Annex I

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

Member State EU/EEA	Applicant / Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Austria	Biovet JSC 39, Petar Racov Str. 4550 Peshtera Bulgaria	Axentyl 200 mg/ml Injektionslösung für Rinder, Schafe, Ziegen und Schweine	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Austria	Ceva Santé Animale 10, av. de La Ballastière 33500 Libourne France	TILJET	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Austria	Richter Pharma AG Feldgasse 19 4600 Wels Austria	Tylan 200 mg/ml - Injektionslösung für Rinder und Schweine	Tylosin base	200 mg/ml	solution for injection	Pigs	Intramuscular use
Austria	Huvepharma N.V. Uitbreidingstraat 80 2600 Antwerpen (Berchen) Belgium	PHARMASIN 200 mg/ml Injektionslösung für Rinder, Schafe, Ziegen und Schweine	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Austria	Vetoquinol Österreich GmbH Gußhausstraße 14/5 1040 Vienna Austria	Tylucyl 200 mg/ml Injektionslösung für Rinder und Schweine	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Belgium	Ceva Santé Animale 10, av. de La Ballastière 33500 Libourne France	Tyljet 200 mg/ml	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use

Member State EU/EEA	Applicant / Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Belgium	Cross Vetpharm Group Ltd. Broomhill Road Tallaght, Dublin 24 Ireland	BILOVET 200 mg/ml	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Belgium	Eli Lilly Benelux NV Division Elanco Animal Health Markiesstraat 1 B-1000 Brussel Belgium	Tylan 200	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Belgium	Huvepharma N.V. Uitbreidingstraat 80 2600 Antwerpen (Berchen) Belgium	PHARMASIN 200 mg/ml	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Belgium	Vetoquinol NV/SA Kontichsesteenweg 42 2630 Aartselaar Belgium	Tylucyl 200	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Bulgaria	Biovet JSC 39, Petar Racov Str. 4550 Peshtera Bulgaria	PHARMASIN 50 solution for injection	Tylosin base	50 mg/ml	Solution for injection	Pigs	Intramuscular use
Bulgaria	Biovet JSC 39, Petar Racov Str. 4550 Peshtera Bulgaria	TYLOVET B -50 solution for injection for cattle, sheep, goats, swine, dogs and cats	Tylosin base	50 mg/ml	Solution for injection	Pigs	Intramuscular use

Member State EU/EEA	Applicant / Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Bulgaria	Biovet JSC 39, Petar Racov Str. 4550 Peshtera Bulgaria	TYLOVET B -200 solution for injection for cattle, sheep, goats, swine and dogs	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Bulgaria	Biovet JSC 39, Petar Racov Str. 4550 Peshtera Bulgaria	TYLMASIN 200 mg/ml solution for injection for cattle, sheep, goats and pigs	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Bulgaria	Ceva Santé Animale 10, av. de La Ballastière 33500 Libourne France	Tyljet 200 mg/ml solution for injection for cattle, sheep, goats and pigs	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Bulgaria	Huvepharma N.V. Uitbreidingstraat 80 2600 Antwerpen (Berchen) Belgium	Pharmasin 200 mg/ml solution for injection for cattle, sheep, goats and pighs	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Croatia	Ceva Santé Animale 10, av. de La Ballastière 33500 Libourne France	Tyljet, 200 mg/ml, otopina za injekciju za goveda i svinje	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Croatia	Vetoquinol SA Magny-Vernois 70200 Lure France	Tylucyl, 200 mg/mL, otopina za injekciju za goveda i svinje	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Cyprus	Cross Vetpharm Group Ltd. Broomhill Road Tallaght, Dublin 24 Ireland	Bilosin 200 mg/ml Solution for Injection for pigs	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use

Member State EU/EEA	Applicant / Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Cyprus	Vetoquinol SA Magny-Vernois 70200 Lure France	Tylucyl 200 mg/ml ενέσιμο διάλυμα για βοοειδή και χοίρους	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Czech Republic	Ceva Santé Animale 10, av. de La Ballastière 33500 Libourne France	Tiljet, 200mg/ml, Injekční roztok pro skot a prasata	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Czech Republic	Vétoquinol s. r. o. Zámečnická 411 288 02 Nymburk Czech Republic	Tylucyl 200 mg/ml injekční roztok pro skot a prasata	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Denmark	Biovet JSC 39, Petar Racov Str. 4550 Peshtera Bulgaria	Tylovet	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Denmark	Ceva Animal Health A/S Ladegårdsvej 2 DK-7100 Vejle Denmark	TILJET	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Denmark	Elanco Animal Health A/S Lyskær 3E, 2. tv. 2730 Herlev Denmark	Tylan Vet.	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Denmark	Huvepharma N.V. Uitbreidingstraat 80 2600 Antwerpen (Berchen) Belgium	Tylamasin	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use

Member State EU/EEA	Applicant / Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Denmark	Vetoquinol Scandinavia AB Lyngbyvej 20 2100 København Ø Denmark	Tylucyl	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Estonia	Ceva Santé Animale 10, av. de La Ballastière 33500 Libourne France	Tyljet	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Estonia	Huvepharma N.V. Uitbreidingstraat 80 2600 Antwerpen (Berchen) Belgium	Pharmasin	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Estonia	Vetoquinol SA Magny-Vernois 70200 Lure France	Tylucyl	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Finland	Ceva Santé Animale 10, av. de La Ballastière 33500 Libourne France	Tyljet	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Finland	Elanco Animal Health A/S Lyskær 3E, 2. tv. 2730 Herlev Denmark	Tylan vet	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
France	Aniserve GmbH Geyerspergerstr. 27 80689 Munchen Germany	TYLOVECTIN 200 SOLUTION INJECTABLE POUR BOVINS, CAPRINS ET PORCINS	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use

Member State EU/EEA	Applicant / Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
France	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Tallaght Dublin 24 Ireland	BILOVET 200 MG/ML SOLUTION INJECTABLE	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
France	Biovet JSC 39, Petar Racov Str. 4550 Peshtera Bulgaria	AXENTYL 200 MG/ML SOLUTION INJECTABLE POUR BOVINS, OVINS, CAPRINS ET PORCINS	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
France	Ceva Santé Animale 10, av. de La Ballastière 33500 Libourne France	TILJET 200 MG/ML SOLUTION INJECTABLE POUR BOVINS OVINS CAPRINS ET PORCINS	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
France	Ceva Santé Animale 10, av. de La Ballastière 33500 Libourne France	TYLOSINE CEVA 200 MG/ML SOLUTION INJECTABLE POUR BOVINS OVINS CAPRINS ET PORCINS	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
France	Huvepharma N.V. Uitbreidingstraat 80 2600 Antwerpen (Berchen) Belgium	Pharmasin 200 mg/ml solution injectable pour bovis ovins caprins et porcins	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
France	Lilly France 24 Boulevard Vital Bouhot 92200 Neuilly Sur Seine France	TYLAN 200	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use

Member State EU/EEA	Applicant / Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
France	Vetoquinol SA Magny-Vernois 70200 Lure France	TYLUCYL 200 MG/ML SOLUTION INJECTABLE POUR BOVINS ET PORCINS	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Germany	Bela-Pharm GmbH & Co.KG Lohner Str. 19 49377 Vechta Germany	Tylobel 25%	Tylosin base	250 mg/ml	Solution for injection	Pigs	Intramuscular use
Germany	Bimeda Chemicals Broomhill Road Tallaght Dublin 24 Ireland	Bilovet 200 mg/ml Injektionslösung für Rinder und Schweine	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Germany	Biovet JSC 39, Petar Racov Str. 4550 Peshtera Bulgaria	Tylmasin 200 mg/ml Injektionslösung für Rinder, Schafe, Ziegen und Schweine	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Germany	Ceva Santé Animale 10, av. de La Ballastière 33500 Libourne France	Tiljet 200 mg/ml solution for injection for cattle, pigs, sheep and goates	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Germany	Huvepharma N.V. Uitbreidingstraat 80 2600 Antwerpen (Berchen) Belgium	PHARMASIN 200 mg/ml Injektionslösung für Rinder, Schafe, Ziegen und Schweine	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use

Member State EU/EEA	Applicant / Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Germany	Lilly Deutschland GmbH Abteilung Elanco Animal Health Werner-Reimers-Str. 2-4 D-61352 Bad Homburg Germany	Tylan 200	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Germany	Selectavet Dr. Otto Fischer Am Kögelberg 5 D-83629 Weyarn/Holzolling Germany	Tylosel-200	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Germany	Vetoquinol GmbH Reichenbachstr. 1 D-85737 Ismaning Germany	Tylucyl 200 mg/ml	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Greece	Biovet JSC 39, Petar Racov Str. 4550 Peshtera Bulgaria	Tylmasin	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Greece	Ceva Hellas LLC 15 Agiou Nikolaou Street 17455 Alimos Greece	Tiljet	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Greece	Eli Lilly Regional Operations GmbH, Elanco Animal Health, Kölblgasse 8 – 10, 1030 Vienna, Austria	Tylan 200	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use

Member State EU/EEA	Applicant / Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Greece	Huvepharma N.V. Uitbreidingstraat 80 2600 Antwerpen (Berchen) Belgium	Pharmasin	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Greece	Vetoquinol SA Magny-Vernois 70200 Lure France	Tylucyl	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Hungary	Biovet JSC 39, Petar Racov Str. 4550 Peshtera Bulgaria	TYLMASIN 200 mg/ml oldatos injekció szarvasmarhák, juhok, kecskék és sertések részére	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Hungary	Ceva-Phylaxia Zrt. Szállás u. 5. 1107 Budapest Hungary	Tiljet 200 mg/ml solution for injection for cattle, pigs, sheep and goats	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Hungary	Huvepharma N.V. Uitbreidingstraat 80 2600 Antwerpen (Berchen) Belgium	PHARMASIN 200 mg/ml oldatos injekció szarvasmarhák, juhok, kecskék és sertések részére	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Hungary	Vetoquinol SA Magny-Vernois 70200 Lure France	Tylucyl 200 mg/ml oldatos injekció szarvasmarhák és sertések részére	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use

Member State EU/EEA	Applicant / Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Ireland	Bimeda Chemicals Broomhill Road Tallaght Dublin 24 Ireland	Bilosin 200mg/ml, Solution for Injection	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Ireland	Biovet JSC 39, Petar Racov Str. 4550 Peshtera Bulgaria	Tylosin Biovet JSC 200 mg/ml solution for injection for cattle, sheep, goats and pigs	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Ireland	Cross Vetpharm Group Ltd. Broomhill Road Tallaght, Dublin 24 Ierland	Bilovet 200 mg/ml Solution for Injection for Cattle and Pigs	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Ireland	Elanco GmbH, Heinz-Lohmann-Strasse 4 27472 Cuxhaven Germany	Tylan 200, 200 mg/ml Solution for Injection	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Ireland	Huvepharma N.V. Uitbreidingstraat 80 2600 Antwerpen (Berchen) Belgium	Pharmasin 200 mg/ml Solution for Injection for Cattle and Pigs	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Ireland	Vetoquinol Ireland Limited First Floor, Segrave House 19-20 Earlsfort Terrace Dublin 2 Ireland	Tylucyl 200 mg/ml Solution for Injection for Cattle and Pigs	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use

Member State EU/EEA	Applicant / Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Italy	Biovet JSC 39, Petar Racov Str. 4550 Peshtera Bulgaria	AXENTYL 200 mg/ml soluzione iniettabile per bovini, ovini, caprini e suini	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Italy	Ceva Santé Animale 10, av. de La Ballastière 33500 Libourne France	TILJET 20, 200 mg/ml, soluzione iniettabile per bovini, suini, cani.	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Italy	Ceva Santé Animale 10, av. de La Ballastière 33500 Libourne France	TYLOSINE CEVA	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Italy	Cross Vetpharm Group Ltd. Broomhill Road Tallaght, Dublin 24 Ierland	Bilovet 200 mg/ml soluzione iniettabile per bovini e suini	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Italy	Eli Lilly Italia SpA Via Gramsci 731-733, 50019 Sesto Fiorentino - FI Italy	TYLAN® 200, 200 mg/ml soluzione iniettabile, per bovini e suini.	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Italy	FATRO S.P.A. Via Emilia, 285 40064 Ozzano Dell'Emilia (Bologna) Italy	SUPRATIL 200 mg/ml soluzione iniettabile per bovini e suini	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use

Member State EU/EEA	Applicant / Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Italy	FATRO S.P.A. Via Emilia, 285 40064 Ozzano Dell'Emilia (Bologna) Italy	VETIL, 200 mg/ml, soluzione iniettabile per bovini, suini e cani	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Italy	Huvepharma N.V. Uitbreidingstraat 80 2600 Antwerpen (Berchen) Belgium	PHARMASIN 200 mg/ml soluzione iniettabile per bovini, ovini, caprini e suini	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Italy	Vetoquinol Italia S.r.l. Via Piana 265 47032 Bertinoro (FC) Italy	TYLUCYL 200 mg/ml soluzione iniettabile per bovini e suini	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Latvia	Ceva Santé Animale 10, av. de La Ballastière 33500 Libourne France	Tylosine Ceva 200 mg/ml šķīdums injekcijām liellopiem un cūkām	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Latvia	Huvepharma N.V. Uitbreidingstraat 80 2600 Antwerpen (Berchen) Belgium	Pharmasin 200 mg/ml šķīdums injekcijām liellopiem, aitām, kazām un cūkām	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Latvia	Vetoquinol SA Magny-Vernois 70200 Lure France	Tylucyl 200 mg/ml šķīdums injekcijām liellopiem un cūkām	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use

Member State EU/EEA	Applicant / Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Lithuania	Ceva Santé Animale 10, av. de La Ballastière 33500 Libourne France	Tilject 200 mg/ml injekcinis tirpals galvijams ir kiaulėms.	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Lithuania	Huvepharma N.V. Uitbreidingstraat 80 2600 Antwerpen (Berchen) Belgium	PHARMASIN 200 mg/ml injekcinis tirpalas kiaulėms, galvijams, avims ir ožkoms	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Lithuania	Huvepharma N.V. Uitbreidingstraat 80 2600 Antwerpen (Berchen) Belgium	PHARMASIN 50 mg/ml injekcinis tirpalas kiaulėms, galvijams, avims, ožkoms, šunims ir katėms	Tylosin base	50 mg/ml	Solution for injection	Pigs	Intramuscular use
Lithuania	Vetoquinol SA Magny-Vernois 70200 Lure France	Tylucyl 200 mg/ml injekcinis tirpalas galvijams ir kiaulėms	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Luxembourg	Ceva Santé Animale 10, av. de La Ballastière 33500 Libourne France	Tyljet 200 mg/ml	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Luxembourg	Cross Vetpharm Group Ltd. Broomhill Road Tallaght, Dublin 24 Ireland	BILOVET 200 mg/ml	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use

Member State EU/EEA	Applicant / Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Luxembourg	Huvepharma N.V. Uitbreidingstraat 80 2600 Antwerpen (Berchen) Belgium	PHARMASIN 200 mg/ml	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Luxembourg	Vetoquinol NV/SA Kontichsesteenweg 42 2630 Aartselaar Belgium	Tylucyl 200	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Netherlands	Aniserve Geyerspergerstrasse 27 80689 Munchen Germany	Tylovectin 200 mg oplossing voor injectie voor runderen, geitenen varkens	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Netherlands	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Tallaght Dublin 24 Ireland	Bilovet 200 mg/ml oplossing voor injectie voor runderen en varkens	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Netherlands	Elanco GmbH, Heinz-Lohmann-Strasse 4 27472 Cuxhaven Germany	Tylan 200 injectie oplossing voor injectie voor rund, kalf en varken	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Netherlands	Floris Veterinaire Produkten B.V. Kempenlandstraat 33-35 5262 GK Vught The Netherlands	Tylosine 20% P.I.	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use

Member State EU/EEA	Applicant / Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Netherlands	Huvepharma N.V. Uitbreidingstraat 80 2600 Antwerpen (Berchen) Belgium	Pharmasin 200 mg/ml oplossing voor injectie voor runderen en varkens	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Netherlands	Vetoquinol B.V. Postbus 3191 Hertogenbosch 5232 DD's Hertogenbosch The Netherlands	Tylucyl 200 mg/ml oplossing voor injectie voor runderen en varkens.	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Norway	Ceva Santé Animale 10, av. de La Ballastière 33500 Libourne France	Tyljet	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Poland	Biovet JSC 39, Petar Racov Str. 4550 Peshtera Bulgaria	Tylozyna Biovet JSC	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Poland	Ceva Animal Health Polska Sp. z o.o. Ul. Okrzei 1a 03-715 Warsaw Poland	Tiljet 200 mg/ml solution for injection for cattle, pigs, sheep and goats	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Poland	Cross Vetpharm Group Ltd. Broomhill Road Tallaght, Dublin 24 Ireland	Bilovet	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use

Member State EU/EEA	Applicant / Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Poland	Drwalewskie Zakłady Przemysłu Bioweterynaryjnego S.A. 6 Grójecka str. 05-651 Drwalew Poland	Biotyl 200	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Poland	Drwalewskie Zakłady Przemysłu Bioweterynaryjnego S.A. 6 Grójecka str. 05-651 Drwalew Poland	Biotyl 50	Tylosin base	50mg/ml	Solution for injection	Pigs	Intramuscular use
Poland	Huvepharma N.V. Uitbreidingstraat 80 2600 Antwerpen (Berchen) Belgium	Pharmasin	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Poland	Vetoquinol Biowet Sp. z o.o. ul. Kosynierów Gdyńskich 13-14 66-400 Gorzów Wielkopolski Poland	Tylucyl	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Portugal	Biovet JSC 39, Petar Racov Str. 4550 Peshtera Bulgaria	TYLMASIN 200 mg/ml solução injetável para bovinos, ovinos, caprinos e suínos	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use

Member State EU/EEA	Applicant / Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Portugal	Huvepharma N.V. Uitbreidingstraat 80 2600 Antwerpen (Berchen) Belgium	PHARMASIN 200 mg/ml solução injetável para bovinos, ovinos, caprinos e suínos	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Portugal	Laboratorios Syva S.A.U Av. del Parroco Pablo Diez, 49 24010 San Andrés del Rabanedo Léon Spain	JECTYL 200 mg/ml solução injetável para bovinos, suínos e cães	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Portugal	Lilly Portugal, Produtos Farmacêuticos, Lda Torre Ocidente Rua Galileu Galilei, N.º 2, Piso 7 Fração A/D 1500-392 Lisboa Portugal	Tylan 200 mg/ml Solução injetável para bovinos e suínos	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Portugal	Vétoquinol, Unipessoal Lda. Rua Consigliéri Pedroso, 123– Edifício H 2730-056 Barcarena Portugal	Tylucyl 200 mg/ml, solução injetável para bovinos e suínos	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Romania	Biovet JSC 39, Petar Racov Str. 4550 Peshtera Bulgaria	Tylmasin	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use

Member State EU/EEA	Applicant / Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Romania	Cross Vetpharm Group Ltd. Broomhill Road Tallaght, Dublin 24 Ireland	BILOVET 200 mg/ml	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Romania	Huvepharma N.V. Uitbreidingstraat 80 2600 Antwerpen (Berchen) Belgium	Pharmasin 200 mg/ml Solution for Injection for Cattle and Pigs	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Romania	Vetoquinol SA Magny-Vernois 70200 Lure France	Tylucyl 200	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Slovak Republic	Biovet JSC 39, Petar Racov Str. 4550 Peshtera Bulgaria	TYLOVET B- 200 mg/ml injekčný roztok pre hovädzí dobytok a ošípané	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Slovak Republic	Ceva Santé Animale 10, av. de La Ballastière 33500 Libourne France	Tyljet 200 mg/ml solution for injection for cattle and pigs	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Slovak Republic	Vétoquinol s.r.o Zámečnická 411 288 02 Nymburg Česká Republika	TYLUCIL 200 mg/ml injekčný roztok pre hovädzí dobytok a ošípané	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Slovenia	Ceva Santé Animale 10, av. de La Ballastière 33500 Libourne France	Tiljet 200 mg/ml solution for injection for cattle and pigs	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use

Member State EU/EEA	Applicant / Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Slovenia	Vetoquinol SA Magny-Vernois 70200 Lure France	Tylucyl 200 mg/ml raztopina za injiciranje za govedo in prašiče	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Spain	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Tallaght Dublin 24 Ireland	BILOVET 200 mg/ml SOLUCION INYECTABLE PARA BOVINO Y PORCINO	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Spain	Biovet JSC 39, Petar Racov Str. 4550 Peshtera Bulgaria	TILOSINA BIOVET JSC 200 mg/ml SOLUCION INYECTABLE PARA BOVINO OVINO CAPRINO Y PORCINO	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Spain	Ceva Salud Animal, S.A. Avinguda Diagonal, 609 - 615 08028 Barcelona Spain	TYLJET 200 MG/ML SOLUTION FOR INJECTION FOR CATTLE AND PIGS	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Spain	Elanco GmbH, Heinz-Lohmann-Strasse 4 27472 Cuxhaven Germany	TRELACON 200.000 UI/ml SOLUCION INYECTABLE	Tylosin base	200 mg/ml	Solution for Injection	Pigs	Intramuscular use
Spain	Huvepharma N.V. Uitbreidingstraat 80 2600 Antwerpen (Berchen) Belgium	PHARMASIN 200 mg/ml SOLUCION INYECTABLE PARA BOVINO OVINO CAPRINO Y PORCINO	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use

Member State EU/EEA	Applicant / Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Spain	Industrial Veterinaria, S.A. Esmeralda, 19 08950 Esplugues de Llobregat Barcelona Spain	TILOSINA 200 mg/ml GANADEXIL solucion inyectable	Tylosin base	200 mg/ml	Solution for Injection	Pigs	Intramuscular use
Spain	Laboratorios e Industrias Iven, S.A. Calle de Luis I, 56 28031 Madrid Spain	TILOSIVEN 200 mg/ml SOLUCION INYECTABLE	Tylosin base	200 mg/ml	Solution for Injection	Pigs	Intramuscular use
Spain	Laboratorios e Industrias Iven, S.A. Calle de Luis I, 56 28031 Madrid Spain	TISERGEN 200 mg/ml	Tylosin base	200 mg/ml	Solution for Injection	Pigs	Intramuscular use
Spain	Laboratorios Syva S.A.U Av. del Parroco Pablo Diez, 49 24010 San Andrés del Rabanedo Léon Spain	TILOSUL	Tylosin base	200 mg/ml	Solution for Injection	Pigs	Intramuscular use

Member State EU/EEA	Applicant / Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Spain	Mevet Polígono Ind El Segre Avenida de la Industria, Parc 410 25191 Lleida, Lérida Spain	TILOVALL 200 mg/ml SOLUCIÓN INYECTABLE	Tylosin base	200 mg/ml	Solution for Injection	Pigs	Intramuscular use
Spain	Vetoquinol Especialidades Veterinarias S.A. Carreta de Fuencarral, 24 Edificio Europa I 28108 Madrid Spain	TYLUCYL 200 mg/ml SOLUCION INYECTABLE PARA BOVINO Y CERDOS	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Sweden	Ceva Animal Health AB Annedalsvägen 9 227 64 Lund Sweden	TILJET	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Sweden	Elanco Animal Health A/S Lyskær 3E, 2. tv. 2730 Herlev Denmark	Tylan Vet	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
Sweden	Vetoquinol Scandinavia AB Torgattan 2 26521 Åstorp Sweden	Tylucyl	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
United Kingdom	Aniserve Geyerspergerstrasse 27 80689 Munchen Germany	Tylovectin 200 Solution for Injection for Cattle, Goats and Pigs	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use

Member State EU/EEA	Applicant / Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
United Kingdom	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Tallaght Dublin 24 Ireland	Bilosin 200mg/ml, Solution for Injection	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
United Kingdom	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Tallaght Dublin 24 Ireland	Bilovet 200 mg/ml Solution for Injection for Cattle and Pigs	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
United Kingdom	Ceva Santé Animale 10, av. de La Ballastière 33500 Libourne France	Tiljet 200 mg/ml Solution for Injection for Cattle and Pigs	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
United Kingdom	Eli Lilly and Company Limited Elanco Animal Health Priestley Road Basingstoke Hampshire RG24 9NL UK	Tylan 200, 200 mg/ml Solution for Injection	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use
United Kingdom	Huvepharma N.V. Uitbreidingstraat 80 2600 Antwerpen (Berchen) Belgium	Pharmasin 200 mg/ml Solution for Injection for Cattle and Pigs	Tylosin base	200 mg/ml	Solution for injection	Pigs	Intramuscular use

Annex II

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

Overall summary of the scientific evaluation of veterinary medicinal products containing tylosin base (as a single active substance) presented as solutions for injection for intramuscular use in pigs (see Annex I)

1. Introduction

Tylosin is a macrolide antibiotic which is produced by *Streptomyces fradiae*. It is active mostly against Gram-positive bacteria and mycoplasmas. It is ineffective against *Enterobacteriaceae*. Tylosin and its phosphate and tartrate salts are used in veterinary medicines for the treatment of conditions caused by sensitive organisms. It may be administered by oral or parenteral routes. Macrolides are categorised as critically important antimicrobials both in human and veterinary medicine, however tylosin is not used in human medicine.

Applications were submitted under Article 13(1) of Directive 2001/82/EC, i.e., a generic application, for a marketing authorisation under the decentralised procedure for two veterinary medicinal products, with France as Reference Member State (FR/V/0325/001/DC and FR/V/0326/001/DC). The reference product was Tylan 200 injectable solution, which has been authorised in various Member States. During the course of the decentralised procedures, it became apparent that there are different approved withdrawal periods for pigs for 'Tylan 200 injectable solution' across the European Union, ranging from 5 to 46 days. Moreover, it was noted that in certain Member States the injection volume is limited, whereas in others it is not. The posology of the different products also varies from 10 to 20 mg/kg bodyweight per day via intramuscular route, administered during 3 to 5 days. The majority of products (124 out of 132) are to be administered at 10 mg/kg bodyweight per day. For four products, the recommended posology is 20 mg/kg bodyweight per day, and for the remaining four products, it is 10 mg/kg bodyweight, twice a day.

France considered that it was necessary to refer the matter to the CVMP in the interest of protecting consumer safety in the Union, and requested the Committee to review all available residue depletion data and recommend a withdrawal period for all veterinary medicinal products containing tylosin base (as a single active substance) presented as solutions for injection for intramuscular use in pigs.

2. Discussion of data available

Qualitative and quantitative composition

Information was received regarding the composition of the affected products (n=132). For 127 products the concentration of tylosin is 200 mg tylosin base/ml. For four products the concentration is 50 mg tylosin base/ml, and for one product it is 250 mg tylosin base/ml.

Regardless of the tylosin strength, the formulation of all products concerned is very similar. All the formulations have propylene glycol and water as main excipients, and benzyl alcohol and/or ethanol as preservatives, which are present in the product at very low concentrations. Propylene glycol is present at different concentrations, but within a range that it is not expected to impact significantly on the viscosity of the product, and consequently the absorption of the active ingredient. Despite the concentration of propylene glycol or type of preservative, all products have a similar target pH values and the density of the products is very close to that of water. Consequently, it is expected that all formulations have the same behaviour with regards to its absorption at the injection site.

Residue depletion in pig meat and offal

Seven residue studies conducted in pigs are available using tylosin injectable solution administered by the intramuscular route. Six studies were conducted with either Tylan 200 mg/ml, Tisergen 200 mg/ml, Bilosin 200 mg/ml or Tilosina 200 mg/ml. For one study, the formulation of the product used is not known.

Two good laboratory practice (GLP) compliant residue depletion studies were available. One of the studies was conducted in 1990, with the product Tylan 200 mg/ml solution for injection. The bodyweight of the treated pigs ranged between 19 to 26 kg. Groups of 6 animals were treated at a dose of 10 mg/kg bodyweight once a day for 5 days, with a maximum volume of injection of 1.3 ml. The animals were slaughtered at 6 hours and at days 3, 7, 14 and 28 post treatment. Kidney, liver, skin + fat, muscle, and injection site (core 200 g) were analysed using a HPLC-UV method for tylosin residues, with a limit of quantification of 50 µg/kg (i.e., half the maximum residue limit (MRL) value of 100 µg/kg). After 3 days, tylosin was detected only at the injection site. Seven days after the last injection, residues in all injection site samples were below the MRL. From this study, the withdrawal period that can be established for a posology of 10 mg/kg bodyweight per day for 5 consecutive days, and calculated based on the 'alternative' method for determining the withdrawal period, in line with CVMP note for guidance on the approach towards harmonisation of withdrawal periods (EMEA/CVMP/036/95)[1], with a 30% safety span, is 10 days. The maximum volume of injection tested in this study (1.3 ml) is, however, smaller than the recommended volume due to the animals in the study being light (VICH GL 48 recommends that the pigs are to be 40-80 kg). Consequently, if this was to be extrapolated to larger pigs (fattening pigs or sows), the total dose would have to be divided requiring multiple injections, which is not considered a feasible option. It is then considered that this study cannot be used to determine a withdrawal period for pigs for the products concerned in this referral procedure.

The other GLP-compliant residue depletion study was conducted in 2010 with the product Tisergen 200 mg/ml. The study was mostly conducted in line with current standards. However, some of the injection sites samples from treated pigs were below the weights recommended by the CVMP guideline of 500 g ± 20% for the core sample and 300 g ± 20% (EMEA/CVMP/542/03)[2], and ranged between 366-440 g (core sample), and 215-288 g (surrounding injection site sample). The pH of the test product (from the certificate of analysis) was slightly more acidic than that of Tisergen 200 reported in the product specifications of the finished product, but the small variation on pH was considered by the CVMP not to impact the results obtained regarding the depletion of residues. The bodyweight of the pigs used for the study ranged between 45.08 to 54.56 kg (in line with the recommendation of VICH GL 48). Groups of 6 animals were treated at a dose of 20 mg/kg bodyweight once a day for 5 days, with a maximum volume of injection of 5.5 ml. Animals were slaughtered at days 7, 12, 17, 22 and 27 post-treatment. Kidney, liver, skin + fat, muscle, and injection site (core and surrounding) were analysed using a validated HPLC-UV method for tylosin A, the marker residue, with a limit of quantification of 50 µg/kg (half the MRL value). Quantifiable levels of tylosin A were measured only in samples from the two first slaughter time points (7 days and 12 days post-treatment). In muscle, liver, kidney and skin + fat, tylosin A concentrations were below the MRL (100 µg/kg) at all time points. In the injection site, tylosin A concentrations were above the limit of quantification in 5 samples out of 6, and above the MRL in two animals out of 6 at day 7 post-treatment. At day 12 post-treatment, only one sample was above the limit of quantification. Consequently, the withdrawal period that can be derived from the data from this study, based on a posology of 20 mg/kg bodyweight per day for 5 consecutive days, and using the 'alternative' method with a 30% safety span (taking into account the sample above the LOQ at day 12), is 16 days with a limited volume of injection of 5 ml.

[1] CVMP note for guidance on the approach towards harmonisation of withdrawal periods (EMEA/CVMP/036/95) - link
[2] CVMP Guideline on injection site residues (EMEA/CVMP/542/03-FINAL) - link

A third study, non-GLP compliant, was conducted in 1992 with the product Bilosin 200 mg/ml solution for injection. The design of this study is not in accordance with current standards. The bodyweight of the pigs used for the study ranged between 64 to 77 kg. Groups of 4 animals were treated at a dose of 5 ml of the product per animal, i.e. 12.5-15.6 mg/kg every 12 hours for 3 days, and slaughtered at days 7, 14 and 21 post-treatment. Kidney, liver, muscle, and injection site were analysed using a partially validated microbiological method for tylosin, with a limit of detection of 200 µg/kg (i.e. twice the MRL). In muscle and kidney all tylosin concentrations were below the limit of detection at all time points. In the injection site, tylosin concentrations were higher than the limit of detection and the MRL in two animals at day 7 post-treatment, and then decrease below the limit of detection at days 14 and 21. In liver, tylosin concentrations were higher than the limit of detection and the MRL in all animals 7 days post-treatment, and in three animals at day 14 post-treatment (between 210 and 320 µg/kg) and then decrease below the limit of detection at day 21. The results from this study are difficult to interpret as it cannot be estimated what proportion of the tylosin concentration detected with this method is tylosin A (as the marker residue for the MRL is tylosin A). The metabolism in the liver is important, and it is likely that the proportion of tylosin A decreases in comparison with that of the initial product. For instance, data from calves show that 4 hours after an intramuscular administration, tylosin A represents 36.7%, 31% and 70% of the microbiological residues present in kidney, liver and muscle respectively, but no information on the injection is available (EMA, 1997)[3]. The CVMP considers that no reliable withdrawal period can be established from this study, due to the abovementioned shortcomings but most significantly resulting from the use of the microbiological method to detect tylosin residues, and the associated high limit of detection being above the MRL.

Two non-GLP compliant residue studies in pigs were conducted in 1993, with the product Bilosin 200 mg/ml solution for injection. The design of these studies is not in accordance with current standards. The bodyweight of pigs used for the study ranged between 63.50 to 82.55 kg. Groups of 4 animals were treated at a dose of 5 ml of the product per animal, i.e., 12.1 to 15.7 mg/kg twice a day for 3 days, and slaughtered at days 21, 28 and 35 post-treatment. Kidney, liver, fat, skin, muscle, and injection site (no information on the injection site sample is available) were analysed using a partially validated microbiological method for tylosin, with a limit of quantification of 100 µg/kg (i.e., equal to the MRL). In muscle, fat, skin, kidney and injection site, all tylosin concentrations were below the limit of quantification (100 µg/kg) at days 21, 28 and 35. In liver, tylosin concentrations were higher than the MRL at days 21 and 28 after the last dose, and then decrease below the MRL at day 35. As in the previous study, the results from these two non-GLP studies are difficult to interpret and use for the purpose of establishing withdrawal periods, particularly as this method does not allow for estimating what proportion of the tylosin concentration detected with this microbiological method corresponds to tylosin A. As a result, the CVMP considers that a reliable withdrawal period cannot be established from this study due to the numerous flaws of the study (notably the use of the microbiological method).

An additional peer-reviewed study conducted by Prats *et al*. 2002[4] with Tilosina 200 mg/ml was available. There is no information on the GLP status of the study in the publication, and the study design is not in accordance with all current standards. The bodyweight of the pigs ranged between 28 to 32 kg. Groups of 4 animals were treated at a dose of 10 mg/kg bodyweight once a day for 5 days, and slaughtered at days 3, 7, 10 and 14 post-treatment. Kidney, liver, skin + fat, muscle, and injection site (core 250 g) were analysed using a HPLC-UV method for tylosin A, the marker residue, with a limit of quantification of 50 µg/kg. At day 10 and day 14 post-treatment, all samples were below the limit of quantification. In liver, tylosin A concentrations were below the MRL (100 µg/kg) at all time points. In muscle, one sample was equal to the MRL at day 7 post-treatment. In kidney and skin + fat,

[3] https://www.ema.europa.eu/en/documents/mrl-report/tylosin-summary-report-3-committee-veterinary-medicinal-products_en.pdf
[4] Prats C., El Korchi G., Francesch R., Arboix M. and Perez B. (2002). Tylosin depletion from edible pig tissues. Res. Vet. Sci. 73, 323-325.

one sample was above the MRL at day 3 and day 7 post-treatment. In the injection site, tylosin A concentrations were above the MRL in all samples at day 3 and day 7 after the last dose. The maximum volume of injection has been estimated to be below 1.6 ml, given the bodyweight of the animals tested. The withdrawal period that can be derived from this dataset, based on the alternative method with a 30% safety span, and relating to a dose of 10 mg/kg bodyweight per day for 5 consecutive days, is 13 days with a limited volume of injection of 1.6 ml. Consequently, if this was to be extrapolated to larger pigs (fattening pigs or sows), the total dose would have to be divided requiring multiple injections, which is not considered a feasible option. For this reason, it is considered that this study cannot be used to determine a withdrawal period for pigs for the products concerned in this referral procedure.

An additional peer-reviewed residue study in pigs (Moats *et al*.1985[5]) was conducted with a tylosin product for which no information on the formulation is available. The study design is not in accordance with current standards. The bodyweight of the treated pigs ranged between 80 to 110 kg. Groups of 3 animals were treated with a single dose of 8.8 mg tylosin per kg bodyweight, and slaughtered at 4 hours and at days 1, 2, 4 and 8 post-treatment. Kidney, liver, muscle, and injection site (no information on the injection site sample is available) were analysed two months after the experiment (no information on the storage conditions and tylosin stability is available), using a HPLC-UV method for tylosin with a limit of detection below 100 µg/kg, and also using a microbiological method for tylosin, with a limit of detection around 500 µg/kg and for which no validation data are available. In muscle, liver and kidney, tylosin concentrations were not detected 24 hours post-treatment by either analytical method. In the injection site, tylosin concentrations were not detected 48 hours post-treatment by either method. Given the number of deficiencies identified, the CVMP could not derive a withdrawal period from this study. It is noted, however, that compared to the other studies reported, it is only after 48 hours post-treatment that all residues are below the MRL. However, in the absence of information regarding the stability of samples during their storage time, this result is strongly questionable.

An additional residue study performed with Tylan 200 is summarised in one of the reports from the Joint FAO/WHO Expert Committee on Food Additives (1991)[6]. This study was submitted with the original marketing authorisation application for Tylan 200 in France. The design is not in accordance with current standards. The bodyweight of the treated pigs was approximately 120 kg. Groups of 3 animals were treated at a dose of 8.8 mg/kg twice a day for 3 days with a maximum volume of injection of 5 ml, and slaughtered at days 0, 2, 4, 7, 14, 21, 28, and 35 post-treatment. Kidney, liver, and injection site (core: 100-110 g) were analysed using a microbiological method for tylosin, with a limit of quantification of 100 µg/kg, equal to the MRL and for which no validation data are available. Residues persisted the longest at the injection site, and were still above the MRL on day 21 post-treatment for one out of 3 animals. At day 28 post treatment, residues in injection site samples had depleted to below the quantification limit of 100 µg/kg. It is notable that residues in all other tissues sampled (kidney and liver) were below the respective MRLs by 14 days post-treatment. No conclusion could be drawn based on this study due to the very poor reporting and the fact that it was based on a microbiological method which does not allow for estimating what proportion of the tylosin concentration detected corresponds to tylosin A.

Discussion

[5] Moats , W. A., Harris, E. W., and Steele, N. C. (1985), J. Assoc. Off. Anal. Chem., Comparison of liquid chromatographic and bioassay procedures for determining depletion of intramuscularly injected tylosin.68, 413.
[6] JECFA (1991). Tylosin. In: Residues of Some Veterinary Drugs in Animals and Foods. FAO Food and Nutrition Paper 41/4, Monographs prepared by the thirty-eight meeting of the Joint FAO/WHO Expert Committee on Food Additives, Rome 22-31 January 1991, FAO, Rome 1991, 109-127.

There are 132 products within the scope of this referral procedure. The formulation of all the concerned products is very similar, with minor differences regarding the concentrations of the excipients used and of the active substance tylosin. Minor differences on concentrations of the same excipients have been considered not to have an impact on residue depletion from the injection site. Given the similarity of the formulations of all the products involved in the referral, and considering that minor differences in tylosin and excipient concentrations will not affect the residue depletion in pig tissues, the CVMP is of the opinion that reliable data from the most robust of the studies can be used to derive withdrawal periods for all products concerned in this referral procedure.

Seven residue studies in pigs were made available to CVMP. Based on the data from all residue depletion studies available, the Committee also concludes that the injection site is the residue determining tissue. From all the seven studies available, the CVMP concludes that the study with the product Tisergen 200 mg/ml, GLP compliant and designed in line with current standards, is the most reliable study available and can be used to derive a withdrawal period for pigs for all products concerned (despite the pH of the product used for this study was slightly more acidic that the pH reported in product specifications). From this study, data show that at day 12 post-treatment, only one sample was above the limit of quantification of 50 µg/kg, and below the MRL (100 µg/kg). An additional safety factor of 30% was added using the 'alternative' method, resulting in a withdrawal period of 16 days.

Based on the results from the residue depletion study conducted with the product Tisergen 200 mg/ml in pigs, the Committee concludes that a withdrawal period of 16 days, with a limit to the injection volume of 5 ml, should be applied to the products concerned by this referral procedure containing a tylosin concentration of up to 200 mg tylosin base per ml. For the veterinary medicinal product Tylobel 25% containing 250 mg tylosin base per ml (marketing authorisation holder: Bela-Pharm GmbH & Co.KG), the Committee considers that the total amount of injectable tylosin to be administered should be equal to that of the other residue depletion study with the product Tisergen 200 mg/ml, and from which a withdrawal period for all other products concerned is being derived. Given that in the study with the product Tisergen 200 mg/ml, the maximum concentration of tylosin injected was 1 g (5 ml * 200 mg/ml), then the maximum volume of injection for Tylobel 25% should be limited to 4 ml. An additional safety factor of 10% is then considered appropriate to account for any uncertainties regarding the impact of a lower volume of injection on the absorption rate of tylosin at the injection site. Consequently, the withdrawal period of Tylobel 25% (marketing authorisation holder: Bela-Pharm GmbH & Co.KG) should be of 18 days, with a limit to the injection volume of 4 ml.

3. Benefit-risk assessment

Introduction

The CVMP was requested to review all available residue depletion data for the veterinary medicinal products containing tylosin base and presented as a solution for injection for intramuscular use in pigs and recommend withdrawal periods for meat derived from treated pigs.

Benefit assessment

While the efficacy of the concerned products in pigs has not been specifically assessed as part of this referral, the products under assessment are considered to be effective in the treatment of conditions caused by sensitive organisms in pigs.

Risk assessment

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

A risk has been identified regarding the length of the authorised withdrawal periods for pigs (meat and offal), which, for some products, may be insufficient to allow residues of tylosin to fall below the authorised MRLs in all edible tissues by the end of the withdrawal period, thereby posing a risk to consumers of meat and offal from pigs treated with these products.

On the basis of a proprietary residue depletion studies in pig tissues, a withdrawal period for pig meat and offal of 16 days with a limit of the injection volume to 5 ml could be derived for all products, except for the product Tylobel 25% (marketing authorisation holder: Bela-Pharm GmbH & Co.KG) for which a withdrawal period of 18 days with a limit of the injection volume to 4 ml is retained. Data extrapolation was done based on the excipients composition of the products concerned.

Risk management or mitigation measures

To ensure the safety of consumers of food and food products derived from animals treated with products containing tylosin, the European Commission has set MRLs for tylosin in the edible tissues of pig. In order for tylosin-derived residues to deplete below the MRLs, a sufficient time between treatment and slaughter must be allowed.

The Committee considered that for the products concerned, the differences in concentrations of excipients will not lead to different rates of absorption from the injection site.

A reliable GLP compliant residue depletion study was provided by one of the marketing authorisation holders involved in the procedure, and the data allowed the recommendation to have a 16 day withdrawal period for meat and offal for 131 concerned products, i.e., for products containing 50 mg/ml and 200 mg/ml tylosin as a solution for injection for intramuscular use in pigs, while limiting the injection volume to 5 ml, and a 18 day withdrawal period for meat and offal for one concerned product (Tylobel 25% (marketing authorisation holder: Bela-Pharm GmbH & Co.KG)) while limiting the injection volume to 4 ml. The additional safety factor of 10% added to the later to account for the higher strength of tylosin and hence to account for any uncertainties regarding the impact of a lower volume of injection on the absorption rate of tylosin at the injection site.

Evaluation and conclusions on the benefit-risk balance

Having considered the grounds for referral and the data available, the CVMP concluded that for 131 products concerned, as referred in Annex I, the withdrawal periods for meat and offal derived from treated pigs should be amended to 16 days and the injection volume limited to 5 ml. For one product concerned (Tylobel 25% (marketing authorisation holder: Bela-Pharm GmbH & Co.KG)), the withdrawal period should be amended to 18 days and the injection volume limited to 4 ml.

For all concerned veterinary medicinal products, the overall benefit-risk balance remains positive subject to the recommended changes in the product information (see Annex III).

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

Whereas

- from the data provided the formulation of the concerned products is very similar, allowing the use of data from a reliable tylosin residue study in pigs, to be used to establish withdrawal periods for all concerned products;

- a GLP compliant residue study conducted with tylosin solution for injection, used intramuscularly in pigs was provided, and from which withdrawal periods could be established for meat and offal of treated pigs for all products concerned, as referred in Annex I. Withdrawal periods were considered adequate to ensure consumer safety when the injection volume was restricted;
- on the basis of the residue depletion data in pigs, the CVMP considered that the withdrawal periods for tylosin for meat and offal derived from treated pigs should be amended to provide assurance of consumer safety, as referred in Annex III;
- the CVMP considered that the overall benefit-risk balance for the products under this procedure (see Annex I) remains positive subject to amendments in the product information;

the CVMP has recommended variations of the marketing authorisations for veterinary medicinal products containing tylosin base (as a single active substance) presented as solutions for injection for intramuscular use in pigs (see Annex I) in order to amend the summaries of product characteristics, labelling and package leaflets in line with recommended changes in the product information as set out in Annex III.

Annex III

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

A. For Tylobel 25% listed in Annex I (Marketing Authorisation Holder: Bela-Pharm GmbH & Co.KG)

4.9 Amounts to be administered and administration route

In pigs do not administer more than 4 ml per injection site.

4.11 Withdrawal period(s)

Pigs:

Meat and offal: 18 days.

Labelling

8. WITHDRAWAL PERIOD

Pigs:

Meat and offal: 18 days.

Package leaflet

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

In pigs do not administer more than 4 ml per injection site.

10. WITHDRAWAL PERIOD

Pigs:

Meat and offal: 18 days.

B. For all other products listed in Annex I

Summary of product characteristics

4.9 Amounts to be administered and administration route

In pigs do not administer more than 5 ml per injection site.

4.11 Withdrawal period(s)

Pigs:

Meat and offal: 16 days.

Labelling

8. WITHDRAWAL PERIOD

Pigs:

Meat and offal: 16 days.

Package leaflet

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

In pigs do not administer more than 5 ml per injection site.

10. WITHDRAWAL PERIOD

Pigs:

Meat and offal: 16 days