Annex I

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

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Austria	Elanco GmbH Heinz-Lohmann-Straße 4 27472 Cuxhaven Germany	Denagard 100 mg/g - Arzneimittelvormischung zur Herstellung von Fütterungsarzneimitteln für Schweine, Geflügel und Kaninchen	Tiamulin (as hydrogen fumarate)	100 mg/g	Premix for medicated feeding stuff	Pigs, chickens, rabbits	Oral
Austria	Elanco GmbH Heinz-Lohmann-Straße 4 27472 Cuxhaven Germany	Denagard 20 mg/g - Arzneimittelvormischung zur Herstellung von Fütterungsarzneimitteln für Schweine, Geflügel und Kaninchen	Tiamulin (as hydrogen fumarate)	20 mg/g	Premix for medicated feeding stuff	Pigs, chickens, rabbits	Oral
Austria	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Vetmulin 100 g/kg Arzneimittel-Vormischung zur Herstellung von Fütterungsarzneimitteln für Schweine, Hühner, Puten und Kaninchen	Tiamulin (as hydrogen fumarate)	100 g/kg	Premix for medicated feeding stuff	Pigs, chickens, turkeys, rabbits	Oral
Belgium	V.M.D. n.v. Hoge Mauw 900 B-2370 Arendonk Belgium	Tiamutin 10%	Tiamulin (as hydrogen fumarate)	100 mg/g	Premix for medicated feeding stuff	Pigs, chickens, turkeys, rabbits	Oral
Belgium	V.M.D. n.v. Hoge Mauw 900 B-2370 Arendonk Belgium	Tiamutin 10% Pulvis	Tiamulin (as hydrogen fumarate)	100 mg/g	Oral powder	Pigs	Oral

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Belgium	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Vetmulin 20 g/kg Premix	Tiamulin (as hydrogen fumarate)	20 g/kg	Premix for medicated feeding stuff	Pigs, chickens, turkeys, rabbits	Oral
Belgium	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Vetmulin 100 g/kg	Tiamulin (as hydrogen fumarate)	100 mg/g	Premix for medicated feeding stuff	Pigs, chickens, turkeys, rabbits	Oral
Bulgaria	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Ветмулин 20 g/kg премикс за медикаментозен фураж	Tiamulin (as hydrogen fumarate)	20 g/kg	Premix for medicated feeding stuff	Pigs, chickens, turkeys, rabbits	Oral
Bulgaria	Farma SIS Ltd., ul.”San Stefano” №6b, et.1, of. 3, Dobrich Bulgaria	НЕУМУТИЛ 10% ПРЕМИКС	Tiamulin (as hydrogen fumarate)	100 g/1000 g	Premix for medicated feeding stuff	Pigs, chickens	Oral
Bulgaria	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Ветмулин 100 g/kg премикс за медикаментозен фураж	Tiamulin (as hydrogen fumarate)	100 g/kg	Premix for medicated feeding stuff	Pigs, chickens, turkeys, rabbits	Oral
Cyprus	Vitatrace Nutrition LTD Οδός Προποντίδος 17, Βιομηχανική Περιοχή Στροβόλου, 2033 Nicosia Cyprus	CM2609 ΦΟΥΜΑΡΙΚΗ ΤΙΑΜΟΥΛΙΝΗ 10%, φαρμακούχο πρόμιγμα για χοίρους	Tiamulin (as hydrogen fumarate)	100 g/kg	Medicated premix	Pigs	Oral

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Cyprus	Dox-al Italia S.p.A. Piazzale Cadorna 10 20123 Milano Italy	COLINDOX 100, 100 mg/g - premix for medicated feed for swine	Tiamulin (as hydrogen fumarate)	100 mg/g	Medicated premix	Pigs	Oral
Cyprus	Elanco GmbH Heinz-Lohmann-Str. 4 27472 Cuxhaven Germany	DENAGARD Πρόμιγμα για φαρμακούχο τροφή για χοίρους, όρνιθες, ινδόρνιθες και κουνέλια	Tiamulin (as hydrogen fumarate)	100 mg/g	Medicated premix	Pigs, chickens, turkeys, rabbits	Oral
Czech Republic	Elanco GmbH Heinz-Lohmann-Str. 4 27472 Cuxhaven Germany	Denagard 100 mg/g perorální prášek	Tiamulin (as hydrogen fumarate)	100 mg/g	Oral powder	Pigs, chickens, turkeys	Oral
Czech Republic	Elanco GmbH Heinz-Lohmann-Str. 4 27472 Cuxhaven Germany	Denagard 100 mg/g premix pro medikaci krmiva pro prasata, drůbež a králíky	Tiamulin (as hydrogen fumarate)	100 mg/g	Premix for medicated feeding stuff	Pigs, chickens, turkeys, rabbits	Oral
Czech Republic	Ceva Animal Health Slovakia, s.r.o., Prievozská 5434/6A, 821 09 Bratislava - mestská časť Ružinov, Slovak Republic	TIAMVET 100 mg/g premix pro medikaci krmiva pro prasata	Tiamulin (as hydrogen fumarate)	100 mg/g	Premix for medicated feeding stuff	Pigs	Oral
Czech Republic	Univit s.r.o., Na Vlčinci 16/3, 779 00 Olomouc Czech Republic	UNI-TIAMULIN 10% perorální prášek	Tiamulin (as hydrogen fumarate)	100 mg/g	Oral powder for use in medicated feeding stuff	Pigs, chickens, turkeys	Oral

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Czech Republic	Univit s.r.o., Na Vlčinci 16/3, 779 00 Olomouc Czech Republic	UNI-TIAMULIN 2% premix pro medikaci krmiva	Tiamulin (as hydrogen fumarate)	20 mg/g	Premix for medicated feeding stuff	Pigs, chickens, turkeys	Oral
Czech Republic	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Vetmulin 100 g/kg premix pro medikaci krmiva pro prasata, kura domácího, krůty a králíky	Tiamulin (as hydrogen fumarate)	100 g/kg	Premix for medicated feeding stuff	Pigs, chickens, turkeys, rabbits	Oral
Denmark	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Vetmulin	Tiamulin (as hydrogen fumarate)	100 mg/g	Premix for medicated feeding stuff	Pigs, chickens, turkeys, rabbits	Oral
Finland	Elanco GmbH Heinz-Lohmann-Str. 4 27472 Cuxhaven Germany	Denagard vet 20 mg/g jauhe, sioille	Tiamulin (as hydrogen fumarate)	20 mg/g	Oral powder	Pigs	Oral
France	Ceva Sante Animale 10 Avenue de la Ballastiere, Libourne 33500 France	Tiamuval premelange medicamenteux Tiamuline 6,5 enterite porc enterocolite lapin	Tiamulin (as hydrogen fumarate)	6.5 mg/g	Premix for medicated feeding stuff	Pigs, rabbits	Oral
France	Huvepharma SA 34 Rue Jean Monnet, Zone Industrielle D'etriche, Segre, Segre-en-Anjou Bleu 49500 France	Tiamuline 6,5 enterite porc enterocolite lapin franvet	Tiamulin (as hydrogen fumarate)	6.5 mg/g	Premix for medicated feeding stuff	Pigs, rabbits	Oral

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
France	Huvepharma Uitbreidingstraat 80 2600 Antwerpen Belgium	Vetmulin 16,2 mg/g premelange medicamenteux pour porcs, poulets, dindes et lapins	Tiamulin (as hydrogen fumarate)	16.2 mg/g	Premix for medicated feeding stuff	Pigs, chickens, turkeys, rabbits	Oral
France	Huvepharma Uitbreidingstraat 80 2600 Antwerpen Belgium	Vetmulin 81 mg/g premelange medicamenteux pour porcs, poulets, dindes et lapins	Tiamulin (as hydrogen fumarate)	81 mg/g	Premix for medicated feeding stuff	Pigs, chickens, turkeys, rabbits	Oral
Germany	Elanco GmbH Heinz-Lohmann-Straße 4 27472 Cuxhaven Germany	Denagard 10% oral, Pulver zum Eingeben über das Futter für Schweine	Tiamulin (as hydrogen fumarate)	100 mg/g	Powder	Pigs	Oral
Germany	Serumwerk Bernburg AG Hallesche Landstr. 105b 06406 Bernburg Germany	Ursomutin 25% Granulat	Tiamulin (as hydrogen fumarate)	250 mg/g	Granules	Pigs, chickens, turkeys	Oral
Germany	Elanco GmbH Heinz-Lohmann-Straße 4 27472 Cuxhaven Germany	Denagard 10% AMV Arzneimittel-Vormischung zur Herstellung von Fütterungsarzneimitteln für Schweine, Geflügel und Kaninchen	Tiamulin (as hydrogen fumarate)	100 mg/g	Premix for medicated feed	Pigs, chickens, turkeys, rabbits	Oral
Greece	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Vetmulin 10% PREMIX, Πρόμιγμα υπό μορφής σκόνης για φαρμακούχο τροφή 10%	Tiamulin (as hydrogen fumarate)	100 mg/g	Premix for medicated feed	Pigs, chickens, turkeys, rabbits	Oral

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Greece	Elanco GmbH Heinz-Lohmann-Straße 4 27472 Cuxhaven Germany	Denagard Πρόμιγμα για φαρμακούχο τροφή 10%	Tiamulin (as hydrogen fumarate)	100 mg/g	Premix for medicated feed	Pigs, chickens, turkeys, rabbits	Oral
Hungary	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Vetmulin 100 g/kg gyógypremix sertések számára A.U.V.	Tiamulin (as hydrogen fumarate)	100 mg/g	Premix for medicated feeding stuff	Pigs, chickens, turkeys, rabbits	Oral
Ireland	Huvepharma N.V. Uitbreidingstraat 80 2600 Antwerpen Belgium	Vetmulin 100 g/kg premix for medicated feeding stuff for pigs, chickens, turkeys and rabbits	Tiamulin (as hydrogen fumarate)	100 g/kg	Premix for medicated feeding stuff	Pigs, chickens, turkeys, rabbits	Oral
Ireland	Huvepharma N.V. Uitbreidingstraat 80 2600 Antwerpen Belgium	Vetmulin 20 g/kg premix for medicated feeding stuff for pigs, chickens, turkeys and rabbits	Tiamulin (as hydrogen fumarate)	20 g/kg	Premix for medicated feeding stuff	Pigs, chickens, turkeys, rabbits	Oral
Italy	Elanco GmbH Heinz-Lohmann-Str. 4 27472 Cuxhaven Germany	Denagard 10% premix plus	Tiamulin (as hydrogen fumarate)	100 mg/g	Premix for medicated feeding stuff	Pigs, chickens, turkeys, rabbits	Oral
Italy	Ceva Salute Animale S.p.A. Viale Colleoni 15 20864 Agrate Brianza Italy	Tiamvet Plus	Tiamulin (as hydrogen fumarate)	100 mg/g	Premix for medicated feeding stuff	Pigs, rabbits	Oral

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Italy	Huvepharma N.V. Uitbreidingstraat 80 2600 Antwerpen Belgium	Vetmulin 100 g/kg	Tiamulin (as hydrogen fumarate)	100 g/kg	Premix for medicated feeding stuff	Pigs, chickens, turkeys, rabbits	Oral
Malta	Andres Pintaluba S.A. Poligono Industrial Agro-Reus C/ Prudenci Bertrana Nº 5 43206- Reus (Tarragona) Spain	Apsamix Tiamulina 100 mg/g	Tiamulin (as hydrogen fumarate)	100 mg/g	Premix for medicated feeding stuff	Pigs	Oral
The Netherlands	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Vetmulin 100 mg/g premix voor gemedicineerd voer voor varkens, kippen, kalkoenen en konijnen	Tiamulin (as hydrogen fumarate)	100 mg/g	Premix for medicated feeding stuff	Pigs, chickens, turkeys, rabbits	Oral
Poland	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Vetmulin 100 g/kg premiks do sporządzania paszy leczniczej dla świń, kur, indyków i królików	Tiamulin (as hydrogen fumarate)	100 g/kg	Premix for medicated feeding stuff	Pigs, chickens, turkeys, rabbits	Oral
Poland	Elanco GmbH Heinz-Lohmann Str. 4 27472 Cuxhaven Germany	Denagard, 100 mg/g, premiks do sporządzania paszy leczniczej dla świń, kur, indyków i królików	Tiamulin (as hydrogen fumarate)	100 mg/g	Premix for medicated feeding stuff	Pigs, chickens, turkeys, rabbits	Oral

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Portugal	Andres Pintaluba S.A. Poligono Industrial Agro-Reus C/ Prudenci Bertrana Nº 5 43206- Reus (Tarragona) Spain	Apsamix Tiamulina 100 mg/g Pré-mistura medicamentosa para suínos (porcos de engorda)	Tiamulin (as hydrogen fumarate)	100 mg/g	Premix for medicated feeding stuff	Pigs	Oral
Portugal	Calier Portugal, S.A. Centro Empresarial Sintra-Estoril II, Ed. C, R. Pé de Mouro Estrada de Albarraque 2710 - 335 Sintra Portugal	Caliermutin, 100 mg/g, pré-mistura para alimento medicamentoso para suínos	Tiamulin (as hydrogen fumarate)	100 mg/g	Premix for medicated feeding stuff as granulated powder	Pigs	Oral
Portugal	Calier Portugal, S.A. Centro Empresarial Sintra-Estoril II, Ed. C, R. Pé de Mouro Estrada de Albarraque 2710 - 335 Sintra Portugal	Caliermutin, 20 mg/g, pré-mistura para alimento medicamentoso para suínos e coelhos.	Tiamulin (as hydrogen fumarate)	20 mg/g	Premix for medicated feeding stuff as granulated powder	Pigs, rabbits	Oral
Portugal	Calier Portugal, S.A. Centro Empresarial Sintra-Estoril II, Ed. C, R. Pé de Mouro Estrada de Albarraque 2710 - 335 Sintra Portugal	Caliermutin, 800 mg/g, pré-mistura medicamentosa para alimento medicamentoso para suínos	Tiamulin (as hydrogen fumarate)	800 mg/g	Premix for medicated feeding stuff as granulated powder	Pigs	Oral

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Portugal	Representagro – Representaçoes LDA, Estrada da Lapa nº 1 2665-540 Venda do Pinheiro Portugal	Nemutin 10 % Premix - P 100 mg/g pré-mistura medicamentosa para alimento medicamentoso para suínos	Tiamulin (as hydrogen fumarate)	100 mg/g	Medicated premix for medicated food	Pigs	Oral
Portugal	Zoopan – Produtos Pecuários, S.A. Rua da Liberdade, 77 2050-023 Aveiras de Baixo Portugal	Tiamuloxi	Tiamulin (as hydrogen fumarate)	100 mg/g	Medicated premix for medicated food	Pigs	Oral
Portugal	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Vetmulin 100 g/kg Pré-mistura para alimento medicamentoso para suínos, galinhas, perus e coelhos	Tiamulin (as hydrogen fumarate)	100 mg/g	Premix for medicated feeding stuff	Pigs, chickens, turkeys, rabbits	Oral
Portugal	Vetlima - SOC. Distribuidora de prod. Agro-pecuarios, SA Centro Empresarial da Rainha, Lote 27 2050-501 Vila Nova da Rainha Portugal	Vetamulin 100 g/kg pré-mistura medicamentosa para alimento medicamentoso para suínos de engorda e frangos de carne	Tiamulin (as hydrogen fumarate)	100 g/kg	Medicated premix for medicated food	Pigs, chickens	Oral
Portugal	Elanco GmbH Heinz-Lohmann Str.4, 27472 Cuxhaven Germany	Denagard 100 g/kg pré-mistura medicamentosa para alimento medicamentoso para suínos, galinhas, perus e coelhos	Tiamulin (as hydrogen fumarate)	100 g/kg	Medicated premix for medicated food	Pigs, chickens, turkeys, rabbits	Oral

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Romania	Lavet Phamaceuticals Ltd. Otto u 14 1161 Budapest Hungary	Lamulin 10%	Tiamulin (as hydrogen fumarate)	100 mg/g	Premix for medicated feeding stuff	Pigs	Oral
Romania	Pasteur - Filiala Filipestii de Padure SRL Str. Principala nr. 944, Filipestii de Padure, Jud. Prahova, Romania	Tiamulin FP 80%	Tiamulin (as hydrogen fumarate)	800 mg/g	Premix	Pigs, chickens	Oral
Romania	Huvepharma NV Uitbreidingstraat 80 2600 Antwerp Belgium	Vetmulin 100 g/kg	Tiamulin (as hydrogen fumarate)	100 mg/g	Premix for medicated feeding stuff	Pigs, chickens, turkeys, rabbits	Oral
Romania	Praxis Trading SRL str. Iancu Capitanu nr. 38, sector 2, Bucuresti Romania	Biomulin 800 mg/g	Tiamulin (as hydrogen fumarate)	800 mg/g	Premix	Pigs	Oral
Romania	Elanco GmbH Heinz-Lohmann-Str. 4, 27472 Cuxhaven Germany	Denagard 80% coated	Tiamulin (as hydrogen fumarate)	800 mg/g	Premix	Pigs, chickens, turkeys	Oral
Slovak Republic	Farmavet s.r.o., Sklabinská 20 036 01 Martin Slovak Republic	Tiafarm 20 mg/g premix na medikáciu krmiva	Tiamulin (as hydrogen fumarate)	20 mg/g	Premix for medicated feeding stuff	Pigs, chickens	Oral

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Slovak Republic	Ceva Animal Health Slovakia, s.r.o., Račianska 153, 831 53 Bratislava Slovak republic	Tiamvet 100 mg/g premix na medikáciu krmiva pre ošípané	Tiamulin (as hydrogen fumarate)	100 mg/g	Premix for medicated feeding stuff	Pigs	Oral
Spain	Andres Pintaluba S.A. Poligono Industrial Agro-Reus C/ Prudenci Bertrana 5 43206- Reus (Tarragona) Spain	Tiamumix 20 mg/g premezcla medicamentosa para porcino y conejos	Tiamulin (as hydrogen fumarate)	20 mg/g	Premix for medicated feeding stuff	Pigs, rabbits	Oral
Spain	Andres Pintaluba S.A. Poligono Industrial Agro-Reus C/ Prudenci Bertrana 5 43206- Reus (Tarragona) Spain	Apsamix Tiamulina 20 mg/g	Tiamulin (as hydrogen fumarate)	20 mg/g	Premix for medicated feeding stuff	Pigs	Oral
Spain	Laboratorios Calier S.A; Barcelones 26. Pla del Ramassa 0852 – Les Franqueses del Valles (Barcelona) Spain	Tiamulina Calier 100 mg/g Premezcla medicamentosa para cerdos	Tiamulin (as hydrogen fumarate)	100 mg/g	Premix for medicated feeding stuff	Pigs	Oral
Spain	Reidesen Pharma Services S.L. C/ Bruc 64 baixos local 3 08009 Barcelona Spain	Z-Mulin 20 g/kg Premezcla medicamentosa	Tiamulin (as hydrogen fumarate)	20 g/kg	Premix for medicated feeding stuff	Pigs, chickens, turkeys, rabbits	Oral

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Spain	Laboratorios Calier S.A; Barcelones 26. Pla del Ramassa 0852 – Les Franqueses del Valles (Barcelona) Spain	Caliermutin 20 mg/g Premezcla	Tiamulin (as hydrogen fumarate)	20 mg/g	Premix for medicated feeding stuff as granulated powder	Pigs, rabbits	Oral
Spain	Andres Pintaluba S.A. Poligono Industrial Agro-Reus C/ Prudenci Bertrana 5 43206- Reus (Tarragona) Spain	Tiamumix 100 mg/g Premezcla medicamentosa para porcino y conejos	Tiamulin (as hydrogen fumarate)	100 mg/g	Premix for medicated feeding stuff as fine white powder	Pigs, rabbits	Oral
Spain	Andres Pintaluba S.A. Poligono Industrial Agro-Reus C/ Prudenci Bertrana 5 43206- Reus (Tarragona) Spain	Apsamix Tiamulina 100 mg/g	Tiamulin (as hydrogen fumarate)	100 mg/g	Premix for medicated feeding stuff	Pigs	Oral
Spain	Elanco Spain SLU Avda. de Bruselas, 13 28108, Alcobendas Spain	Denagard 100 mg/g Premezcla medicamentosa	Tiamulin (as hydrogen fumarate)	100 mg/g	Premix for medicated feeding stuff	Pigs, chickens, turkeys, rabbits	Oral
Spain	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Vetmulin 100 g/kg Premezcla medicamentosa para porcino, pollos, pavos y conejos	Tiamulin (as hydrogen fumarate)	100 g/kg	Premix for medicated feeding stuff as granulated powder	Pigs, chickens, turkeys, rabbits	Oral

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Spain	S.P. Veterinaria, S. A.; Ctra. Reus – Vinyols, Km. 4,1 43330 Riudoms (Tarragona) Spain	Nemutin 100 mg/g Premix	Tiamulin (as hydrogen fumarate)	100 mg/g	Premix for medicated feeding stuff	Pigs	Oral
Spain	Laboratorios Calier S.A; Barcelones 26. Pla del Ramassa 0852 – Les Franqueses del Valles (Barcelona) Spain	Caliermutin 100 mg/g Premezcla medicamentosa para cerdos	Tiamulin (as hydrogen fumarate)	100 mg/g	Premix for medicated feeding stuff as granulated powder	Pigs	Oral
Spain	Elanco Spain SLU Avda. de Bruselas, 13 28108, Alcobendas Spain	Denagard 20 mg/g Premezcla medicamentosa	Tiamulin (as hydrogen fumarate)	20 mg/g	Premix for medicated feeding stuff	Pigs, chickens, turkeys, rabbits	Oral
Spain	Laboratorios Calier S.A; Barcelones 26. Pla del Ramassa 0852 – Les Franqueses del Valles (Barcelona) Spain	Caliermutin 800 mg/g Premezcla para porcino	Tiamulin (as hydrogen fumarate)	800 mg/g	Premix for medicated feeding stuff as granulated powder	Pigs	Oral
Spain	Cenavisa, S.L. Camí Pedra Estela s/n 43205 Reus Spain	Cenamutin 100 mg/g Premix	Tiamulin (as hydrogen fumarate)	100 mg/g	Premix for medicated feeding stuff	Pigs	Oral

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
United Kingdom	Elanco Europe Ltd Lilly House Priestley Road Basingstoke Hampshire RG24 9NL United Kingdom	Denagard 10% w/w premix for medicated feeding stuff for pigs, chickens, turkeys and rabbits	Tiamulin (as hydrogen fumarate)	100 mg/g	Premix for medicated feeding stuff	Pigs, chickens, turkeys, rabbits	Oral
United Kingdom	Elanco Europe Ltd Lilly House Priestley Road Basingstoke Hampshire RG24 9NL United Kingdom	Denagard 2% w/w premix for medicated feed for pigs, chickens, turkeys and rabbits	Tiamulin (as hydrogen fumarate)	20 mg/g	Premix for medicated feeding stuff	Pigs, chickens, turkeys, rabbits	Oral
United Kingdom	Elanco Europe Ltd Lilly House Priestley Road Basingstoke Hampshire RG24 9NL United Kingdom	Denagard 80% w/w premix for medicated feed for pigs, chickens and turkeys	Tiamulin (as hydrogen fumarate)	800 mg/g	Premix for medicated feeding stuff	Pigs, chickens, turkeys	Oral
United Kingdom	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Vetmulin 100 g/kg premix for medicated feeding stuff for pigs, chickens, turkeys and rabbits	Tiamulin (as hydrogen fumarate)	100 g/kg	Premix for medicated feeding stuff	Pigs, chickens, turkeys, rabbits	Oral

Annex II

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

Overall summary of the scientific evaluation of veterinary medicinal products containing tiamulin hydrogen fumarate presented as premix for medicated feeding stuff and oral powder for in-feed use to be administered to pigs (see Annex I)

1. Introduction

Tiamulin is a bacteriostatic semi-synthetic antibiotic belonging to the class of the pleuromutilins and it acts at the ribosomal level to inhibit bacterial protein synthesis. It is only used in veterinary medicine. Tiamulin has shown *in vitro* activity against porcine and avian *Mycoplasma* species as well as gram-positive aerobes (streptococci and staphylococci), anaerobes (clostridia), gram-negative anaerobes (*Brachyspira hyodysenteriae*, *Brachyspira pilosicoli),* and gram-negative aerobes (*Actinobacillus pleuropneumoniae* and *Pasteurella multocida*).

Tiamutin 10% Premix for medicated feeding stuff contains 100 mg/g tiamulin hydrogen fumarate and has been authorised in Belgium since 28 August 2006 and marketed by VMD NV. In 2010, the product was subject to a CVMP referral procedure (EMEA/V/A/042)[1] under Article 34 of Directive 2001/82/EC, as a result of which the following indication, and respective dosage regimen, in pigs was recommended:

"For the treatment and prevention, when the disease is present at herd level, of swine dysentery caused by *Brachyspira hyodysenteriae* susceptible to tiamulin. The presence of the disease in the herd should be established before use. *[…]*"

The dosage for the treatment is 5-10 mg tiamulin hydrogen fumarate (equivalent to 4.05-8.1 mg tiamulin base) per kg body weight (bw) daily administered for 7 to 10 consecutive days.

For prevention of swine dysentery caused by *B. hyodysenteriae* the dosage is 2 mg tiamulin hydrogen fumarate (equivalent to 1.62 mg tiamulin base) per kg bw daily administered for 2 to 4 weeks.

Vetmulin 100 g/kg premix for medicated feeding stuff was authorised via a decentralised procedure (BE/V/0020/001) with Belgium as the reference Member State. The application was submitted in accordance with Article 13(1) of Directive 2001/82/EC (generic application), citing Tiamutin 10% Premix for medicated feeding stuff as authorised in Belgium as the reference product.

For Vetmulin 100 g/kg premix for medicated feeding stuff as authorised in Belgium, the above-mentioned indication is for 'treatment and metaphylaxis' (the term 'prevention' as accepted for the reference product Tiamutin 10% premix has the meaning of the term 'metaphylaxis' in its current use).

In 2019, during the renewal procedure for the generic product Vetmulin 100 g/kg premix for medicated feeding stuff, Belgium identified an issue that would require reconsideration of the authorised dosage regimen for metaphylaxis (when not associated with treatment) of swine dysentery caused *B. hyodysenteriae* susceptible to tiamulin, i.e. the low dose with a long duration of administration (2 mg tiamulin hydrogen fumarate (equivalent to 1.62 mg tiamulin base) per kg bw daily administered for 2 to 4 weeks).

[1] Commission Decision concerning, in the framework of Article 34 of Directive 2001/82/EC of the European Parliament and of the Council, the marketing authorisations for all veterinary medicinal products containing "Tiamutin premix and associated names", veterinary medicinal products which contain the active substance "Tiamulin hydrogen fumarate" (C(2010)5372 of 27 July 2010) – link

According to recent scientific literature[2][3][4][5][6], the minimum inhibitory concentration (MIC) distribution of *B. hyodysenteriae* has changed since the first authorisation of the reference product and multi-resistant strains of *B. hyodysenteriae* have been reported. This put into question the adequacy of the recommended dosage regimen for the prevention or metaphylaxis (not associated with treatment) of swine dysentery caused by *B. hyodysenteriae.*

In addition, according to the CVMP Reflection paper on use of pleuromutilins (EMA/CVMP/AWP/119489/2012-Rev 1)[7], the *"duration of treatment should be limited to the time needed for cure of diseases".* In view of the widespread pleuromutilin resistance of *Brachyspira* spp, the long duration of administration for metaphylaxis or prevention (when not associated with treatment) and the very low dose, the risk of antimicrobial resistance selection was of concern.

Based on the above information, Belgium considered that the dosage regimen for prevention or metaphylaxis (when not associated with treatment) is no longer appropriate and may affect the benefit-risk balance of those products.

It was noted that across the EU Member States the aforementioned dosage regimen is also authorised for a number of veterinary medicinal products containing tiamulin hydrogen fumarate presented as premix for medicated feeding stuff and oral powder for in-feed use to be administered to pigs.

In view of the elements described above and the necessity to take action at EU level, Belgium considered that the matter should be referred to the CVMP in the interest of protecting animal health in the Union.

The CVMP was requested to review the recommended posology for the metaphylaxis (or prevention) of swine dysentery caused by *B. hyodysenteriae* for the above-mentioned veterinary medicinal products and to recommend whether the benefit-risk balance remains positive for this indication and posology and whether the marketing authorisations for the above-mentioned products should be maintained, varied, suspended, or withdrawn.

2. Discussion of data available

For the veterinary medicinal products falling within the scope of this referral procedure the recommended dose for the prevention or metaphylaxis (when not associated with treatment) ranges from 2 to 5 mg tiamulin as hydrogen fumarate per kg bw per day for a duration of 5 days to 6 weeks. One product has a higher dose for prevention of 7.5 to 10 mg tiamulin as hydrogen fumarate per kg bw per day for 21 days. The dose recommended for treatment (and associated, concomitant metaphylaxis) ranges from 4 to 10 mg tiamulin as hydrogen fumarate per kg bw per day for up to 10 days. The dose of 2 mg tiamulin as hydrogen fumarate per kg bw corresponds to an inclusion rate in feed of 38.5 ppm when considering a feed intake of 50 grams per 10 kg of bw.

To support the indications and dosage regimens concerned by this referral procedure, several marketing authorisation holders provided proprietary preclinical and clinical data, data on susceptibility of *B. hyodysenteriae* to tiamulin, as well as published scientific literature.

---

[2] Card, R.M. *et al*. (2018) Identification of a new antimicrobial resistance gene provides fresh insights into pleuromutilin resistance in *Brachyspira hyodysenteriae,* aetiological agent of swine dysentery. *Front Microbial* **9**, 1183.
[3] Hampson, D.J. *et al*. (2019) Antimicrobial resistance in *Brachyspira* - An increasing problem for disease control. *Veterinary Microbiology* **229**, 59-71.
[4] Massacci, F.R. *et al*. (2018) Multiresistant *Brachyspira hyodysenteriae* shedding by pigs during the fattening period. *Vet Rec* **183 (8)**, 264.
[5] Rugna G. *et al.* (2015) Sequence types and pleuromutilin susceptibility of *Brachyspira hyodysenteriae* isolates from Italian pigs with swine dysentery: 2003-2012. *The Veterinary Journal*, **203**, 115-119.
[6] Van Duijkeren, E. *et al*. (2014) Pleuromutilins: use in food-producing animals in the European Union, development of resistance and impact on human and animal health. *Journal of Antimicrobial Chemotherapy* **69 (8)**, 2022-2031.
[7] CVMP Reflection paper on use of pleuromutilins in food-producing animals in the European Union: development of resistance and impact on human and animal health (EMA/CVMP/AWP/119489/2012-Rev 1) – link

Data on resistance

The marketing authorisation holders provided proprietary data on MIC determinations of tiamulin against *B. hyodysenteriae,* as well as a number of scientific publications on resistance mechanisms. The CVMP considered that the susceptibility data from the public literature covering reports of resistance in Europe and worldwide, despite the disparity in methodologies and interpretations, showed increasing MICs. There were a number of reports describing resistance mechanisms, notably the tva(A) gene recently discovered by Card *et al.* (2018)[8]; and correlation of the presence of resistance determinants with increased MICs of isolates, described by Hampson *et al.* (2019)[9]. Even if no validated microbiological interpretation criteria and no antibiotic susceptibility test were available before the recent EU ring trial by Stubberfield *et al.* (2020)[10], many reports showed a tendency of MIC increase over time.

According to Pringle *et al.* (2012)[11], in *Brachyspira* spp. decreased susceptibility to tiamulin develops in a stepwise manner. The author considered therefore that it is more important for monitoring purposes to consider the low-level resistance (or decreased susceptibility) than to find the isolates with the highest MICs, as the low-level resistance could be the first step towards higher MIC. In a monitoring study carried out in Sweden over a long period with the same methodology, cases of clinical failures associated with resistance were reported.

Furthermore, some marketing authorisation holders provided susceptibility data coming from their own collection of European isolates. While some of them were recent (2016) and others were not (2005), and both had limited size (34 and 30 isolates, respectively), a wide range of MICs, 0.25 to >16 µg/mL was noted; this variability should be kept in mind when discussing the pharmacokinetic/pharmacodynamic (PK/PD) models.

Altogether, these observations confirm that despite a lack of comparability between results, because there has been no harmonised methods for culture, antimicrobial susceptibility testing and interpretation of the results (cut-off values and breakpoints) until 2020, the increase and variability of MICs along with the high percentage of non-wild type of isolates cannot be denied. Furthermore, different mechanisms of resistance have been demonstrated recently, such as the tva(A) gene. One of the reasons for this decrease of susceptibility of *B. hyodysenteriae* to tiamulin could be the current use of veterinary medicinal products, particularly at low doses and for long periods of time (see below, section Preclinical data).

Preclinical data

To justify the prevention or metaphylaxis indication (when not associated with treatment) and the respective dosage regimen of 2 mg tiamulin as hydrogen fumarate per kg bw per day for 2 to 4 weeks or 5 mg tiamulin as hydrogen fumarate per kg bw per day for 14 days, experimental data and bibliographic references were provided by the concerned marketing authorisation holders.

The mechanism of action of tiamulin has been well described as well as the resistance mechanisms.

A proprietary pharmacokinetic study was provided by the MAHs SP Veterinaria and Cenavisa, carried out in 2005 in pigs receiving a medicated feed (286 ppm tiamulin hydrogen fumarate) twice daily equivalent to a dose of 10 mg tiamulin as hydrogen fumarate per kg bw per day for 14 consecutive

[8] Card, R.M. *et al*. (2018) Identification of a new antimicrobial resistance gene provides fresh insights into pleuromutilin resistance in *Brachyspira hyodysenteriae,* aetiological agent of swine dysentery. *Front Microbial* **9**, 1183.
[9] Hampson, D.J. *et al*. (2019) Antimicrobial resistance in *Brachyspira* - An increasing problem for disease control. *Veterinary Microbiology* **229**, 59-71.
[10] Stubberfield, E. *et al.* (2020). Validation of an antimicrobial susceptibility testing protocol for *Brachyspira hyodysenteriae* and *Brachyspira pilosicoli* in an international ring trial. *Veterinary Microbiology*. **244**, 108645. https://doi.org/10.1016/j.vetmic.2020.108645
[11] Pringle, M. *et al*. (2012). Antimicrobial susceptibility of porcine *Brachyspira hyodysenteriae* and *Brachyspira pilosicoli* isolated in Sweden between 1990 and 2010. *Acta veterinaria Scandinavica.* **54(1)** 54. doi:10.1186/1751-0147-54-54

days. This treatment dose is 2 to 5 times higher than the approved preventive dose. Tiamulin was present in colon contents of all 8 animals in the range of 0.423–0.599 µg tiamulin base per gram. In order to predict the efficacy, susceptibility data were provided for *B. hyodysenteriae* and a PK/PD analysis was performed. The susceptibility data of *B. hyodysenteriae* were collected in 2005 but all details of the origin of isolates were unknown (date, geographic region and animals). The MIC of susceptible strains were calculated: MIC_{50} = 0.25 µg/mL and MIC_{90} = 1 µg/mL. The colon content concentrations measured by a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method did not exceed the MIC_{90} of the sampled *B. hyodysenteriae* isolates.

The MAH Elanco provided another PK/PD analysis published by Burch and Hammer (2013)[12] based on the data of an old residue study conducted by Anderson (1994)[13]. The colon content concentrations of tiamulin determined with a microbiological method, had been measured in 3 groups of 5 pigs fed a feed containing tiamulin at a dose of 38.5, 110 and 220 ppm or 2, 6.6 and 13.2 mg per kg bw per day, respectively. The colon content concentrations were below the limit of quantification at 38.5 ppm (estimated by the authors to be 0.99 µg/g), 2.84 µg/g at 110 ppm and 8.05 µg/g at 220 ppm. According to the authors, tiamulin at 38.5 ppm in feed could be expected to be inhibitory to most of the wild type isolates of *B. hyodysenteriae, i.e.* with a MIC up to 0.5 µg/mL.

The different dosage methods (microbiological analysis *versus* LC-MS/MS) may explain the lower colon content concentrations in the more recent study at similar tiamulin dose levels.

Treating preventively a large population of animals at a low dose for a long duration of administration was considered to represent a large exposure that would select for resistance that will finally be observed clinically. It could be speculated that the long duration of treatment at a sub-therapeutic dose may have contributed to the widespread pleuromutilin resistance of *Brachyspira* spp.

Nevertheless, the CVMP considered that the PK/PD analyses are not conclusive as there is no PK/PD criterion and no threshold value validated specifically for tiamulin and *B. hyodysenteriae*. Moreover, the simple comparison of MICs to the colon content concentration was not considered relevant. Those data were not considered pivotal.

Clinical data

To justify the dosage regimen for prevention or metaphylaxis (when not associated with treatment), experimental data and bibliographic references were provided by the concerned marketing authorisation holders.

The historical studies of Taylor, Burch and others from the early 1980s, provided by the marketing authorisation holder Elanco, investigated the efficacy of tiamulin for the prevention of the clinical signs and shedding of *B. hyodysenteriae* after artificial infection and in the field. Some general comments on these studies are that no MICs were reported; there was no post-treatment follow-up period in order to assess relapses after treatment; and although *B. hyodysenteriae* was isolated from treated animals, the number of sampling and isolations were not always optimal to conclude on the full elimination of the pathogen.

In the experimental studies conducted by Taylor[14], it is important to note that *B. hyodysenteriae* was isolated from some animals in the 35 ppm and 40 ppm tiamulin dose groups at post-mortem. This demonstrated that these doses did not completely prevent the establishment of *B. hyodysenteriae* in

[12] Burch DGS and Hammer JM. (2013). Managing *Lawsonia* and *Brachyspira* infections using pharmacokinetic and pharmacodynamic principles. American Association of Swine Veterinarians. 2013 AASV Annual Meeting: Purpose-Inspired Practice, 231-6.
[13] Anderson, M. *et al*. (1994). Tiamulin (Denagard) activity in certain swine tissues following oral and intramuscular administration. Proceedings of the American Association of Swine Practitioners Meeting, Chicago, Illinois, USA, 115-118.
[14] Taylor D.J. (1980). Tiamulin in the treatment and prophylaxis of experimental swine dysentery. *The veterinary record*. **106**; 526-528.

some pigs although clinical signs and post-mortem lesions of experimental swine dysentery had been prevented. In another study conducted by Taylor[15], relapses occurred and *B. hyodysenteriae* was isolated in some pigs of the tiamulin-treated groups during medication or the post-treatment observation period. Even at 160 ppm, *B. hyodysenteriae* was detected in the faeces as soon as 10 days after withdrawal of treatment.

In the field trials cited by Burch[16], where efficacy of tiamulin hydrogen fumarate was tested at 20 and 30 ppm in feed for 4-6 weeks for prevention and control of swine dysentery, no *B. hyodysenteriae* was found at 30 ppm. However, there was no post-treatment observation in this trial.

In a clinical field study carried out in 2005, provided by the marketing authorisation holders SP Veterinaria and Cenavisa, asymptomatic piglets from an infected Spanish herd were treated with tiamulin in the feed at a dose of 4 mg of tiamulin (equivalent to 5 mg tiamulin as hydrogen fumarate, or 100 ppm) per kg bw per day for 2 weeks and compared with a negative control group. A significant difference in the incidence of diarrhoea between the treated group and a negative control group was observed during the treatment. However, the diarrhoea resumed during the one-week post treatment period. Relapses were significantly more frequent in the treated group. This is in line with the results of the above-mentioned historic studies.

In this study, the susceptibility of the strains was not tested and the target pathogen was not isolated neither at the end of the study nor in the relapsing animals. It could therefore be concluded that this dosage regimen (equivalent to 5 mg of tiamulin as hydrogen fumarate per kg bw per day for 14 days) was effective to prevent the occurrence of clinical signs, but only during the treatment period and against a strain of unknown sensitivity. The results of this study illustrated that preventive use without characterising resistance or susceptibility can lead to therapeutic failure. It is likely that this dosage regimen does not eliminate the causative agent, and that it favours resistance emergence.

Following a previous referral procedure, preventive use was approved as part of a program including other measures regarding management aiming at eradication or control of the disease. In addition, the duration of administration had been reduced to a maximum of 4 weeks. The scientific literature provided by the marketing authorisation holders demonstrated that these eradication plans are only successful when they are undertaken in a global approach (farm management, good husbandry and hygiene practices, strict disinfection, isolation and characterisation of the pathogen, depopulation, etc.) together with a higher dose of tiamulin for a longer treatment duration than currently approved. Therefore, these data were not considered as supportive of the currently approved dosage regimen for prevention or metaphylaxis (when not associated with treatment) concerned by this referral procedure.

In conclusion, no clinical data or justifications were provided which could support the use of tiamulin for prevention of swine dysentery caused by *B. hyodysenteriae* at any dose. A clinical study on the metaphylaxis of swine dysentery (not associated with treatment) at a dose of 5 mg tiamulin as hydrogen fumarate per kg bw per day demonstrated that this dosage regimen was only efficacious for the temporary prevention of clinical signs, but not for the eradication of the pathogen which would likely lead to the selection for pleuromutilin resistance.

[15] Taylor, DJ. (1982). In feed medication with tiamulin in the treatment of experimental swine dysentery. Proceedings of the 7th IPVS Congress, Mexico City, Mexico, p47.
[16] Burch DG. (1982). Tiamulin feed premix in the prevention and control of swine dysentery under farm conditions in the UK. *Vet Rec.* **110(11)**:244-246. doi:10.1136/vr.110.11.244

3. Benefit-risk assessment

Introduction

Tiamulin is an antibiotic belonging to the pleuromutilin group. These antibiotics are classified as important antimicrobials for human medicine and as highly important antimicrobials in veterinary medicine due to the limited number of options for treatment of swine dysentery in pigs.

This referral procedure concerns the recommended dosage regimen for the prevention or metaphylaxis (not associated with treatment) of swine dysentery caused by *B. hyodysenteriae* for veterinary medicinal products containing tiamulin hydrogen fumarate, presented as premix for medicated feeding stuff and oral powder for in-feed use to be administered to pigs.

Benefit assessment

The currently authorised dosage regimens for treatment and associated, concomitant metaphylaxis of swine dysentery were outside the scope of the referral and the supporting efficacy data have not been assessed. Accordingly, the benefit-risk balance of these dosage regimens continues to be regarded as positive.

Based on the available pre-clinical and clinical data, the dosage regimens of 2 mg tiamulin as hydrogen fumarate per kg bw per day for 2 to 4 or 2 to 6 weeks and 5 mg tiamulin as hydrogen fumarate per kg bw per day for 5 to 14 days are only effective temporarily for the prevention of clinical signs of swine dysentery caused by *B. hyodysenteriae*. It could not be demonstrated that these dosage regimens ensure the eradication of the pathogen. On the contrary, the observed relapses after treatment could explain partly the selection for resistance or for an increased MIC in strains exposed to tiamulin.

No data were provided to demonstrate the benefit of the concerned dosage regimens as part of an eradication plan. Only higher treatment doses for longer periods in combination with further measures (such as farm management, good husbandry and hygiene practices, strict disinfection, isolation and characterisation of the pathogen, depopulation, etc.) were used to fully eliminate *B. hyodysenteriae* from infected farms.

Risk assessment

Quality, target animal safety, user safety, consumer safety and the environmental risk for the concerned veterinary medicinal products have not been assessed in this referral procedure.

A risk has been identified regarding the dosage regimens for prevention or metaphylaxis (when not associated with treatment), which may be insufficient to protect animal health, and in addition could contribute to the development of antimicrobial resistance. Based on the available data, *B. hyodysenteriae* could not be eliminated from infected pigs following administration of tiamulin at the dosage regimens currently approved for prevention or metaphylaxis (when not associated with treatment), thereby leading to therapeutic failure and promoting resistance emergence.

Decreased susceptibility of *B. hyodysenteriae* isolates to tiamulin is a cause for concern as there are only a limited number of antimicrobials available for the treatment of swine dysentery and widespread resistance to pleuromutilins would pose a threat to pig health.

A large literature review showed numerous cases of resistance across Europe and worldwide for the last 20 years. A significant trend in the reduction of susceptibility over time was observed. The prevalence of multidrug-resistant strains is also increasing. Knowing that the development of resistance of *B. hyodysenteriae* occurs stepwise, populations of decreased susceptibility are at risk for further selection of highly resistant bacteria. Repeated exposure to sub-inhibitory concentrations of tiamulin leads to the development of clinical resistance. These dosage regimens correspond to an oral

group treatment to prevent disease at a low dose for a long duration period that will directly expose the digestive tract microbiota, the main reservoir at risk during the treatment course.

Pleuromutilin use in animals selects for the multidrug-resistance gene cfr in methicillin-resistant *Staphylococcus aureus* (MRSA), including livestock-associated MRSA (LA-MRSA), which is a hazard of zoonotic relevance. The cfr gene mediates cross-resistance to oxazolidinones. Also, other resistance genes of concern have been identified such as vga, which confers resistance to streptogramin A. Of importance, it should be noted that vga and cfr genes can be located in mobile genetic elements and hence are transferable between bacteria and different bacterial species.

Altogether, these observations validate the urgent need to reduce the resistance risk for this critically important antimicrobial in order to maintain its effectiveness.

Risk management or mitigation measures

To limit the selection pressure for bacteria, unnecessary use should be avoided. Limiting the use of oral tiamulin in pigs against swine dysentery caused by *B. hyodysenteriae* to the treatment and metaphylaxis of the disease at the currently authorised treatment dosage regimens would reduce the risk for selection for resistance without hampering the effective use of these products for this indication.

Evaluation and conclusions on the benefit-risk balance

Oral tiamulin is regarded as an effective medicine against several diseases in pigs and also as a highly important antimicrobial in the treatment of swine dysentery caused by *B. hyodysenteriae*. Extended periods of use of the substance at sub-therapeutic doses for the prevention or metaphylaxis (not associated with treatment) present a risk from a resistance perspective and would not be justifiable from a scientific point of view taking into account disease epidemiology as well as current awareness regarding the need to always combine antibiotic use with appropriate sanitary measures.

Provided the dosage regimens for prevention or metaphylaxis (not associated with treatment) are removed and the use is limited to the treatment and metaphylaxis of swine dysentery at the currently authorised treatment dosage regimens, the benefit-risk balance of veterinary medicinal products containing tiamulin hydrogen fumarate presented as premix for medicated feeding stuff and oral powder for in-feed use to be administered to pigs could continue to be regarded as positive.

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

Whereas

- the available data demonstrated that the dose regimens of 2 mg tiamulin as hydrogen fumarate per kilogram body weight per day for 2 to 4 or 2 to 6 weeks and 5 mg tiamulin as hydrogen fumarate per kilogram body weight per day for 5 to 14 days were only effective temporarily for the prevention of clinical signs of swine dysentery;
- a significant trend in the reduction of susceptibility of *B. hyodysenteriae* to tiamulin over time was observed and a risk for the selection of resistant strains has been identified;
- to limit the selection pressure for bacteria unnecessary use of oral tiamulin in pigs should be avoided;
- the CVMP considered that the overall benefit-risk balance for the products under this procedure remains positive subject to amendments in the product information;

the CVMP has recommended the amendment of the marketing authorisations for veterinary medicinal products containing tiamulin hydrogen fumarate presented as premix for medicated feeding stuff and oral powder for in-feed use to be administered to pigs as referred in Annex I for which the summary of product characteristics, labelling and package leaflet are set out in Annex III.

Annex III

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

Summary of product characteristics

4.2 Indications for use, specifying the target species

Pigs:

For the treatment and metaphylaxis, when the disease is present in the group, of swine dysentery caused by *Brachyspira hyodysenteriae* susceptible to tiamulin. The presence of the disease in the group must be established before the product is used. *[…]*

4.9 Amounts to be administered and administration route

Delete, where applicable, any specific dosing recommendation (different from the treatment dose) related to the prevention or metaphylaxis of swine dysentery caused by *Brachyspira hyodysenteriae*.

Replace, where applicable, recommendations for 'treatment' or 'treatment and prevention' with 'treatment and metaphylaxis'.

4.11 Withdrawal period(s)

Delete, where applicable, any specific withdrawal period related to the prevention or metaphylaxis of swine dysentery caused by *Brachyspira hyodysenteriae*.

Labelling

6. INDICATION(S)

Pigs:

For the treatment and metaphylaxis, when the disease is present in the group, of swine dysentery caused by *Brachyspira hyodysenteriae* susceptible to tiamulin. The presence of the disease in the group must be established before the product is used. *[…]*

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Delete, where applicable, any specific dosing recommendation (different from the treatment dose) related to the prevention or metaphylaxis of swine dysentery caused by *Brachyspira hyodysenteriae*.

Replace, where applicable, recommendations for 'treatment' or 'treatment and prevention' with 'treatment and metaphylaxis'.

8. WITHDRAWAL PERIOD(S)

Delete, where applicable, any specific withdrawal period related to the prevention or metaphylaxis of swine dysentery caused by *Brachyspira hyodysenteriae*.

Package leaflet

4. INDICATION(S)

Pigs:

For the treatment and metaphylaxis, when the disease is present in the group, of swine dysentery caused by *Brachyspira hyodysenteriae* susceptible to tiamulin. The presence of the disease in the group must be established before the product is used. *[…]*

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

Delete, where applicable, any specific dosing recommendation (different from the treatment dose) related to the prevention or metaphylaxis of swine dysentery caused by *Brachyspira hyodysenteriae*.

Replace, where applicable, recommendations for 'treatment' or 'treatment and prevention' with 'treatment and metaphylaxis'.

10. WITHDRAWAL PERIOD(S)

Delete, where applicable, any specific withdrawal period related to the prevention or metaphylaxis of swine dysentery caused by *Brachyspira hyodysenteriae*.