimatisation, different lactation stage) were included. The animals were treated with the test

[1] VICH topic GL48: Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: marker residue depletion studies to establish product withdrawal periods (EMA/CVMP/VICH/463199/2009) – link
[2] CVMP guideline on determination of withdrawal periods for edible tissues (EMA/CVMP/SWP/735325/2012-Rev. 1) – link

product (Valbazen) using a commercially available oral drench gun at a target dose level of 15 mg albendazole per kg body weight.

Milk samples (250 ml sub-samples from the total milking of each cow) were collected from the animals at day -1 before administration, at 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156 and 168 hours after administration. Additionally, tissue samples (whole liver, both kidneys, muscle [ca 500 g of loin muscle], fat [ca 500 g of omental and renal fat]) were collected from four animals following sacrifice at 168 hours after administration.

The residues of albendazole (as albendazole sulphoxide, albendazole sulphone and amino albendazole sulphone) were quantified with a validated high-performance liquid chromatography assay with fluorescence detection, with a LOQ of 15 µg/kg for each metabolite. The study was carried out without the addition of an internal standard, with an old analysis method. This can lead to uncertainties in the quantification of the samples.

Residues above the MRL were measured in milk until 60 hours after administration.

Based on the statistical approach, a withdrawal period of 75 hours for milk of treated animals was considered but, according to the CVMP note for guidance on determination of withdrawal periods for milk (EMEA/CVMP/473/1998)[3] , the withdrawal period should be rounded up to the next 12-hour milking interval.

Therefore, the Committee concluded that the withdrawal period for milk should be 84 hours (statistical approach rounded up to the next 12-hour milking interval).

3. Benefit-risk assessment

Introduction

The CVMP was requested to review all available residue depletion data for Valbazen and associated names, including its generic/hybrid products, and to recommend appropriate withdrawal periods for milk, meat and offal derived from treated cattle.

Benefit assessment

While the efficacy of the concerned products in cattle has not been specifically assessed as part of this referral, the veterinary medicinal products under assessment are considered to be effective in cattle for the treatment of gastrointestinal infestations with roundworms, lungworms and tapeworms and adult flukes of *Fasciola hepatica*. The recommended dose ranges from 7.5 to 15 mg albendazole per kg body weight.

Risk assessment

Quality, target animal safety, user safety and the environmental risk for the concerned veterinary medicinal products have not been assessed in this referral procedure. Furthermore, for generic and hybrid products (including products with different concentration of active substance compared to the reference product), bioequivalence was not evaluated since this has been done within the respective marketing authorisation procedures.

A risk has been identified regarding the different lengths of authorised withdrawal periods for cattle (milk, meat and offal) in different Member States, which, for some veterinary medicinal products may be insufficient to allow residues of the marker residue of albendazole to fall below the respective MRLs

[3] CVMP note for guidance on determination of withdrawal periods for milk (EMEA/CVMP/473/1998) – link

in edible tissues and milk, thereby posing a risk to consumers after oral intake of foodstuffs from cattle treated with these products.

Risk management or mitigation measures

Based on the available data, revised withdrawal periods for Valbazen and associated names, including its generic/hybrid products have been established:

Cattle

Meat and offal: 7 days

Milk: 84 hours

These withdrawal periods are considered adequate to ensure consumer safety.

Evaluation and conclusions on the benefit-risk balance

Having considered the grounds for referral and the available data, the CVMP concluded that the withdrawal periods for cattle should be amended as recommended to provide assurance for consumer safety.

As bioequivalence of the generic and hybrid products (including products with different concentrations of active substance) was demonstrated within the marketing authorisation procedures for those products, the Committee considered that the withdrawal periods are applicable to all products concerned by this referral.

The overall benefit-risk balance for the veterinary medicinal products Valbazen and associated names, including its generic/hybrid products remains positive, subject to the recommended changes in the product information.

Grounds for amendment of the summary of product characteristics, labelling and package leaflet

Whereas

- on the basis of the available residue depletion data, the CVMP considered that the withdrawal periods for milk, meat and offal derived from treated cattle should be amended to provide assurance for consumer safety;
- the CVMP considered that the overall benefit-risk balance for the products under this procedure remains positive subject to amendments in the product information;

the CVMP has recommended the amendment of the marketing authorisations for Valbazen 100 mg/ml oral suspension and associated names, including its generic/hybrid products as referred in Annex I for which the summary of product characteristics, labelling and package leaflet are set out in Annex III.

Annex III

Amendments in the relevant sections of the Summary of product characteristics, labelling and package leaflet

Summary of product characteristics

4.11 Withdrawal period(s)

Cattle:

Meat and offal: 7 days

Milk: 84 hours

Labelling

8. WITHDRAWAL PERIOD(S)

Cattle:

Meat and offal: 7 days

Milk: 84 hours

Package leaflet

10. WITHDRAWAL PERIOD(S)

Cattle:

Meat and offal: 7 days

Milk: 84 hours