Annex I

List of nationally authorised veterinary medicinal products

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Austria	Industrial Veterinaria S.A. Calle de la Esmeralda 19 08950 Esplugues de Llobregat Barcelona Spain	Valbendis 100 mg/ml oral suspension for cattle and sheep	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Austria	Alphavet Zrt. Hofherr Albert Utca Kerulet 42 1194 Budapest XIX Hungary	Alphalben 100 mg/ml oral suspension for cattle and sheep	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Bulgaria	Interchemie Werken De Adelaar B.V., Metaalweg 8 5804 CG, Venray, The Netherlands	Albenol-100 Oral	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Bulgaria	Asklep-Pharma OOD, Sofia, Lyulin 7, bl. 711A, shop 3, Republic of Bulgaria	Албекс БГ 100 mg/ml перорална суспензия за говеда и овце	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Bulgaria	Ceva Sante Animale, 10 av. de la Ballastière – 33500 Libourne, France	Вермитан 100 mg/ml суспензия	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Bulgaria	Sudachim Ltd., Sofia 1700, Vitosha, str. Jordan Stubel 10A Bulgaria	Албендазол 2,5 %	albendazole	25 mg/ml	Oral suspension	Cattle, sheep, goat	Oral use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Bulgaria	Farma Vet OOD, Shumen 9700, str. Aleko Konstantinov 6 Bulgaria	Албендазол суспензия	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Bulgaria	Alpha-Vet Kft., Hofherr A. u. 42., Budapest, H-1194, Hungary	Alphalben 100 mg/ml oral suspension for cattle and sheep	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Croatia	Industrial Veterinaria Calle De La Esmeralda 19 Esplugues De Llobregat Barcelona 08950 Spain	Albendis 100 mg/mL oralna suspenzija za goveda i ovce	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Croatia	Alpha-Vet Állatgyógyászati Kft. Hofherr Albert str. 42. H-1194 Hungary	Alphalben 100 mg/ml oralna suspenzija za goveda i ovce	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Croatia	Mount Trade d.o.o. Industrijska cesta 13 43280 Garesnica Croatia	Albix 100 mg/mL, oralna suspenzija za goveda i ovce	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Cyprus	Ceva Sante Animale Zone Industrielle Tres Le Bois, Loudeac, France	Vermitan 10% πόσιμο εναιώρημα	albendazole	100 mg/ml	Oral suspension	Cattle, sheep, goat	Oral use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Cyprus	Industrial Veterinaria S.A. Calle de la Esmeralda 19 08950 Esplugues de Llobregat Barcelona Spain	Albendis 100 mg/ml oral suspension for cattle and sheep	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Cyprus	Alpha-Vet Kft Hofherr Albert Utca 42, Kerulet, Budapest XIX, Hungary	Alphalben 100 mg/ml oral suspension for cattle and sheep	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Czechia	Pharmagal spol. s r.o. Murgašova 5, 949 01 Nitra, Slovakia	Aldiverm, 100mg/ml, Perorální suspenze	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Czechia	Mikrochem spol. s r.o. Za dráhou 33 902 01 Pezinok Slovenská republika	Aldifal, 25mg/ml, Perorální suspenze	albendazole	25 mg/ml	Oral suspension	Sheep	Oral use
Czechia	Mikrochem spol. s r.o. Za dráhou 33 902 01 Pezinok Slovenská republika	Aldifal, 100mg/ml, Perorální suspenze	albendazole	100 mg/ml	Oral suspension	Sheep	Oral use
Czechia	Chanelle Pharmaceuticals Manufacturing Limited Ida Industrial Estate, Dublin Road, Loughrea, Co. Galway, Ireland	Albex, 10%, Perorální suspenze	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Czechia	Industrial Veterinaria S.A. Calle de la Esmeralda 19 08950 Esplugues de Llobregat Barcelona Spain	Albendis 100 mg/ml oral suspension for cattle and sheep	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Czechia	Alpha-Vet Kft. Hofherr Albert Utca 42, Kerulet, Budapest XIX, Hungary	Alphalben 100 mg/ml oral suspension for cattle and sheep	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Denmark	Zoetis Animal Health ApS, Øster Alle 48, 7. th., DK-2100 Copenhagen Ø Denmark	Valbazen Vet.	albendazole	19 mg/ml	Oral suspension	Cattle, sheep	Oral use
Denmark	Zoetis Animal Health ApS, Øster Alle 48, 7. th., DK-2100 Copenhagen Ø Denmark	Valbazen Vet.	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Estonia	Industrial Veterinaria S.A. Calle de la Esmeralda 19 08950 Esplugues de Llobregat Barcelona Spain	Valbendis	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Estonia	Alphavet Zrt. Hofherr Albert Utca 42, Kerulet, Budapest XIX, Hungary	Alphalben	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
France	Industrial Veterinaria S.A. Calle de la Esmeralda 19 08950 Esplugues de Llobregat Barcelona Spain	Albendis 100 mg/ml oral suspension for cattle and sheep	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
France	Zoetis France 107 Avenue De La Republique Chatillon 92320 France	Valbazen moutons et chevres 1,9 %	albendazole	19 mg/ml	Oral suspension	Sheep, goat	Oral use
Germany	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Albendazol 10% suspension aniMedica	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Germany	Industrial Veterinaria S.A. Calle de la Esmeralda 19 08950 Esplugues de Llobregat Barcelona Spain	Albendis 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 holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Greece	Provet S.A. Eleftherias Avenue 120 Eleousa Ioannina Epirus 455 00 Greece	Albendazole/Provet 5% w/v ποσιμο εναιωρημα	albendazole	5 mg/100 ml	Oral suspension	Cattle (calf), sheep, goat	Oral use
Greece	Candilidis S.A. Ilektras 4b Maroussi Attica 151 22 Greece	Albendazole 2,5%-Chanelle ποσιμο εναιωρημα	albendazole	25 mg/ml	Oral suspension	Cattle, sheep	Oral use
Greece	Chanelle Pharmaceuticals Manufacturing Limited Ida Industrial Estate Dublin Road Loughrea Co Galway H62 FH90 Ireland	Albex 10% Πόσιμο εναιώρημα	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Greece	Industrial Veterinaria S.A. Calle de la Esmeralda 19 08950 Esplugues de Llobregat Barcelona Spain	Albendis 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 holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Greece	Alpha-Vet Kft. Koves Janos Utca 13 Babolna 2943 Hungary	Alphalben 100 mg/ml oral suspension for cattle and sheep	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Greece	Provet S.A. Eleftherias Avenue 120 Eleousa Ioannina Epirus 455 00 Greece	Albendazole/Provet 2,5% W/V ΠΟΣΙΜΟ ΕΝΑΙΩΡΗΜΑ	albendazole	2.5 mg/100 ml	Oral suspension	Cattle (calf), sheep, goat	Oral use
Greece	Provet S.A. Eleftherias Avenue 120 Eleousa Ioannina Epirus 455 00 Greece	Albendazole/Provet 10% W/W ΠΟΣΙΜΟ ΕΝΑΙΩΡΗΜΑ	albendazole	100 mg/ml	Oral suspension	Cattle, sheep, goat	Oral use
Greece	Provet S.A. Eleftherias Avenue 120 Eleousa Ioannina Epirus 455 00 Greece	Albendazole/Provet 1,9% W/V ΠΟΣΙΜΟ ΕΝΑΙΩΡΗΜΑ	albendazole	19 mg/ml	Oral suspension	Cattle (calf), sheep, goat	Oral use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Greece	Ceva Sante Animale 10 Avenue De La Ballastiere Libourne 33500 France	Vermitan 10 g/100 ml ΠΟΣΙΜΟ ΕΝΑΙΩΡΗΜΑ	albendazole	100 mg/ml	Oral suspension	Cattle, sheep, goat	Oral use
Greece	Chanelle Pharmaceuticals Manufacturing Limited Ida Industrial Estate Dublin Road Loughrea Co Galway H62 FH90 Ireland	Albex 2,5% ΠΟΣΙΜΟ ΕΝΑΙΩΡΗΜΑ	albendazole	25 mg/ml	Oral suspension	Cattle, sheep, goat	Oral use
Hungary	Pharma VIM Kft. 1029 Budapest, Adyliget, Pipitér utca 5., Hungary	Albendanin 2,5% belsőleges szuszpenzió A.U.V.	albendazole	25 mg/ml	Oral suspension	Cattle, sheep	Oral use
Hungary	Pharma VIM Kft., 1029 Budapest, Adyliget, Pipitér utca 5., Hungary	Albendanin 10% belsőleges szuszpenzió A.U.V.	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Hungary	Industrial Veterinaria S.A., Calle De La Esmeralda 19 Esplugues De Llobregat Barcelona 08950 Spain	Albendis 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 holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Hungary	Divasa Farmavic S.A. Carretera De Sant Hipolit 71, Gurb, Spain	Albendavet 1,9% szuszpenzió	albendazole	19 mg/ml	Oral suspension	Sheep	Oral use
Hungary	C&H Generics Limited Seville House, 5 New Dock Street, The Docks, Galway, H91 CKV0, Co. Galway, Ireland	Chanalben 100 mg/ml belsőleges szuszpenzió juhok részére A.U.V.	albendazole	100 mg/ml	Oral suspension	Sheep	Oral use
Hungary	Alpha-Vet Kft., H-8000 Székesfehérvár, Homoksor 7., Hungary	Alphalben 100 mg/ml oral suspension for cattle and sheep	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Ireland	Univet Limited Tullyvin, Cootehill, County Cavan, Ireland	Tramazole 2.5% oral drench	albendazole	25 mg/ml	Oral suspension	Cattle, sheep	Oral use
Ireland	Bimeda Animal Health Limited 2, 3 & 4 Airton Close, Airton Road, Tallaght, Dublin, 24, Ireland	Endospec 100 mg/ml SC oral suspension for cattle and sheep	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Ireland	Bimeda Animal Health Limited 2, 3 & 4 Airton Close, Airton Road, Tallaght, Dublin, 24, Ireland	Keelogane SC 25 mg/ml oral suspension for cattle and sheep	albendazole	25 mg/ml	Oral suspension	Cattle, sheep	Oral use
Ireland	Univet Limited Tullyvin, Cootehill, County Cavan, Ireland	Tramazole 10% oral drench	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Ireland	Chanelle Pharmaceuticals Manufacturing Limited Ida Industrial Estate, Dublin Road, Loughrea, Co. Galway, Galway, Ireland	Albex 100 mg/ml oral suspension	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Ireland	Bimeda Animal Health Limited 2, 3 & 4 Airton Close, Airton Road, Tallaght, Dublin, 24, Ireland	Flexiben 100 mg/ml SC oral suspension for cattle and sheep	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Ireland	Chanelle Pharmaceuticals Manufacturing Limited Ida Industrial Estate, Dublin Road, Loughrea, Co. Galway, Galway, Ireland	Albex 25 mg/ml oral suspension	albendazole	25 mg/ml	Oral suspension	Cattle, sheep	Oral use
Ireland	Bimeda Animal Health Limited 2, 3 & 4 Airton Close, Airton Road, Tallaght, Dublin, 24, Ireland	Endospec 25 mg/ml SC oral suspension for cattle and sheep	albendazole	25 mg/ml	Oral suspension	Cattle, sheep	Oral use
Ireland	Alpha-Vet Állatgyógyászati Kft Hofherr Albert Utca 42, Kerulet, Budapest XIX, Hungary	Alphalben 100 mg/ml oral suspension for cattle and sheep	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Italy	Izo S.r.l. Via San Zeno, 99/A Brescia 25124 Italy	Contruerme 100 mg/ml sospensione per uso orale per ovini	albendazole	100 mg/ml	Oral suspension	Sheep	Oral use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Italy	Zoetis Italia S.r.l Via Andrea Doria n.41 M Roma 00192 Italy	Valbazen 50 mg/ml sospensione per uso orale per bovini ed ovini	albendazole	50 mg/ml	Oral suspension	Cattle, sheep	Oral use
Italy	Fatro S.p.A. Via Emilia 285 Ozzano dell'Emilia (BO) 40064 Italy	Sverminator, 19 mg/ml, sospensione orale, per bovini ed ovini	albendazole	19 mg/ml	Oral suspension	Cattle, sheep	Oral use
Italy	Zoetis Italia S.r.l Via Andrea Doria n.41 M Roma 00192 Italy	Valbazen 100 mg/ml sospensione per uso orale per bovini ed ovini	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Italy	Zoetis Italia S.r.l Via Andrea Doria n.41 M Roma 00192 Italy	Valbazen 19 mg/ml sospensione per uso orale per bovini ed ovini	albendazole	19 mg/ml	Oral suspension	Cattle, sheep	Oral use
Italy	Alpha-Vet Kft. Budapest, Hoffner A. utca 38-40, h-1194 Hungary	Alphalben 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 holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Italy	Industrial Veterinaria S.A. Calle de la Esmeralda 19 08950 Esplugues de Llobregat Barcelona Spain	Albendis 100 mg/ml oral suspension for cattle and sheep	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Italy	Fatro S.p.A. Via Emilia 285 Ozzano dell'Emilia (BO) 40064 Italy	Sverminator 10, 100 mg/ml, sospensione orale per bovini ed ovini	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Latvia	Alphavet Zrt. Hofherr Albert Utca 42, Kerulet, Budapest XIX, Hungary	Alphalben 100 mg/ml suspensija iekšķīgai lietošanai liellopiem un aitām	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Latvia	Industrial Veterinaria S.A. Calle de la Esmeralda 19 08950 Esplugues de Llobregat Barcelona Spain	Valbendis 100 mg/ml suspensija iekšķīgai lietošanai liellopiem un aitām	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Lithuania	Alpha-Vet Kft. Hofherr Albert Utca 42, Kerulet, Budapest XIX, Hungary	Alphalben 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 holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Lithuania	Industrial Veterinaria S.A. Calle de la Esmeralda 19 08950 Esplugues de Llobregat Barcelona Spain	Albendis 100 mg/ml oral suspension for cattle and sheep	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Malta	Fatro S.p.A. Via Emilia 285 Ozzano Emilia (BO), Italia	Sverminator 10, 100 mg/ml, sospensione orale per bovini ed ovini	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Norway	Zoetis Animal Health ApS Øster Alle 48 DK-2100 København Denmark	Valbazen vet. 19 mg/ml mikstur, suspensjon til sau og storfe	albendazole	19 mg/ml	Oral suspension	Cattle, sheep	Oral use
Poland	ALPHA-VET Kft. Hofherr A. u. 42. H-1194 Budapest Hungary	Alphalben 100 mg/ml oral suspension for cattle and sheep	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Poland	Ceva Sante Animale 8 Rue De Logrono 33500 Libourne France	Vermitan 100 mg/ml Zawiesina doustna dla bydła i owiec	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Poland	Zoetis Polska Sp. z o.o. ul. Postępu 17 B 025-676 Warszawa Poland	Valbazen 10%, 10 g/ 100 ml zawiesina doustna dla bydła i owiec	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Poland	Industrial Veterinaria S.A. Calle de la Esmeralda 19 08950 Esplugues de Llobregat Barcelona Spain	Albendis 100 mg/ml oral suspension for cattle and sheep	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Portugal	Industrial Veterinaria S.A. Av. Universitat Autònoma 29, 08290 Cerdanyola del Vallès Barcelona Spain	Albendis 100 mg/ml oral suspension for cattle and sheep	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Portugal	Alpha-Vet Kft. H-1194 Budapest, Hofherr A. u. 42. Hungary	Alphalben 100 mg/ml oral suspension for cattle and sheep	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Portugal	Divasa Farmavic S.A. Avenida del Párroco Pablo Díez 49-57 San Andrés del Rabanedo 24010 Leon Spain	Albendavet 19mg/ml suspensão oral para ovinos	albendazole	19 mg/ml	Oral suspension	Sheep	Oral use
Portugal	Iapsa Portuguesa pecuaria, LDA. Av. Do Atlàntico nº 16 11º Piso – Escritório 12 1990-019 Lisboa Portugal	Sinvermin 28,5 mg/ml suspensão oral para ovinos e caprinos	albendazole	28.5 mg/ml	Oral suspension	Sheep, goat	Oral use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Romania	Delos Impex '96 S.R.L. Street Horia, Cloşca and Crişan, no. 81, Otopeni City, Ilfov, Romania	Vermicid 10	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Romania	Provet S.A. Eleftherias Avenue 120, Eleousa, Zitsa, Ioannina, 45500, Greece	Albendazole Provet 25 mg/ml, suspensie orală pentru ovine	albendazole	25 mg/ml	Oral suspension	Sheep	Oral use
Romania	Ceva Sante Animale 10 Avenue de la Ballastiere, 33500 Libourne, France	Vermitan 100 mg/ml, suspensie orală	albendazole	100 mg/ml	Oral suspension	Cattle, sheep, goat, wild ruminants	Oral use
Romania	Bistri-Vet S.R.L. Street Libertăţii no. 13, 420155 Bistriţa City, Bistriţa - Năsăud, Romania	Albendakel 2.5%	albendazole	25 mg/ml	Oral suspension	Cattle, sheep, goat	Oral use
Romania	ALPHA-VET Állatgyógyászati Kft. Hofherr A. u. 42., Budapesta, H-1194, Hungary	Alphalben 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 holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Romania	Industrial Veterinaria S.A. Calle de la Esmeralda 19 08950 Esplugues de Llobregat Barcelona Spain	Albendis 100 mg/ml oral suspension for cattle and sheep	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Romania	S.C. Romvac Company S.A. Voluntari City, Street Centurii no.7, Ilfov, Romania	Rombendazol 10%	albendazole	100 mg/ml	Oral suspension	Cattle, sheep, goat	Oral use
Romania	Bistri-Vet S.R.L. Street Libertăţii no. 13, 420155 Bistriţa City, Bistriţa – Năsăud, Romania	Albendakel 10%	albendazole	100 mg/ml	Oral suspension	Cattle, sheep, goat, camel	Oral use
Romania	Pasteur Filiala Filipesti S.A. Street Principală no. 944, Filipeştii de Pădure City, Prahova, Romania	Helmizol A 2.5	albendazole	2.5 mg/100 ml	Oral suspension	Cattle, sheep, goat	Oral use
Romania	Intervet International B.V. Wim de Körverstr. 35 5831 AN Boxmeer, The Netherlands	Gardal 10%	albendazole oxide	100 mg/ml	Oral suspension	Cattle, sheep	Oral use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Slovak Republic	Pharmagal spol. s r.o. Murgasova 5, Cerman, Nitra, Slovakia	Dicrosol 100 mg/ml perorálna suspenzia	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Slovak Republic	Alpha-Vet Kft. Hofherr Albert Utca 42, Kerulet, Budapest XIX, Hungary	Alphalben 100 mg/ml oral suspension for cattle and sheep	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Slovak Republic	Divasa Farmavic S.A Carretera De Sant Hipolit 71, Gurb Spain	Albendavet 19 mg/ml perorálna suspenzia	albendazole	19 mg/ml	Oral suspension	Sheep	Oral use
Slovak Republic	Industrial Veterinaria S.A. Calle de la Esmeralda 19 08950 Esplugues de Llobregat, Barcelona Spain	Albendis 100 mg/ml oral suspension for cattle and sheep	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Slovak Republic	Mikrochem spol. s r.o. Za Drahou 33, Pezinok, Slovakia	Aldifal 25 mg/ml perorálna suspenzia	albendazole	25 mg/ml	Oral suspension	Sheep	Oral use
Slovenia	Industrial Veterinaria S.A. Calle de la Esmeralda 19 08950 Esplugues de Llobregat Barcelona Spain	Albendis 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 holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Slovenia	Alpha-Vet Kft. Hofherr Albert Utca 42, Kerulet, Budapest XIX, Hungary	Alphalben 100 mg/ml peroralna suspenzija za govedo in ovce	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Spain	S P Veterinaria S.A. Calle Vinyols Km 4.1 43330 Riudoms Tarragona Spain	Albendex 100 mg/ml suspensión oral	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Spain	Industrial Veterinaria S.A. Calle de la Esmeralda 19 08950 Esplugues de Llobregat, Barcelona Spain	Albendazol 25 mg/ml Ganadexil suspensión oral para ovino	albendazole	25 mg/ml	Oral suspension	Sheep	Oral use
Spain	Laboratorios Maymo S.A.U. Via Augusta 302 08017 Barcelona Spain	Maybensol 20 mg/ml suspensión oral	albendazole	20 mg/ml	Oral suspension	Sheep	Oral use
Spain	Laboratorios Syva S.A. Calle Del Marques De La Ensenada 16 28004 Madrid Spain	Sinvermin ovino 28,50 mg/ml suspensión oral para ovino	albendazole	28.5 mg/ml	Oral suspension	Sheep	Oral use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Spain	Divasa Farmavic S.A. Carretera De Sant Hipolit 71 08503 Gurb Barcelona Spain	Albendavet 19 mg/ml	albendazole	19 mg/ml	Oral suspension	Sheep	Oral use
Spain	Cenavisa S.L. Carrer Dels Boters 4 43205 Reus Tarragona Spain	Albecorin lanar 20 mg/ml suspensión oral para ovino y caprino	albendazole	20 mg/ml	Oral suspension	Sheep, goat	Oral use
Spain	Industrial Veterinaria S.A. Calle de la Esmeralda 19 08950 Esplugues de Llobregat Barcelona Spain	Albendis 100 mg/ml oral suspension for cattle and sheep	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
Sweden	Zoetis Animal Health ApS Øster Alle 48 DK-2100 Copenhagen Denmark	Valbazen vet	albendazole	19 mg/ml	Oral suspension	Sheep	Oral use
United Kingdom (Northern Ireland)	Chanelle Pharmaceuticals Manufacturing Ltd Loughrea H62 FH90 Ireland	Benzimole 25 mg/ml SC oral suspension	albendazole	25 mg/ml	Oral suspension	Cattle, sheep	Oral use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
United Kingdom (Northern Ireland)	Bimeda Animal Health Limited 2/3/4 Airton Close, Tallaght D24 FH9V Ireland	Endospec SC 10% w/v oral suspension	albendazole	10 % w/v	Oral suspension	Cattle, sheep	Oral use
United Kingdom (Northern Ireland)	Bimeda Animal Health Limited 2/3/4 Airton Close' Tallaght D24 FH9V Ireland	Endospec SC 2.5% w/v oral suspension	albendazole	2.5 % w/v	Oral suspension	Cattle, sheep	Oral use
United Kingdom (Northern Ireland)	Bimeda Animal Health Limited 2/3/4 Airton Close' Tallaght D24 FH9V Ireland	Ovidrench S & C 10% w/v oral suspension for cattle and sheep	albendazole	10 % w/v	Oral suspension	Cattle, sheep	Oral use
United Kingdom (Northern Ireland)	Bimeda Animal Health Limited 2/3/4 Airton Close' Tallaght D24 FH9V Ireland	Ovidrench S & C 2.5% w/v oral suspension for cattle and sheep	albendazole	2.5 % w/v	Oral suspension	Cattle, sheep	Oral use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
United Kingdom (Northern Ireland)	Tulivin Laboratories Ltd 35 Abbeydale Park, Newtownards BT23 8RE Northern Ireland	Tramazole 100 mg/ml oral suspension for cattle and sheep	albendazole	100 mg/ml	Oral suspension	Cattle, sheep	Oral use
United Kingdom (Northern Ireland)	Tulivin Laboratories Ltd 35 Abbeydale Park, Newtownards BT23 8RE Northern Ireland	Tramazole 2.5% w/v SC oral suspensito	albendazole	2.5 % w/v	Oral suspension	Cattle, sheep	Oral use

Annex II

Scientific conclusions and grounds for amendment of the product information

Overall summary of the scientific evaluation of veterinary medicinal products containing albendazole as a single active substance presented as oral suspension for sheep (see Annex I)

Introduction

Albendazole is a broad-spectrum anthelmintic substance of the benzimidazole class. In susceptible parasites, benzimidazoles act by disrupting the intracellular microtubular transport system by binding selectively and damaging tubulin, preventing tubulin polymerisation, and inhibiting microtubule formation (Plumb, 2005)[1].

Veterinary medicinal products containing albendazole have been widely used for decades in cattle, sheep, goats, pigs, rabbits, birds, dogs, and cats. In ruminants, and in particular in sheep, albendazole-containing VMPs are used for the treatment of gastrointestinal (GIT) nematodes, lungworms, tapeworms, and adult liver flukes. However, emerging benzimidazole resistance has been reported throughout Europe for GIT nematodes in sheep (Borgsteede *et al.,* 2007[2], Cernanská *et al.,* 2006[3], Kaplan & Vidyashankar, 2012[4], Scheuerle *et al.,* 2009[5]).

During a recent decentralised procedure (ES/V/0431/001/DC) submitted in accordance with Article 18 of Regulation (EU) 2019/6, it has been noticed that there are several VMPs on the market, including "Valbazen 1,9% Suspension zum Eingeben für Schafe", the reference product in the aforementioned decentralised procedure, which are indicated for the treatment of GIT nematodes in sheep with doses or lower dose limits of 3.75 mg-5 mg albendazole/kg bodyweight (bw). In fact, a number of scientific publications suggest that doses up to 5 mg albendazole/kg bw may pose a serious risk of insufficient efficacy against GIT nematodes in sheep (Borgsteede *et al.,* 2007[2], Cernanská *et al.,* 2006[3], Claerebout *et al.,*2020[6], Domke *et al.,* 2012a[7], Höglund *et al.,* 2022[8], Kowal *et al.,* 2016[9], Scheuerle *et al.,* 2009[5], Untersweg *et al.,* 2021[10], Vineer *et al.,* 2020[11], Voigt *et al.,* 2022[12]), and, in addition, of selecting for albendazole resistance in the context of the benzimidazole resistance already present in sheep GIT nematodes in Europe.

[1] Plumb, Donald C. Plumb's Veterinary Drug Handbook. Stockholm,Wis:Ames,Iowa:PhrmaVet;Distrib by Blackwell Pub,2005
[2] Borgsteede FHM, Dercksen DD, Huijbers R: Doramectin and albendazole resistance in sheep in the Netherlands, Veterinary Parasitology 144, 180-183, 2007.
[3] Cernanská D, Várady M, Corba J: A survey on anthelmintic resistance in nematode parasites of sheep in the Slovak Republic, Veterinary Parasitology 135, 39-45, 2006.
[4] Kaplan RM and Vidyashankar AN: An inconvenient truth: Global worming and anthelmintic resistance, Veterinary Parasitology 186, 70-78, 2012.
[5] Scheuerle MC, Mahling M, Pfister K: Anthelmintic resistance of *Haemonchus contortus* in small ruminants in Switzerland and Southern Germany, Wiener klinische Wochenschrift 121, 46-49, 2009.
[6] Claerebout E, Wilde ND, Mael EV, Casaert S, Velde FV, Roeber F, Veloz PV, Levecke B, Geldhof P:Anthelmintic resistance & common worm control practices in sheep farms Flanders, Belgium, Vet Parasitology:Regional studies and reports 20, 2020
[7] Domke AV, Chartier C, Gjerde B, Stuen S. Benzimidazole resistance of sheep nematodes in Norway confirmed through controlled efficacy test. Acta Vet Scand. 2012;54(1):48. 2012a
[8] Höglund J, Baltrusis P, Enweji N, Gustafsson K: Signs of multiple anthelmintic resistance in sheep gastrointestinal nematodes in Sweden, Veterinary Parasitology, Regional Studies and Reports 36, 2022.
[9] Kowal J, Wyrobisz A, Nosal P, Kucharski M, Kaczor U, Skalska M, Sendor P: Benzimidazole resistance in the ovine Haemonchus contortus from southern Poland – coproscopical and molecular findings, Annals of parasitology 62(2), 119-123, 2016.Plumb DC, 6. Edition: pp 17-19, 2008.
[10] Untersweg F, Ferner V, Wiedermann S, Göller, M, Hörl-Ramnegger M, Kaiser W, Joachim A, Rinaldi L, Krücken J, Hinney B: Multispecific resistance of sheep trichostrongyloids in Austria, Parasite 28, 50, 2021.
[11] Vineer HR, Morgan ER, Hertzberg H, Bartley DJ, Bosco A, Charlier J, Chartier C, Claerebout E, de Waal T, Hendrickx G, Hinney B, Höglund J, Jezek J, Kasny M, Keane OM, Martinez-Valladares M, Mateus TL, McIntyre J, Mickiewicz M, Munoz AM, Phytian CJ, Ploeger HW, Rataj AV, Skuce PJ, Simin S, Sotiraki S, Spinu M, Stuen S, Thamsborg SM, Vadlejch J, Varady M, von Samson-Himmelstjerna G, Rinaldi L: Increasing importance of anthelmintic resistance in European livestock: creation and meta-analysis of an open database, Parasite 27, 69, 2020.
[12] Voigt K., Geiger M., Jäger M.C., Knubben-Schweizer G., Strube C., Zablotski Y., Effectiveness of anthelmintic treatments in small ruminants in Germany, Animals 12, 1501, 2022.

Moreover, Germany noticed that the doses of albendazole VMPs against GIT nematodes in sheep are disharmonised across the European Union, ranging between 3.75 – 15 mg albendazole per kg bw.

For the reasons outlined above, Germany considered it necessary to review VMPs containing albendazole as a single active substance, presented as oral suspensions and indicated against GIT nematodes in sheep, with doses or lower dose limits of 3.75 mg - 5 mg albendazole/kg bw. Therefore, Germany referred the matter to the Agency's Committee for Veterinary Medicinal Products (CVMP) under Article 82 of Regulation (EU) 2019/6 in the interest of the Union.

The aim of this review was to ensure the safe and effective use of these VMPs and to avoid unnecessary risks related to the development of antiparasitic resistance. Beyond that, Germany also considered it necessary to evaluate residue studies, target animal safety studies and environmental safety studies, since a potential increase in the recommended dosage may have implications for consumer, target animal and environmental safety.

Overall summary of the scientific evaluation

In this procedure, the Committee was to consider what dosage regimen (i.e. dose rate, dosing interval and treatment duration) of albendazole is required for the concerned VMPs to ensure adequate efficacy against gastrointestinal nematodes in sheep while limiting the risk of development of resistance to albendazole. If a change to the dosage regimen was deemed necessary, consideration also needed to be given to establishing an adequate withdrawal period for sheep and to assessing the potential impact of the new recommended dose on the target animal safety as well as the environmental risk assessment of the concerned VMPs. Further to this request, the CVMP considered it necessary to also evaluate the potential impact of any proposed changes to the dosage regimen on the user safety.

Ten marketing authorisation holders (MAHs) submitted responses to the CVMP list of questions for this referral procedure. While some MAHs provided extensive documentation, literature packages and summaries, others provided only limited information, restricted mainly to qualitative and quantitative composition of their VMPs.

A substantial proportion of the proprietary and published studies submitted were generated more than 15–20 years ago and reflected the scientific standards, parasite susceptibility patterns, and resistance situation prevailing at the time of original authorisation. In contrast, relatively few field studies specifically addressing current efficacy of albendazole at the authorised doses were available.

In order to facilitate the critical assessment and support the derivation of an effective dose, the CVMP identified additional references from the published literature.

Due to concerns regarding the limited relevance of historical data, only literature and field studies (including dose determination and dose confirmation field studies) published or conducted from 2011 onwards have been taken into account for the efficacy assessment of the current situation, including the additional references identified by the CVMP. As the assessment aimed to evaluate the present-day efficacy of albendazole at doses or lower dose limits of 3.75–5 mg/kg bw in the context of emerging resistance, the CVMP restricted its evaluation to data generated within the past 15 years. Although no formal cut-off period is defined for antiparasitic veterinary medicinal products, unlike antibiotics for which a 5-year limit is specified in the CVMP guideline on the assessment of the risk to public health from antimicrobial resistance due to the use of an antimicrobial veterinary medicinal product in food-producing animal species (EMA/CVMP/AWP/706442/2013)[13], the CVMP sought to achieve a balance

[13] Guideline on the assessment of the risk to public health from antimicrobial resistance due to the use of an antimicrobial veterinary medicinal product in food producing animal species (EMA/CVMP/AWP/706442/2013) - link

between the age and scientific relevance of the available evidence while avoiding the exclusion of an excessive number of references. This resulted in the acceptance of a 15-year time frame.

Historical data were considered supportive for characterisation of pharmacokinetics, safety, and general efficacy patterns, but were of limited relevance for assessing present-day efficacy and resistance.

The CVMP evaluated the data submitted by the MAHs and the additional literature identified by the CVMP for VMPs containing albendazole presented as oral suspensions authorised for the treatment of gastrointestinal nematodes in sheep at doses or lower dose limits of 3.75–5 mg/kg bw.

Qualitative and quantitative composition

Eight MAHs provided the qualitative and quantitative composition of their VMPs, and seven of these also submitted the corresponding product specifications.

Although the formulations of the VMPs differ in terms of excipient composition and specifications, all VMPs contain the same active substance and are administered via the same route of administration.

Most of the listed excipients were generally regarded as pharmacologically inactive, i.e. no excipients that affect bioavailability after oral administration were identified in the compositions provided. On this basis, these excipients were not expected to influence the absorption, distribution, metabolism, or excretion of the active substance or exert substantial formulation-related effects on bioavailability and pharmacokinetics.

However, taking into account the known properties of certain excipients present in some formulations, a potential effect on the pharmacokinetic profile could not be completely excluded. Nonetheless, the formulations concerned have been marketed for many years and, in some cases, are supported by product-specific pharmacokinetic data (see section on pharmacokinetics below).

Considering the extensive presence on the market of these VMPs, any hypothetical excipient-related influence on pharmacokinetics was not expected to translate into a clinically relevant impact on efficacy. Therefore, the observed differences in excipient composition were not considered to have a clinically relevant impact on systemic exposure, and the CVMP considered it scientifically justified to derive and apply a uniform dosing regimen for all formulations of the VMPs. Even though not all MAHs provided the composition and specifications of their VMPs, the absence of these data was not expected to influence the overall assessment or the conclusions reached.

Pharmacokinetics

Five MAHs submitted information on the pharmacokinetics of orally administered albendazole, consisting of proprietary data and references from published scientific literature. Overall, proprietary studies were relatively old, which is consistent with the fact that albendazole-containing VMPs have been authorised since the 1960s. However, the age of the studies generally has no influence on the pharmacokinetics of a substance; only the analytical methods may have improved over time. As such, the data provided were considered valid in the context of this referral procedure.

Some of the submitted studies or publications on pharmacokinetics used pure albendazole or different approved VMPs containing albendazole as the active substance. It should be noted that the studies and publications were conducted independently of each other at different locations by different researchers using different equipment. Thus, variability of the pharmacokinetic parameters within the same dosage could be due to the different formulations.

Bioequivalence data indicated no significant impact of formulation differences on systemic exposure when identical doses were administered. This was demonstrated in bioequivalence studies provided by two MAHs (where three strengths at 7.5 mg/kg bw and two VMPs at 10 mg/kg bw were assessed, respectively). Another study evaluated the pharmacokinetics and efficacy of two approved VMPs at a dose of 7.5 mg/kg bw, demonstrating comparable efficacy against *F. hepatica*, *O. circumcincta*, *T. colubriformis,* and *N. battus*.

In addition, four published literature references (1991–2004) complemented the proprietary data. Two studies evaluated the PK of pure albendazole rather than authorised VMPs. Swarnkar *et al.,* (1998)[14] investigated the pharmacokinetics of orally and intraruminally administered albendazole at a dose of 5 mg/kg bw, observing an increased bioavailability of albendazole given by the intraruminal route. Galtier *et al.,* (1991)[15] examined the metabolisation of albendazole administered orally, intravenously or intraruminally at doses up to 3.8 mg/kg bw, demonstrating that albendazole was metabolised mainly in the liver, irrespective of the route of administration.

Two further publications investigated the relationship between plasma pharmacokinetics and clinical efficacy of albendazole in infected animals. Moreno *et al.,* (2004)[16] examined two different dose rates, 3.8 mg/kg bw and 7.5 mg/kg bw and observed a proportional relationship between the administered albendazole dose and the measured plasma concentrations of both albendazole metabolites. Over a 100% increment on the plasma AUC values for the anthelmintic active metabolite albendazole sulphoxide was observed at the 7.5 mg/kg bw dose compared to 3.8 mg/kg bw. The higher and prolonged plasma drug concentration measured after the 7.5 mg/kg bw treatment resulted in an improved efficacy pattern (estimated by both faecal egg and adult worm counts) against most of the GI nematodes studied compared to that obtained at the lower dose rate. The low nematocidal activity (<24%) observed against the GI nematodes investigated indicate a high level of resistance to albendazole given at 3.8 mg/kg bw. In conclusion, administering a higher dose could result in a higher exposure and an efficacy improvement (that could be of importance for being effective against the least susceptible helminths).

In the second study, Lanusse *et al.,* (1995)[17] characterised the plasma disposition kinetics of albendazole, fenbendazole, and oxfendazole following their oral administration (5 mg/kg bw) to adult sheep. Overall, it was shown that albendazole sulfoxide exhibited faster absorption and a higher C_{max} than oxfendazole and declined relatively rapidly in plasma, reaching non-detectable concentrations at 60h post albendazole administration.

Important conclusions can be extracted from the pharmacokinetic data. It is known that albendazole is a pro-drug and the active form is the metabolite albendazole sulphoxide, being formed in the liver. An increase of the albendazole dose in sheep is associated with enhanced plasma metabolites exposure (Moreno *et al.,* 2004)[16]. Furthermore, a direct relationship between drug pharmacokinetic behaviour and anthelmintic efficacy against benzimidazole-resistant nematodes in sheep was shown in the work of Moreno *et al.* (2004)[16]. Although this is not a classic pharmacokinetic study, it was nevertheless possible to show that an increase of the albendazole dose in sheep is clearly associated with enhanced plasma metabolites exposure and higher drug concentration, which resulted in increased efficacy.

[14] Swarnkar CP, Sanyal PK, Singh D, Khan FA, Bhagwan PS. Comparative disposition kinetics of albendazole in sheep following oral and intraruminal administration. Vet Res Commun. 1998 Dec;22(8):545-51.
[15] Galtier P, Alvinerie M, Steimer JL, Francheteau P, Plusquellec Y, Houin G. Simultaneous pharmacokinetic modeling of a drug and two metabolites: application to albendazole in sheep. J Pharm Sci. 1991 Jan;80(1):3-10.
[16] Moreno L, Echevarria F, Muñoz F, Alvarez L, Sanchez Bruni S, Lanusse C. Dose-dependent activity of albendazole against benzimidazole-resistant nematodes in sheep: relationship between pharmacokinetics and efficacy. Exp Parasitol. 2004;106(3-4):150-157.
[17] Lanusse CE, Gascon LH, Prichard RK. Comparative plasma disposition kinetics of albendazole, fenbendazole, oxfendazole and their metabolites in adult sheep. J Vet Pharmacol Ther. 1995;18(3)196-203

Dosage regimen of authorised VMPs

With regard to the dosing interval, all concerned VMPs are authorised for single administration, irrespective of their dose. The documentation submitted by the MAHs did not include evidence suggesting that this dosing interval might not be adequate. Furthermore, the scientific literature research performed did not identify data indicating that an alternative dosing interval would provide improved efficacy. On this basis, there is no evidence that a single administration is not adequate. Therefore, the single administration of albendazole is not further discussed, and the subsequent evaluation of the dosage regimen focuses on the appropriateness of the dose level.

Dose determination / Dose confirmation

Several proprietary pre-clinical studies on dose determination and dose confirmation were provided, some of which were conducted under field conditions in sheep and likely originating from the original marketing authorisation procedures. Since most of the VMPs in the scope of this referral have been on the market for many years, none of the proprietary studies provided was less than 22 years old.

The studies assessed albendazole doses of 2.5, 3.75, 3.8, 5, 5.7, or 7.6 mg per kg bw and covered a variety of GIT nematodes, including the most common genera *Haemonchus*, *Trichostrongylus*, *Teladorsagia*, *Nematodirus,* and *Cooperia*. Overall, most studies showed efficacy rates over 90% for most GIT nematodes at the time of authorisation of the VMPs. Nevertheless, even these old studies showed that low doses of 2.5, 3.5 and 3.8 mg/kg bw achieved variable efficacy below the necessary threshold of 90% against *Oesophagostomum columbianum* (L3, L4, adult), which seems to be the least susceptible GIT nematode to albendazole. Although the studies were not conducted in accordance with current guidelines, most were considered acceptable in terms of the study design.

A dose confirmation study conducted by Zoetis around 1991 demonstrated that the dose of 7.6 mg albendazole per kg bw was sufficiently effective against thiabendazole resistant strains (with efficacy values of 100% and 99.7% against *H. contortus* and *T. colubriformis*, respectively), whereas the 5.7 mg albendazole/kg bw dose did not achieve sufficient effect (91% and 89.6% efficacy against *H. contortus* and *T. colubriformis*, respectively). Although the study design is outdated and involved small animal treatment groups, the results are considered supportive.

In a later publication, Moreno *et al.,* 2004[16] examined the efficacy of two doses of albendazole (3.8 and 7.5 mg/kg bw) by means of egg counts in addition to measuring albendazole metabolites in plasma. The authors concluded that higher plasma metabolite levels were associated with a higher efficacy. The 7.5 mg/kg bw dose achieved a greater reduction of 49.1% in sheep infected with benzimidazole-resistant nematodes, compared with a reduction of 27% following administration of the 3.8 mg/kg bw dose. Despite the wide variation in efficacy values with similar C_{max} values, the data from Moreno *et al*., 2004[16] indicate that higher C_{max} values lead to increased efficacy, which can be achieved by administering a higher dose of albendazole. Differences in efficacy can be attributed to various factors, such as artificial or natural infection, the region where the study was conducted, and the parasite's resistance level.

Since the studies were conducted more than two decades ago, and consequently the actual resistance situation could not be considered, it remains uncertain to what extent the efficacy data from these studies can be applied to the current situation. While efficacy at doses ranging from 3.75 to 5 mg/kg body weight was confirmed at the time of authorisation more than twenty years ago, the efficacy of these doses at that time is not within the scope of this referral.

Overall, the conclusions drawn from the dose determination and confirmation studies provided may no longer be valid, as doses higher than 5 mg/kg bw were not tested, the studies are more than 20 years old, and they have design limitations from the current perspective.

Efficacy / Resistance

Resistance mechanisms

Several publications on resistance mechanisms, especially of detection of Single nucleotide polymorphisms (SNPs) on codon 167, 198 and 200 of the beta-tubulin gene in *Haemonchus contortus* (Barrère *et al.,* 2012[18], Claerebout *et al.,* 2020[6]), *Teladorsagia circumcincta* (Esteban-Ballesteros *et al.,* 2017[19], Martínez-Valladares *et al.,* 2012[20], Claerebout *et al.,* 2020[6]) and *Trichostrongylus colubriformis* (Esteban-Ballesteros *et al.,* 2017[19], Claerebout *et al.,* 2020[6]) were provided. SNPs related to benzimidazole resistance are well characterised.

Benzimidazole resistance in nematodes can be due to a mutation in the gene coding for the target site; however, the same mutation does not seem to cause resistance to triclabendazole in the trematode *Fasciola hepatica* (Wilkinson *et al.,* 2012)[21]. In addition, within a single worm species, different mutations can lead to resistance to the same anthelmintic. For instance, benzimidazole resistance in *Haemonchus contortus* can be caused by a phenylalanine to tyrosine mutation at amino acid position 200 of the isotype 1β-tubulin gene (Kwa *et al.,* 1994)[22]. However, the frequency of this resistance point mutation (single nucleotide polymorphism, SNP) varies considerably and it can be low in benzimidazole-resistant populations (James *et al.,* 2009[23], Ghisi *et al.,* 2007[24]) which carry other mutations (e.g. codon 167). Although genetic selection contributes to resistance, changes in drug transport mechanisms or in the metabolism of the drug within a worm species also account for different resistance mechanisms to the same anthelmintic (Blackhall *et al.,* 2008[25], Vokral *et al.,* 2013[26]). The P-glycoprotein, a cell membrane transport protein able to transport many different drugs (including ivermectin, benzimidazoles and imidazothiazole derivatives), may lead to multi-drug resistance by increasing the active transport of drugs (James *et al.,* 2009[23], Kerboeuf *et al.,* 2003[27], Xu *et al.,* 1998[28]).

[18] Barrère V, Alvarez L, Suarez G, et al.,Relationship between increased albendazole systemic exposure and changes in single nucleotide polymorphisms on the β-tubulin isotype 1 encoding gene in Haemonchus contortus. Vet Parasitol. 2012;186(3-4):344-349.
[19] Esteban-Ballesteros M, Rojo-Vázquez FA, Skuce PJ, Melville L, González-Lanza C, Martínez-Valladares M. Quantification of resistant alleles in the β-tubulin gene of field strains of gastrointestinal nematodes and their relation with the faecal egg count reduction test. BMC Vet Res. 2017;13(1):71.
[20] Martínez-Valladares M, Famularo MR, Fernández-Pato N, Cordero-Pérez C, Castañón-Ordóñez L, Rojo-Vázquez FA. Characterization of a multidrug resistant Teladorsagia circumcincta isolate from Spain. Parasitol Res. 2012;110(5):2083-87.
[21] Wilkinson R, Law CJ, Hoey EM, Fairweather I, Brennan GP, Trudgett A. An amino acid substitution in Fasciola hepatica P-glycoprotein from triclabendazole-resistant and triclabendazole-susceptible populations. Mol Biochem Parasitol. 2012;186(1):69-72.
[22] Kwa MS, Veenstra JG, Roos MH. Benzimidazole resistance in Haemonchus contortus is correlated with a conserved mutation at amino acid 200 in beta-tubulin isotype 1. Mol Biochem Parasitol. 1994 Feb;63(2):299-303.
[23] James CE, Davey MW. Increased expression of ABC transport proteins is associated with ivermectin resistance in the model nematode Caenorhabditis elegans. Int J Parasitol. 2009;39(2):213-220.
[24] Ghisi M, Kaminsky R, Mäser P. Phenotyping and genotyping of Haemonchus contortus isolates reveals a new putative candidate mutation for benzimidazole resistance in nematodes. Vet Parasitol. 2007;144(3-4):313-320.
[25] Blackhall WJ, Prichard RK, Beech RN. P-glycoprotein selection in strains of Haemonchus contortus resistant to benzimidazoles. Vet Parasitol. 2008;152(1-2):101-107.
[26] Vokřál I, Jirásko R, Stuchlíková L, et al.,Biotransformation of albendazole and activities of selected detoxification enzymes in Haemonchus contortus strains susceptible and resistant to anthelmintics. Vet Parasitol. 2013;196(3-4):373-81.
[27] Kerboeuf D, Blackhalls W, Kaminskyc R and von Samson-Himmelstjerna G: P-glycoprotein in helminths: function and perspectives for anthelmintic treatment and reversal of resistance. Efflux pumps and antibiotic resistance of microorganisms International Journal of Antimicrobial Agents 2003; 22: 332–346.
[28] Xu M, Molento M, Blackhall W, Ribeiro P, Beech R and Prichard R (1998): Ivermectin resistance in nematodes may be caused by alteration of P-glycoprotein homolog, Molecular and Biochemical Parasitology, 91: 327-335.

Data of Barrère *et al.,*2012[18] showed that specific *H. contortus* genotypes, particularly the 200 genotypes, are selectively enriched by increased albendazole exposure and that there is a strong association between SNPs at codon 167 and 200 in ß-tubulin. However, the conclusion does not correspond with the findings of Leathwick and Luo (2017)[29] that evaluated the variables which can influence the selection of resistance. Besides the administration route and the formulation itself (both not in the scope of this referral), it was clearly established that the use of lower doses resulted in a higher gene frequency after treatment and therefore a higher probability of resistance development and that a high variability in the dose is more likely to lead to resistance than a low variability. Furthermore, it was concluded that, in the early stages of resistance development, when resistance genes are still rare in a population, mating probabilities determine that these genes are almost entirely present in the heterozygote form. Therefore, if these worms are killed by drug treatment (i.e. they are effectively recessive) then resistance development is delayed whereas if they survive treatment due to an ineffective dose (i.e. they are effectively dominant) resistance develops relatively rapidly. Therefore, it can be concluded that higher doses and a low variability led to a delay in the development of resistance.

Efficacy data provided by MAHs

Five MAHs provided efficacy or resistance data, of which four submitted pre-clinical and clinical studies evaluating efficacy of albendazole against various parasites such as GIT nematodes, lungworms, tapeworms and liver flukes at doses ranging from 2.5 to 15 mg/kg bw in sheep. In these studies, both naturally and artificially infected sheep were included and albendazole was administered orally, either as a suspension or in capsules.

Across the studies, it was consistently demonstrated that dependent on the target parasites different doses of albendazole were needed for adequate efficacy. Against GIT nematodes, even low doses starting at 3.75 mg/kg bw were effective. However, due to varying susceptibilities, *Oesophagostomum columbianum* showed the lowest susceptibility of the tested GIT nematodes to albendazole, requiring at least 5 mg albendazole/kg bw to achieve sufficient efficacy. Doses of 7.5 mg albendazole/kg bw or higher demonstrated efficacy close to 100% against GIT nematodes, independent of the parasite species. Efficacy against lungworms, tapeworms or liver flukes needed higher doses (starting at 7.5 mg albendazole/kg bw) to achieve sufficient efficacy of ≥90% reduction.

It should be noted that the study designs were not in line with VICH GL13 (Efficacy of anthelmintics: Specific recommendations for ovines) with regard to the number of infective stages for artificial infection and timepoints of infection, treatment and autopsy. However, these approaches reflected the prevailing scientific standards at the time, considering that VICH GL13 was adopted by the CVMP in 1999. Whilst the historical efficacy of 3.75–5 mg albendazole/kg bw against GIT nematodes at the time of the VMP's authorisation (more than 20 years ago) is still not in question today, the above once again highlights that the age of the studies limits their relevance for this referral procedure. Consequently, given the objective of evaluating the present-day efficacy of these doses in the context of emerging resistance, the CVMP only considered data generated within the past 15 years.

Based on the evaluation of the submitted information, the CVMP concluded that the data presented reflect the age and historical context of these VMPs, and therefore, the conclusions reached at that time are not necessarily valid now. Although the studies demonstrated effective dose ranges between 3.75 and 7.5 mg/kg bw for different parasites at the time, the current situation is different, as the

[29] Leathwick DM, Luo D: Managing anthelmintic resistance-Variability in the dose of drug reaching the target worms influences selection for resistance?. Vet Parasitol. 2017;243:29-35.

development and spread of resistance among GIT nematodes has significantly impacted the efficacy of the VMPs, thus limiting the relevance of the conclusions to contemporary field conditions.

Efficacy data after treatment with doses or lower dose limits of 3.75–5 mg albendazole per kg bw against GIT nematodes in Europe since 2011

In total, 15 publications were considered relevant for the evaluation of albendazole efficacy in sheep and have been included in the assessment. Adequate efficacy above the threshold of 90% was demonstrated by Martinez-Valladares et al. 2012[20] and Rinaldi et al. 2014[30] after the oral administration of 3.8 - 5 mg albendazole/kg bw. However, variable efficacy was observed in the other studies[31] at doses from 3.75 to 5 mg albendazole per kg bw. Whilst sufficient efficacy against GIT nematodes was demonstrated in some cases, others documented suboptimal efficacy at or below 90%.

The provided field studies were performed across Europe (Austria, Belgium, Estonia, France, Germany, Greece, Italy, Latvia, the Netherlands, Norway, Poland, Slovakia, Spain, Sweden, Switzerland, and the United Kingdom). After administration of albendazole at the authorised doses of 3.75 - 3.8 mg/kg bw and 5 mg/kg bw, the most abundant and resistant genera observed were *Haemonchus* spp., *Trichostrongylus* spp. and *Teladorsagia* spp., which are usually targeted by albendazole treatments. In these studies, naturally and artificially infected sheep were included, respectively. Efficacy was calculated based on faecal egg count reduction test (FECRT) and results were in some cases further confirmed by pyrosequencing of SNPs at codon 167, 198 and 200 on the ß1 tubulin gene. Additionally, multidrug resistance was observed in some cases where different anthelmintics such levamisole, ivermectin, or moxidectin were tested.

Numerous publications reported insufficient efficacy after the oral administration of albendazole at a dose of 3.75 – 5 mg/kg bw in sheep within the past 15 years. These findings indicate the presence of anthelmintic resistance in GIT nematodes across Europe, which has been frequently detected in areas where studies have been conducted. It is acknowledged, however, that there was a bias towards preferential sampling of individual farms with suspected anthelmintic resistance, and research efforts were biased towards Western Europe. Regions in Eastern Europe appear to be underrepresented; however, it could not be inferred that there are no potential problems with insufficient efficacy against GIT nematodes in sheep in these regions of Europe, but rather that this is due to a lack of data originating from these areas. Since continuous monitoring data are rare due to cost- and labour-intensive investigations, variable compliance of farmers, the data on resistance in the field is sparse and may not fully reflect the broader "real-world situation" regarding the efficacy of anthelmintic treatments with albendazole in sheep in the field.

For the assessment of data, it should be noted that efficacy was calculated primarily on the basis of FECRT alone in all of the studies. Although the FECRT is adequate to determine lack of efficacy under field conditions, determination of resistance should be ideally confirmed by investigations such as

[30] Rinaldi L, Morgan ER, Bosco A, Coles GC, Cringoli G. The maintenance of anthelmintic efficacy in sheep in a Mediterranean climate. Vet Parasitol. 2014 Jun 16;203(1-2):139-43. doi: 10.1016/j.vetpar.2014.02.006. Epub 2014 Feb 17

[31] Anupõld AM, Hinney B, Joachim A. Die Resistenzlage von Magen-darm- Strongyliden gegenüber Anthelminthika in drei estnischen Schafherden [The resistance status of gastrointestinal strongyles against anthelmintics in three Estonian sheep flocks]. Berl Munch Tierarztl Wochenschr. 2014;127(1-2):50-55.
Bosco A, Kießler J, Amadesi A, et al.,The threat of reduced efficacy of anthelmintics against gastrointestinal nematodes in sheep from an area considered anthelmintic resistance-free. Parasit Vectors. 2020;13(1):457.
Höglund J, Gustafsson K, Ljungström BL, Skarin M, Varady M, Engström F: Failure of ivermectin treatment in Haemonchus contortus infected-Swedish sheep flocks. Veterinary Parasitology: Regional Studies and Reports, 1, 10-15. 2015.
Keidāne D, Kļaviņa A, Bergmane MB, Kovaļčuka L: Parasitofauna and current status of anthelmintic resistance in Latvian sheep farms. Veterinary World, 15(2), 414. 2022.
Maurizio A, Dotto G, Fasoli A, et al.,Treatment ineffectiveness towards Haemonchus contortus is highly prevalent in sheep and goat farms of North-Eastern Italy. BMC Vet Res. 2024;20(1):498. 2024 Oct 30
Domke et al., 2012ª; Geurden et al., 2014; Höglund et al., 2022; Kowal et al., 2016; Martínez Valladares et al., 2015; Untersweg et al., 2021; Vineer et al., 2020; Voigt et al., 2022

pyrosequencing to detect the responsible SNPs. In studies where pyrosequencing was performed following FECRT, the in vivo data were confirmed. Benzimidazole resistance was detected at the codon positions 167 (8%) and 200 (92%) of the isotype-1 beta tubulin gene in H. contortus, codon positions 198 (47%) and 200 (43%) in T. circumcincta, and position 200 (100%) in T. colubriformis (Claerebout et al., 2020)6. However, as stated above, in most studies merely FECRT results were the basis for the assessment of efficacy and resistance. The World Association for the Advancement of Veterinary Parasitology Guideline (Kaplan et al., 2023)32 specified the conditions that need to be fulfilled for conclusions on anthelmintic resistance based on insufficient efficacy calculated from FECRT. These conditions include an appropriate dosage and administration, use of a properly stored VMP within the expiration date, sampling of the same animals both before and after treatment at an appropriate interval, correctly labelled and stored fresh faecal samples, the method used to determine the faecal egg count is suitable for FECR and appropriate laboratory techniques were used, the drug tested had previously been proven effective against the target parasites at the tested dosage, a sufficient number of animals and excreted eggs were available, appropriate statistical methods were used, and the quality of the anthelmintic can be guaranteed. Most of these standards are consistent with good veterinary practice, and although this is not explicitly stated, it is assumed that these conditions were therefore met in studies with an approved VMP. Consequently, results based on FECRT are considered valid and suitable for detection of resistance under field conditions (provided that conditions were met). Although anthelmintic resistance was confirmed using FECRT according to the above study results, it should be kept in mind that at least 25% of the worm population has to be resistant in order to obtain reliable results, so that initially weak resistance may remain undetected. Despite the limitations of the FECRT, this is an established diagnostic method, which is practicable under field conditions.

However, where data were available, the findings were concerning. Across Europe, an increase in the occurrence of the development of resistance was observed over the last 15 years, as discussed in more detail below. This is particularly problematic given the limited number of anthelmintic classes authorised for the treatment of GIT nematodes in sheep (benzimidazoles, macrocyclic lactones, imidazothiazoles, amino-acetonitrile derivates, salicylanilide). Furthermore, several studies documented multidrug resistance to all tested active substances (Untersweg et al., 202110, Martinez-Valladares et al., 201533, Geurden et al., 201434), significantly restricting therapeutic alternatives. This was substantiated within the German nationwide survey conducted by Voigt et al., 202212 in which it was shown that the use of benzimidazoles or macrocyclic lactones against GIT nematodes in sheep resulted in an efficacy level below the necessary threshold of ≥90%.

Kaplan & Vidyashankar (2012)[4] gave an overview of the worldwide prevalence of anthelmintic resistance in different target species. Although this referral procedure focused on the efficacy of albendazole in sheep in Europe, the highly insufficient efficacy results and multidrug resistance in non-European countries are concerning. While the resistance prevalence levels in Europe were described as much lower in comparison to other continents and countries, resistance to benzimidazole is widely prevalent. Potential underdosing, repeated use of the same class of substances and inadequate number of susceptible worms maintained within an 'in refugia' population, have led to the development

[32] Kaplan RM, Denwood MJ, Nielsen MK, et al.,World Association for the Advancement of Veterinary Parasitology (W.A.A.V.P.) guideline for diagnosing anthelmintic resistance using the faecal egg count reduction test in ruminants, horses and swine. Vet Parasitol. 2023;318:109936.
[33] Martínez-Valladares M, Geurden T, Bartram DJ, et al.,Resistance of gastrointestinal nematodes to the most commonly used anthelmintics in sheep, cattle and horses in Spain. Vet Parasitol. 2015;211(3-4):228-233. doi:10.1016/j.vetpar.2015.05.024
[34] Geurden T, Hoste H, Jacquiet P, et al.,Anthelmintic resistance and multidrug resistance in sheep gastro-intestinal nematodes in France, Greece and Italy. Vet Parasitol. 2014;201(1-2):59-66.

of resistance. Therefore, it is noted that the resistance situation against benzimidazoles is very different worldwide; however, only European data were considered in this referral procedure.

Furthermore, one MAH provided an overview of pharmacovigilance reports of suspected lack of expected efficacy (LEE) cases against GIT nematodes in sheep treated with an albendazole VMP worldwide over the period from 1 January 2015 to 31 December 2024. However, due to limited information provided in these reports (about confirmed infections prior to treatment, the confirmation of infestation based on clinical symptoms rather than parasitological methods, the lack of information regarding additional treatments, the exact timing of the success of the treatment, and thus the question of whether parasites have been detected after treatment due to insufficient efficacy or reinfection), an association with anthelmintic resistance could not be confirmed based on the pharmacovigilance data submitted by this MAH. In addition, although there were no further pharmacovigilance data from companies reporting reduced efficacy, it should be noted that pharmacovigilance data can only provide indications of potential resistance; the true extent in the field may be much greater but remains undetected due to underreporting of such events.

Overall, the CVMP concluded that while the available evidence demonstrates variability across regions, treatments, and reports of lack of efficacy, the collective data indicate a lack of consistent efficacy at the recommended doses of 3.75 – 5 mg/kg bw in sheep, together with indications of potential anthelmintic resistance. The data obtained in those studies did not always reach the ≥90% efficacy threshold recommended to avoid resistance. Although resistance detection is methodologically challenging, there is evidence that at the above-mentioned recommended doses there are treatment failures, as demonstrated by the scientific publications and pharmacovigilance reports. Hence, the CVMP considered that higher doses would be required to reach a uniform and certain level of efficacy under current field conditions.

Efficacy data after treatment with doses of 7.5 mg albendazole /kg bw or higher against GIT nematodes in Europe since 2011

A dose of 7.5 mg albendazole/kg bw is recommended for the treatment of infections with GIT nematodes in sheep in the United States (Plumb 6th edition). In Europe, only a few albendazole VMPs with doses of 7.5 mg/kg bw or higher are authorised against GIT nematodes in sheep. In the study of Esteban-Ballesteros *et al.,* 2017[19], adequate efficacy was confirmed after the administration of 7.5 mg albendazole per kg bw in ten naturally infected sheep farms in Spain. Additionally, allele frequencies, which correspond to benzimidazole resistance, were detected before and after treatment in *T. circumcincta* and *T. colubriformis*. SNP200 was present in *T. colubriformis* on multiple farms and at high frequency before (between 48.5 and 87.8%) and after treatment with albendazole (mean in positive flocks=95.1%), except for one farm where high efficacy between 98.5–100% was achieved. Interestingly, the farm with the lowest efficacy (91.4%) had a very low frequency of SNPs before and after treatment, which did not correlate with the results of farms with a higher prevalence of SNPs that had higher efficacy rates. In all other farms with excellent efficacy, the prevalence of SNPs increased among the individual surviving larvae. The results showed that very high efficacy close to 100% was achieved with a dose of 7.5 mg/kg bw, irrespective of the degree of SNP prevalence prior to treatment.

Dărăbuș *et al.,* 2021[35] published a study in which the therapeutic effect against GIT nematodes of 7.5 mg albendazole per kg bw, p.o. or 0.2 mg ivermectin per kg bw, s.c. were tested comparatively in 40 Romanian sheep after increased resistance in the geographical area were reported. Even though the

[35] Dărăbus G, Morariu S, Mederle N, Ilie MS, Luca I, Ciresan AC: A comparative study regarding the efficacy of anthelmintic treatment for gastrointestinal parasitism in sheep, Revista Româna de Medicina Veterinara, 77-80. 2021

resistance risk on farm level was not described in detail, adequate efficacies of 99.84% after albendazole treatment and 99.73% after ivermectin treatment were achieved at group level.

Babják *et al.,* 2023[36] published evidence of lack of efficacy after doses of 5 mg/kg bw albendazole as single dose or divided in half and administered at 6-hours interval, 10 mg albendazole/kg bw as single dose, or 0.2 mg/kg bw ivermectin in a highly resistant sheep farm in Slovakia. This study furthermore identified multidrug resistance in GIT nematodes in sheep. In the second phase of the study, 100% efficacy after administration of levamisole was achieved, which was not surprising due to unavailability of levamisole on the local market for a long time and, therefore, the absence of exposure of nematodes to this active substance.

Although only a few publications are available, the studies from Esteban-Ballesteros[19], Dărăbuș[35], and Babják[36] illustrate in which cases an increase of the dosage of albendazole would be beneficial and in which cases a dose adjustment would no longer have any effect on efficacy. Esteban-Ballesteros *et al.,* 2017[19] showed that despite a frequency of 48.5–87.8% of SNP200 in *T. colubriformis* prior to treatment, a dose of 7.5 mg albendazole/kg bw achieved very high efficacy of nearly 100% in almost all groups. It is noted that the frequencies of resistant nematodes were higher after treatment compared to the frequencies before treatment, which is substantiated by Barrère *et al.,* 2012[18]. This is conclusive since at lower doses resistant nematodes being less susceptible will survive, whereas at higher doses these nematodes will be killed and almost only resistant nematodes survive the treatment (if they are present). As such, the frequency of resistant nematodes will be higher after the treatment than before, because only resistant nematodes are left. To prevent the development of a resistant population after such treatment, the dilution with a susceptible population is pivotal. Therefore, strategies for preserving susceptible parasites in refugia, e.g. through targeted selective treatment (TST) or pasture management strategies (e.g. move and then dose), are used to achieve a true dilution effect with resistant nematodes after treatment and susceptible nematodes from pasture and are regarded as a key measure for slowing the development of resistance. The refugia population is the proportion of the total population that is unexposed to anthelmintic treatment. These may be larvae on pasture and/or worms in untreated animals. Therefore, if there is an increased risk of resistance, the highest possible dose should be used to achieve the most effective treatment for the animals being treated, together with strategies such TST and pasture management. This was also demonstrated by Dărăbuș *et al.,* 2021[35] in Western Romania, where an increased resistance in the geographical area was reported. Even though the resistance on farm level was not described in detail, the increased dose of 7.5 mg albendazole/kg bw was sufficiently effective. Babják *et al.,* 2023[36] showed that if resistance has reached a certain level, a dose adjustment was without any effect. In his study, the high level of resistance was confirmed by in vitro data from egg hatched test and larval development test, whereby at all tested doses of thiabendazole, both the eggs hatched (more than 90% mean hatching at the cut-off concentration of 0.05 µg/ml thiabendazole) and the larvae developed to the L3 larval stage (approximately 50% of the larvae at threshold concentration of 0.08 µg/ml thiabendazole). Additionally, a multidrug resistance was confirmed and demonstrated also insufficient efficacy against ivermectin. In this special case, the use of levamisole, which had never been administered before, showed an efficacy of 100%. This scenario illustrates, on the one hand, the consequences of decades of too frequent uses of a certain class of anthelmintics and, on the other hand, that the only solution to overcome resistance is administration of an active substance of a class which has a different mode of action and that has ideally not yet been used.

[36] Babják M, Königová A, Komáromyová M, Kuzmina T, Nosal P, Várady M. Multidrug resistance in Haemonchus contortus in sheep - can it be overcome? J Vet Res. 2023 Dec 19;67(4):575-581.

Overall CVMP summary on efficacy/resistance and recommended dosage

The development of resistance is a complex process influenced by many factors. For this reason, managing the risk of resistance involves a range of interrelated measures and it is comprehensible why implementing only one measure is unlikely to be successful.

Among the generally known control measures, the key factors in delaying the development of resistance include preventing underdosing, keeping susceptible populations in refugia, parasitological monitoring if treatment is necessary, assessment of treatment success, and the use of highly effective anthelmintic treatment. Due to the well-known global problem of resistance to benzimidazoles in small ruminants, this referral procedure was initiated to assess whether the authorised doses or lower dose limits of 3.75 – 5 mg of albendazole per kg bw continue to achieve sufficient efficacy in field populations of gastrointestinal nematodes in sheep in Europe, or whether an increased dose may be required to provide adequate efficacy.

Several reports published across Europe have demonstrated insufficient efficacy against GIT nematodes after the administration of 3.75 – 3.8 or 5 mg albendazole/kg bw in sheep, and indicated resistant field populations. Within this referral procedure, the references provided by the MAHs were assessed, and an independent literature search was performed by the CVMP to determine the available evidence on whether higher doses of albendazole could be beneficial in terms of efficacy under current field conditions without compromising tolerability in sheep.

In conclusion, based on the assessment of the available data, the evidence supported the need for an adjustment of the albendazole dose for the treatment of gastrointestinal nematodes in sheep. As reports after the administration of doses of 7.5 mg albendazole/kg bw or higher are rare, no definite picture could be derived from the published reports. However, it could be observed that administration of doses of 3.75 – 5 mg albendazole/kg bw has led to insufficient efficacy in numerous cases. Resistance to albendazole could be a contributing cause of reduced efficacy. Multiple reports demonstrate reduced efficacy at these lower doses, confirming that resistance has become a significant and persistent issue in many regions.

Furthermore, the administration of higher doses of albendazole results in higher C_{max} and also in a higher reduction rate of GIT nematodes. A dose confirmation study conducted by one of the concerned MAHs showed that higher doses (7.6 mg albendazole/kg bw) were sufficiently effective against resistant strains whereas the conventional dose did not achieve sufficient effect. Except for cases involving very advanced multidrug resistance, such as those described by Babják *et al.,* (2023)[36], there was no evidence of treatment failures after the administration of 7.5 mg albendazole/kg bw. Furthermore, 7.5 mg/kg bw is also the established dose in the US for the treatment of GIT nematodes in sheep and the studies of Esteban-Ballesteros (2017)[19] and Dărăbuș (2021)[35] demonstrated efficacy close to 100% in Europe at this dose, despite reported presence of resistant nematodes in the former study. No reports have been identified demonstrating a lack of efficacy after administration of 7.5 mg albendazole/kg bw or higher doses and currently no other concerns, such as reduced target animal tolerance, would preclude the use of a dose of 7.5 mg/kg bw. Therefore, in accordance with parasitological principles for managing the risk of developing anthelmintic resistance, the maximum effective dose, which is defined as the dose above which no efficacy improvement is suspected and/or obtained, should be used. Although data of Barrère *et al.,* 2012[18] showed that increased doses of albendazole administered intraruminally selectively enrich *H. contortus* resistant genotypes, these data should be interpreted with caution due to 94% efficacy after treatment with 45 mg albendazole per kg bw and thus limited number of nematodes for genotyping, which is stated by the authors themselves. Moreover, the results of Leathwick and Luo (2017)[29] showed that the use of lower doses with high

variability has a greater impact on resistance development on the genetic level in comparison to higher doses with low variability.

Therefore, to minimise the risk of developing resistance to albendazole and to ensure maximum efficacy, the CVMP recommended a dose of 7.5 mg albendazole/kg bw for the treatment of GIT nematodes in sheep. This adjustment optimises efficacy without compromising safety, and it aligns with best parasitological practices for delaying the development of anthelmintic resistance.

In addition, the data further emphasised that dose adjustment alone is not sufficient to control resistance in the long term. Sustainable parasite management must incorporate additional strategies, including the prevention of underdosing, maintenance of refugia, targeted selective treatment, and routine parasitological monitoring. These measures are essential to slow the selection and spread of resistant nematode populations. Hence, the CVMP also proposed to amend the product information (Summary of Product Characteristics, labelling and package leaflet) of the VMPs falling within the scope of this referral procedure accordingly, to include information in line with the CVMP guideline on the summary of product characteristics for antiparasitic VMPs (EMA/CVMP/EWP/170208/2005-Rev.1)[37].

For further details on the CVMP proposed changes in SPC section *3.4 Special warnings (QRD template v9.1) / 4.4 Special warnings for each target species (QRD template v8.2)* and SPC section *3.9 Administration routes and dosage (QRD template v9.1) / 4.9 Amounts to be administered and administration route (QRD template v8.2)*, see Annex III.

Withdrawal period

The residue depletion studies submitted for the albendazole-containing VMPs concerned by this referral procedure showed considerable heterogeneity in terms of study quality, administered doses (7.5, 10, 15, 16, 16.2 mg albendazole/kg bw), study design, and analytical test methods used. In addition, the results and the conclusions drawn from the data regarding the establishment of withdrawal periods are heterogeneous. With the exception of three residue depletion studies in edible tissues and one study in milk (for which only a summary was provided), the majority of the submitted studies do not comply with current regulatory guidelines (e.g. VICH GL48 and 49). In particular, deviations were observed in key aspects of study design (number of animals, sampling time points, body weights, etc.) and the analytical test methods used. Furthermore, detailed residue depletion studies were not submitted for all concerned VMPs and, in some cases, only summaries or publications were provided lacking the essential information for assessment. In some of the cases, the residue data provided were predominantly below the limit of quantification or detection (LOQ/LOD), precluding the statistical analysis of withdrawal periods.

The evaluation of residue data submitted by the MAHs yielded no additional insights into withdrawal periods within existing marketing authorisations. The data available did not suggest that the authorised withdrawal periods pose a risk to consumer safety.

The residue data provided by the MAHs were requested and assessed by the CVMP in the context of this referral, in anticipation of a potential recommendation of a new dosage regimen. However, since the dose recommended by the CVMP for the treatment of GIT nematodes is already authorised for a different indication in all the concerned VMPs (i.e. no previously unauthorised dose has been recommended), the CVMP concluded that the recommended dose is therefore not expected to give rise to additional concerns regarding consumer safety or necessitate changes to the established withdrawal periods.

[37] Guideline on the summary of product characteristics for antiparasitic veterinary medicinal products (EMA/CVMP/EWP/170208/2005-Rev.1 Corr.1) - link

Target animal safety

A large data set on target animal safety in sheep was submitted by the concerned MAHs. One MAH provided proprietary data and the CVMP summary report 2004 – Albendazole (extrapolation to all ruminants), and another MAH referred to published literature and provided a comprehensive summary addressing potential target animal safety concerns.

Available target animal safety studies cover single administrations of albendazole at doses up to 500 mg/kg bw. A single administration of albendazole at doses of up to 37.5 mg/kg bw in sheep was well tolerated. Even at overdose levels of 100 mg/kg bw, albendazole was well tolerated, with no gross pathological abnormalities or histopathological changes reported. However, higher doses of 200 or 500 mg/kg bw seemed to exceed the albendazole margin of safety (observed mortalities of up to 100%).

Reproductive safety was investigated in three studies (summaries only provided), in which ewes were treated with doses up to 15 mg/kg bw. In two of these studies, no abnormalities occurred in lambs and no differences in lambing rates compared to the untreated control group were described. However, in one of these studies, ewes were treated at different stages during pregnancy with some rare adverse events including congenital abnormalities and a higher incidence of stillborn lambs.

Additionally, developmental studies in sheep also observed malformations, including visceral, craniofacial and bone defects (CVMP summary report, 2004). However, albendazole VMPs include a corresponding contraindication stating that albendazole must not be used in pregnant animals, so this aspect has been adequately addressed. The fertility of rams was also investigated with an albendazole dose of up to 15 mg/kg bw, with no effects on semen quality observed (fertility study in rams, 1977).

In an additional target animal safety study, two groups of six 9-month-old sheep received 3 times the recommended dose of 7.5 mg/kg bw and the other received 5 times the recommended dose (22.5 and 37.5 mg/kg bw, respectively) of an albendazole-containing VMP. No side effects or adverse reactions were reported after examination at 2, 4, 6, 12, 24, 48, 72, 96 and 120 hours post treatment (summary provided only).

Although the available tolerance studies in the target species are dated, exponentially higher doses than those authorised have been investigated and have not shown signs of intolerance. This demonstrates a wide margin of safety, which is attributed to the greater selective affinity of albendazole for parasitic beta tubulin than for mammalian beta tubulin.

Overall, the CVMP concluded that the recommendation of a dose of 7.5 mg/kg bw for use in the target animal species sheep does not pose any concern with regard to target animal safety. This conclusion is further supported by the fact that a dose of 7.5 mg/kg bw is already authorised for the treatment of *Fasciola hepatica* in sheep for all the VMPs concerned by this referral procedure.

User Safety

No toxicological studies addressing user safety nor a revised user risk assessment were submitted by the MAH, since this was not within the scope of the questions asked by the CVMP in this referral procedure. However, the safety aspects to be considered as part of the benefit-risk assessment for veterinary medicinal products include user safety.

Given that the recommended dose of 7.5 mg albendazole/kg bw in sheep for GIT nematodes is already authorised for all VMPs concerned by this referral procedure for a different indication (i.e. for the treatment of liver flukes in sheep), user safety has already been evaluated and is covered by existing product authorisations. Therefore, no additional concerns regarding user safety are expected in connection with an increased dose to 7.5 mg/kg bw for the treatment of GIT nematodes.

Environmental safety

Responses from three MAHs were received submitting an ERA with respective studies and references. The submitted data were evaluated by the CVMP in terms of scientific validity and regulatory suitability regarding study and ERA requirements according to current guidelines. Therefore, only data from reliable and valid studies meeting those criteria were used in the CVMP assessment.

Considering the data provided by the MAHs, no risk for the aquatic environment was identified, however, a risk for the terrestrial environment and specifically for dung fauna could be identified based on the use of albendazole in sheep according to the dosage regimen recommended in this procedure (7.5 mg/kg bw, single dose).

The ERA data provided by the MAHs were assessed by the CVMP as it was requested in the context of this referral in the event that a new dose were to be recommended by the Committee. Nevertheless, since the dose recommended by the CVMP for GIT indications is already authorised in all the concerned VMPs for a different indication (i.e. no previously unauthorised dose has been recommended), the CVMP did not further consider the ERA data within this referral procedure and concluded that no new environmental risks, beyond those already known, have been identified for the proposed dose.

Benefit-risk balance

Direct therapeutic benefit

Albendazole is a well-established, broad-spectrum anthelmintic agent belonging to the benzimidazoles. Its mode of action is well characterised and involves selective binding of ß-tubulin in susceptible helminths, leading to disruption of microtubule formation, impaired glucose uptake, energy depletion, and parasite death.

It is used to treat a variety of intestinal parasitic infections, including gastrointestinal infections with roundworms, lungworms, tapeworms and treatment of adult liver flukes.

Veterinary medicinal products containing albendazole within the scope of this referral have been used for decades in sheep to effectively treat a wide range of gastrointestinal nematodes infections.

Additional benefits

Veterinary medicinal products containing albendazole are well-tolerated, causing no serious systemic adverse events in the target animal species sheep.

Risk assessment

Quality was not within the scope of this referral procedure and therefore was not specifically assessed.

For the veterinary medicinal products involved in this referral procedure, a risk has been identified indicating an inappropriate dosage regimen, i.e. too low doses related to their indication against gastrointestinal nematodes.

The risk of an inappropriate dosage regimen is interconnected with an increased risk of anthelmintic resistance development. Anthelmintic resistance to albendazole is well described.

Overall, based on the available data, the adjustment of the dose to 7.5 mg albendazole/kg bw in the target animal species sheep for the treatment of gastrointestinal nematodes due to resistance concerns, is not expected to have any impact for the safety of the target animals, user safety,

consumer safety nor introduce any new environmental safety concerns. This conclusion is further supported by the fact that a dose of 7.5 mg albendazole/kg bw is already authorised in all concerned VMPs for another indication, i.e., for the treatment of *Fasciola hepatica* in sheep.

Risk management or mitigation measures

By adjusting the dose to 7.5 mg albendazole per kg bw in sheep for the treatment of gastrointestinal nematodes, the risks related to lack of efficacy are reduced and the development of anthelmintic resistance is considered to be delayed.

Further risk management measures are the inclusion of warnings in the product information to state additional strategies, including the prevention of underdosing, maintenance of refugia, targeted selective treatment, and routine parasitological monitoring. These measures are essential to slow the selection and spread of resistant nematode populations.

Moreover, given that the recommended dose of 7.5 mg albendazole/kg bw is already authorised in all concerned VMPs for another indication, no further risk mitigation measures with regard to consumer safety, target animal safety, user safety or environmental safety were considered necessary.

Any risk mitigation measures already existing in the product information of the concerned veterinary medicinal products will remain.

Evaluation of the overall benefit-risk balance

Veterinary medicinal products containing albendazole as a single active substance presented as oral suspension are considered to be effective against various parasites in the target animal species sheep.

Albendazole is a broad-spectrum anthelmintic agent belonging to the benzimidazoles. As with any other anthelmintic, albendazole should be used prudently and only when medically needed. Moreover, any unnecessary use, overly long treatment periods, and underdosing should be avoided.

Overall, following the assessment of all available data, the CVMP concluded that, under current European field conditions, the authorised albendazole doses or lower dose limits of 3.75–5.0 mg/kg bw for the treatment of gastrointestinal nematodes in sheep no longer ensure consistent and reliable efficacy and may contribute to further resistance development to albendazole. Consequently, an adjustment of the dose to 7.5 mg albendazole/kg bw is considered necessary to ensure effective treatment for the above-mentioned indication, and to contribute to delaying the anthelmintic resistance development.

In addition, the inclusion of appropriate warnings in the product information is recommended as a complementary risk management measure to further mitigate the emergence and spread of resistant nematode populations.

The recommended dose of 7.5 mg albendazole/kg bw is already authorised for another indication in all concerned VMPs, and no new risks were identified with regard to target animal safety, consumer safety, user safety or environmental protection.

Conclusion on the benefit-risk balance

Having considered the grounds for the referral procedure and the available data, including those provided by the MAHs, the CVMP concluded that for the veterinary medicinal products concerned, the overall benefit-risk balance remains positive, subject to the recommended changes in the product information (see Annex III).

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

Whereas

- The CVMP considered the referral procedure under Article 82 of Regulation (EU) 2019/6 for veterinary medicinal products containing albendazole as a single active substance presented as oral suspension with doses or lower dose limits of 3.75-5 mg albendazole per kg bodyweight (bw) to ensure adequate efficacy against gastrointestinal nematodes in sheep while limiting the risk of development of resistance to albendazole.
- The CVMP reviewed the available data in support of the dosage regimen, residue depletion, environmental risk, target animal safety, and risk to antiparasitic resistance.
- The CVMP noted that veterinary medicinal products containing albendazole as a single active substance presented as oral suspension for sheep have been authorised for decades.
- The CVMP considered that albendazole is a broad-spectrum anthelmintic substance of the benzimidazole class. Veterinary medicinal products containing albendazole have been widely used for decades in cattle, sheep, goats, pigs, rabbits, birds, dogs and cats. In ruminants, and in particular in sheep, albendazole-containing VMPs are used for the treatment of gastrointestinal (GIT) nematodes, lungworms, tapeworms and adult liver flukes. However, emerging benzimidazole resistance has been reported throughout Europe for GIT nematodes in sheep.
- The CVMP considered which dosage regimen (dose rate, dosing interval and duration of treatment) would be appropriate for VMPs with doses or lower dose limits of 3.75-5 mg albendazole/kg bodyweight (bw), in order to ensure adequate efficacy against gastrointestinal nematodes in sheep while limiting the risk of developing albendazole resistance.
- In view of the above considerations and based on the available data, the CVMP concluded that the doses of the concerned veterinary medicinal products need to be revised.
- In order to minimise the risk of developing resistance to albendazole and to ensure maximum efficacy, the CVMP recommended a dose of 7.5 mg albendazole/kg bw for the treatment of gastrointestinal nematodes in sheep. This adjustment optimises efficacy without compromising safety, and it aligns with best parasitological practices for delaying the development of anthelmintic resistance.
- The adjustment of the dose to 7.5 mg albendazole/kg bw in the target animal species sheep for the treatment of gastrointestinal nematodes due to resistance concerns is not expected to have any impact on the safety of the target animals, users, consumers nor introduce any new environmental safety concerns. This conclusion is further supported by the fact that a dose of 7.5 mg albendazole/kg bw is already authorised in all concerned VMPs for other indication, i.e., for the treatment of *Fasciola hepatica* in sheep.
- The CVMP considered it beneficial to include additional information in the product information, i.e., appropriate warnings as a complementary risk management measure to further mitigate the emergence and spread of resistant nematode populations.

CVMP opinion

The CVMP, as a consequence, considers that the benefit-risk balance of veterinary medicinal products containing albendazole as a single active substance presented as oral suspension for sheep remains favourable subject to the amendments to the product information as described in Annex III.

Therefore, the CVMP recommends the variation to the terms of the marketing authorisations for veterinary medicinal products containing albendazole as a single active substance presented as oral suspension for sheep.

Annex III

Amendments to relevant sections of the product information

Note:

These amendments to the relevant sections of the product information are the outcome of the referral procedure.

Amendments to relevant sections of the product information

The existing product information shall be amended (insertion, replacement or deletion of the text as appropriate) to reflect the agreed wording as provided below.

A. Summary of Product Characteristics

3.4 Special warnings (QRD template v9.1) **/ 4.4 Special warnings for each target species** (QRD template v8.2)

Add the following advice to all veterinary medicinal products and replace existing outdated wording (where applicable) with this text:

Unnecessary use of antiparasitic veterinary medicinal products may increase the resistance selection pressure and lead to reduced efficacy. The decision to use the veterinary medicinal product should be based on confirmation of the parasitic species and burden, or of the risk of infection based on its epidemiological features, for each herd/flock.

Repeated use for an extended period, particularly when using the same class of substances, increases the risk of resistance development. Within a herd/flock, maintenance of susceptible refugia is essential to reduce that risk. Systematically applied interval-based treatment and treatment of a whole herd/flock should be avoided. Instead, if feasible, only selected individual animals or subgroups should be treated (targeted selective treatment). This should be combined with appropriate husbandry and pasture management measures. Guidance for each specific herd/flock should be sought from the responsible veterinarian.

Resistance to benzimidazoles (which includes albendazole) has been reported in *Haemonchus contortus*, *Teladorsagia circumcincta*, *Cooperia curticei* and *Trichostrongylus* spp. in small ruminants across Europe. Multidrug resistance to benzimidazoles, imidazothiazoles and macrocyclic lactones has been reported in *H. contortus*, as well as side-resistance to all benzimidazoles.

The use of this veterinary medicinal product should take into account local information about susceptibility of the target parasites, where available.

It is recommended to further investigate cases of suspected resistance, using an appropriate diagnostic method (e.g. Faecal Egg Count Reduction Test).

Confirmed resistance should be reported to the marketing authorisation holder or to the competent authorities.

3.9 Administration routes and dosage (QRD template v9.1) **/ 4.9 Amounts to be administered and administration route** (QRD template v8.2)

Replace, in all veterinary medicinal products, the current dosage regimen for the treatment of gastrointestinal nematodes in sheep, with the following wording:

Sheep:

Gastrointestinal nematodes: 7.5 mg albendazole per kg bodyweight in a single treatment.

In case specific types of nematodes are detailed in the product information of certain veterinary medicinal products, these should be maintained.

Specific dosage regimen recommendations for liver flukes and lungworms should be maintained, where applicable.

Add the following advice to all veterinary medicinal products and replace existing outdated wording (where applicable) with this text:

Underdosing could result in ineffective use and may favour resistance development.

To ensure a correct dosage, body weight should be determined as accurately as possible.

Accuracy of the dosing device should be thoroughly checked.

C. Package Leaflet

6. Special warnings (QRD template v9.0) **/ 12. SPECIAL WARNING(S)** (QRD template v8.2)

Special warnings: (QRD template v9.0) / Special warnings for each target species: (QRD template v8.2)

Add the following advice to all veterinary medicinal products and replace existing outdated wording (where applicable) with this text:

Unnecessary use of antiparasitic veterinary medicinal products may increase the resistance selection pressure and lead to reduced efficacy. The decision to use the veterinary medicinal product should be based on confirmation of the parasitic species and burden, or of the risk of infection based on its epidemiological features, for each herd/flock.

Repeated use for an extended period, particularly when using the same class of substances, increases the risk of resistance development. Within a herd/flock, maintenance of susceptible refugia is essential to reduce that risk. Systematically applied interval-based treatment and treatment of a whole herd/flock should be avoided. Instead, if feasible, only selected individual animals or subgroups should be treated (targeted selective treatment). This should be combined with appropriate husbandry and pasture management measures. Guidance for each specific herd/flock should be sought from the responsible veterinarian.

Resistance to benzimidazoles (which includes albendazole) has been reported in *Haemonchus contortus*, *Teladorsagia circumcincta*, *Cooperia curticei* and *Trichostrongylus* spp. in small ruminants across Europe. Multidrug resistance to benzimidazoles, imidazothiazoles and macrocyclic lactones has been reported in *H. contortus*, as well as side-resistance to all benzimidazoles.

The use of this veterinary medicinal product should take into account local information about susceptibility of the target parasites, where available.

It is recommended to further investigate cases of suspected resistance, using an appropriate diagnostic method (e.g. Faecal Egg Count Reduction Test).

Confirmed resistance should be reported to the marketing authorisation holder or to the competent authorities.

8. Dosage for each species, routes and method of administration (QRD template v9.0) **/ 8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION** (QRD template v8.2)

Replace, in all veterinary medicinal products, the current dosage regimen for the treatment of gastrointestinal nematodes in sheep, with the following wording:

Sheep:

Gastrointestinal nematodes: 7.5 mg albendazole per kg bodyweight in a single treatment.

In case specific types of nematodes are detailed in the product information of certain veterinary medicinal products, these should be maintained.

Specific dosage regimen recommendations for liver flukes and lungworms should be maintained, where applicable.

Add the following advice to all veterinary medicinal products and replace existing outdated wording (where applicable) with this text:

Underdosing could result in ineffective use and may favour resistance development.

To ensure a correct dosage, body weight should be determined as accurately as possible.

Accuracy of the dosing device should be thoroughly checked.