Annex I

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

Member State EU/EEA	Applicant/Marketing authorisation holder	Name	INN	Pharmaceutical form	Strength	Animal species	Route of administration
Austria	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	PHARMASIN 200 mg/ml Injektionslösung für Rinder, Schafe, Ziegen und Schweine	Tylosin	Solution for injection	200,000 IU/ml	Cattle Sheep Goats Pigs	IM slow IV (cattle)
Austria	Biovet JSC 39 Petar Rakov Str. 4550 Peshtera Bulgaria	TYLAXEN 200 mg/ml Injektionslösung für Rinder, Schafe, Ziegen und Schweine	Tylosin	Solution for injection	200,000 IU/ml	Cattle Sheep Goats Pigs	IM slow IV (cattle)
Austria	Vana GmbH Wolfgang Schmälzl-Gasse 6 1020 Wien Austria	Vanatyl 200 mg/ml - Injektionslösung für Tiere	Tylosin	Solution for injection	200,000 IU/ml	Cattle Calves Sheep Goats Pigs Dogs	IM
Belgium	Cross Vetpharma Group Ltd Broomhill Road, Tallagh Dublin 24 Ireland	Bilovet	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs	IM
Belgium	VETOQUINOL SA/NV Kontichsesteenweg 42 2630 Aartselaar Belgium	Tylucyl	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs	IM slow IV (cattle)
Bulgaria	Biovet JSC 39, Petar Rakov Str. 4550 Pesthera Bulgaria	PHARMASIN 200 mg/ml solution for injection for cattle, sheep, goats and pigs	Tylosin	Solution for injection	200,000 IU/ml	Cattle Sheep Goats Pigs	IM slow IV (cattle)

Member State EU/EEA	Applicant/Marketing authorisation holder	Name	INN	Pharmaceutical form	Strength	Animal species	Route of administration
Croatia	VETOQUINOL SA Magny-Vernois 70200 Lure France	Tylucyl 200 mg/mL otopina za injekcije za goveda i svinje	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs	IM slow IV (cattle)
Cyprus	VETOQUINOL SA Magny-Vernois 70200 Lure France	Tylucyl 200 mg/ml raztopina za injiciranje za govedo in prašiče	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs	IM slow IV (cattle)
Denmark	Biovet JSC 39, Petar Rakov Str. 4550 Pesthera Bulgaria	Tylaxene	Tylosin	Solution for injection	200,000 IU/ml	Cattle Sheep Goats Pigs	IM slow IV (cattle)
Denmark	Huvepharma NV Uitbreidingstraat 80 BE-2600 Antwerpen Belgium	Tylmasin	Tylosin	Solution for injection	200,000 IU/ml	Cattle Sheep Goats Pigs	IM slow IV (cattle)
Denmark	Vetoquinol Scandinavia AB Lyngbyvej 20 DK-2100 København Denmark	Tylucyl	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs	IM slow IV (cattle)
Estonia	Vétoquinol SA, Magny-Vernois 70200 Lure France	Tylucyl	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs	IM slow IV (cattle)

Member State EU/EEA	Applicant/Marketing authorisation holder	Name	INN	Pharmaceutical form	Strength	Animal species	Route of administration
Finland	VETOQUINOL SA/NV Kontichsesteenweg 42 2630 Aartselaar Belgium	Tylucyl	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs	IM slow IV (cattle)
France	LILLY France 24 Boulevard Vital Bouhot 92200 Neuilly Sur Seine France	TYLAN 200	Tylosin	Solution for injection	200,000 IU/ml	Cattle Sheep Goats Pigs	IM slow IV (cattle)
France	HUVEPHARMA Uitbredingstraat 53 2600 Antwerp Belgium	PHARMASIN 200 MG/ML SOLUTION INJECTABLE POUR BOVINS OVINS CAPRINS ET PORCINS	Tylosin	Solution for injection	200,000 IU/ml	Cattle Sheep Goats Pigs	IM slow IV (cattle)
France	Biovet JSC 39, Petar Rakov Str. 4550 Pesthera Bulgaria	TYLAXEN 200 MG/ML SOLUTION INJECTABLE POUR BOVINS, OVINS, CAPRINS ET PORCINS	Tylosin	Solution for injection	200,000 IU/ml	Cattle Sheep Goats Pigs	IM slow IV (cattle)
France	CROSS VETPHARM GROUP Broomhill Road Dublin 24 Tallaght Ireland	BILOVET 200 MG/ML SOLUTION INJECTABLE	Tylosin	Solution for injection	200,000 IU/ml	Cattle Sheep Goats Pigs	IM slow IV (cattle)
France	VETOQUINOL Magny Vernois 70200 Lure France	TYLUCYL 200 MG/ML SOLUTION INJECTABLE POUR BOVINS ET PORCINS	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs	IM slow IV (cattle)

Member State EU/EEA	Applicant/Marketing authorisation holder	Name	INN	Pharmaceutical form	Strength	Animal species	Route of administration
Germany	Biovet JSC 39 Petar Rakov Str. 4550 Peshtera Bulgaria	Tylmasin 200 mg/ml Injektionslösung für Rinder, Schafe, Ziegen und Schweine	Tylosin	Solution for injection	200,000 IU/ml	Cattle Sheep Goats Pigs	IM slow IV (cattle)
Germany	Vétoquinol GmbH Parkstr. 10 88212 Ravensburg Germany	Tylucyl 200 mg/ml	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs	IM slow IV (cattle)
Germany	HUVEPHARMA NV Uitbreidingstraat 80 2600 Antwerpen Belgium	Pharmasin 200 mg/ml Injektionslösung für Rinder, Schafe, Ziegen und Schweine	Tylosin	Solution for injection	200,000 IU/ml	Cattle Sheep Goats Pigs	IM slow IV (cattle)
Germany	Bimeda Chemicals Export a Division of Cross Vetpharm Group, Ltd. Broomhill Road, Tallagh Dublin 24 Ireland	Bilovet 200 mg/ml Injektionslösung für Rinder und Schweine	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs	IM
Greece	Biovet JSC 39 Petar Rakov Str. 4550 Peshtera Bulgaria	TYLAXEN	Tylosin	Solution for injection	200,000 IU/ml	Cattle Sheep Goats Pigs	IM slow IV (cattle)

Member State EU/EEA	Applicant/Marketing authorisation holder	Name	INN	Pharmaceutical form	Strength	Animal species	Route of administration
Hungary	Huvepharma N.V. Uitbreidingstraat 80 2600 Antwerpen Belgium	PHARMASIN 200 mg/ml oldatos injekció szarvasmarhák, juhok, kecskék és sertések részére	Tylosin	Solution for injection	200,000 IU/ml	Cattle Sheep Goats Pigs	IM slow IV (cattle)
Hungary	Biovet JSC 39 Petar Rakov Str. 4550 Peshtera Bulgaria	TYLAXEN 200 mg/ml oldatos injekció szarvasmarhák, juhok, kecskék és sertések részére	Tylosin	Solution for injection	200,000 IU/ml	Cattle Sheep Goats Pigs	IM slow IV (cattle)
Hungary	VETOQUINOL SA Magny Vernois 70200 LURE France	Tylucyl 200 mg/ml oldatos injekció szarvasmarhák és sertések részére	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs	IM slow IV (cattle)
Ireland	Eli Lilly & Company Limited Elanco Animal Health Priestley Road Basingstoke Hampshire RG24 9NL United Kingdom	Tylan 200, 200mg/ml Solution for Injection	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs	IM
Ireland	Biovet JSC 39 Petar Rakov Str. 4550 Peshtera Bulgaria	Tylaxen 200 mg/ml solution for injection for cattle, sheep, goats and pigs.	Tylosin	Solution for injection	200,000 IU/ml	Cattle Sheep Goats Pigs	IM slow IV (cattle)

Member State EU/EEA	Applicant/Marketing authorisation holder	Name	INN	Pharmaceutical form	Strength	Animal species	Route of administration
Ireland	Huvepharma N.V. Uitbreidingsstraat 80 2600 Antwerpen Belgium	Pharmasin 200 mg/ml solution for injection for cattle, sheep, goats and pigs	Tylosin	Solution for injection	200,000 IU/ml	Cattle Sheep Goats Pigs	IM slow IV (cattle)
Ireland	Cross Vetpharm Group Ltd. Broomhill Road, Tallaght Dublin 24 Ireland	Bilovet 200 mg/ml Solution for Injection for cattle and pigs.	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs	IM
Italy	Vetoquinol Italia S.r.l. Via Piana 265 47032 Bertinoro (FC) Italy	TYLUCYL 200 mg/ml soluzione iniettabile per bovini e suini	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs	IM slow IV (cattle)
Italy	FATRO S.p.A. Via Emilia 285 40064 Ozzano Emilia (BO) Italy	VETIL	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs Dogs	IM
Italy	Biovet JSC 39 Petar Rakov Str. 4550 Peshtera Bulgaria	TYLAXEN 200 mg/ml. soluzione iniettabile	Tylosin	Solution for injection	200,000 IU/ml	Cattle Sheep Goats Pigs	IM slow IV (cattle)
Italy	ELI LILLY ITALIA S.p.A. Via Gramsci, 731/733 50019 Sesto Fiorentino Firenze Italy	TYLAN 200	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs	IM

Member State EU/EEA	Applicant/Marketing authorisation holder	Name	INN	Pharmaceutical form	Strength	Animal species	Route of administration
Italy	HUVEPHARMA NV Uitbreidingstraat 80 2600 Anversa Belgium	PHARMASIN 200 mg/ml soluzione iniettabile per bovini, ovini, caprini e suini	Tylosin	Solution for injection	200,000 IU/ml	Cattle Sheep Goats Pigs	IM slow IV (cattle)
Latvia	Vetoquinol S.A. Magny-Vernois B.P. 189 Lure Cedex France	Tylucyl	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs	IM slow IV (cattle)
The Netherlands	Cross Vetpharm Group Ltd. Broomhill Road, Tallaght Dublin 24 Ireland	BILOVET 200 mg/ml oplossing voor injectie voor runderen en varkens	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs	IM
Poland	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpia Belgium	Pharmasin	Tylosin	Solution for injection	200,000 IU/ml	Cattle Sheep Goats Pigs	IM slow IV (cattle)
Poland	Biovet JSC 39 Petar Rakov Str. 4550 Peshtera Bulgaria	Tylaxen	Tylosin	Solution for injection	200,000 IU/ml	Cattle Sheep Goats Pigs	IM slow IV (cattle)
Poland	Aniserve UG Geyerspergerstrasse 27 80689 Munich Germany	Bilovet 200	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs	IM

Member State EU/EEA	Applicant/Marketing authorisation holder	Name	INN	Pharmaceutical form	Strength	Animal species	Route of administration
Poland	Vetoquinol Biowet Sp. z o.o. ul. Kosynierów Gdyńskich 13-14 66-400 Gorzów Wielkopolski Poland	Tylucyl 200 mg/ ml solution for injection	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs	IM slow IV (cattle)
Portugal	Vetoquinol S.A. Magny-Vernois B.P. 189 Lure Cedex France	Tylucyl 200 mg/ml, solução injetável para bovinos e suínos	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs	IM slow IV (cattle)
Portugal	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	PHARMASIN 200 mg/ml solução injetável para bovinos, ovinos, caprinos e suínos	Tylosin	Solution for injection	200,000 IU/ml	Cattle Sheep Goats Pigs	IM slow IV (cattle)
Portugal	Biovet JSC 39 Petar Rakov Str. 4550 Peshtera Bulgaria	TYLAXEN 200 mg/ml solução injetável para bovinos, ovinos, caprinos e suínos	Tylosin	Solution for injection	200,000 IU/ml	Cattle Sheep Goats Pigs	IM slow IV (cattle)
Portugal	Lilly Portugal - Produtos Farmacêuticos, Ldª R. Cesário Verde, 5 - piso 4 Linda-a-Pastora 2790-326 Queijas Portugal	Tylan 200 mg/ml Solução injetável para bovinos e suínos	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs	IM

Member State EU/EEA	Applicant/Marketing authorisation holder	Name	INN	Pharmaceutical form	Strength	Animal species	Route of administration
Romania	Biovet JSC 39 Petar Rakov Str. 4550 Peshtera Bulgaria	Tylaxen 200 mg/ml	Tylosin	Solution for injection	200,000 IU/ml	Cattle Sheep Goats Pigs	IM slow IV (cattle)
Romania	Cross Vetpharm Group Ltd. Broomhill Road, Tallaght Dublin 24 Ireland	Bilovet 200 mg/ml	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs	IM
Slovak Republic	Vétoquinol s.r.o. Zámečnická 411 288 02 Nymburk Czech Republic	TYLUCYL 200 mg/ml injekčný roztok pre hovädzí dobytok a ošípané	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs	IM slow IV (cattle)
Slovak Republic	Biovet JSC 39 Petar Rakov Str. 4550 Peshtera Bulgaria	TYLOVET B- 200 mg/ml injekčný roztok	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs	IM
Slovenia	VETOQUINOL SA Magny-Vernois 70200 Lure France	Tylucyl 200 mg/ml raztopina za injiciranje za govedo in prašiče	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs	IM slow IV (cattle)
Spain	Cross Vetpharm Group Ltd. Broomhill Road, Tallaght Dublin 24 Ireland	BILOVET 200 mg/ml SOLUCION INYECTABLE PARA BOVINO Y PORCINO	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs	IM

Member State EU/EEA	Applicant/Marketing authorisation holder	Name	INN	Pharmaceutical form	Strength	Animal species	Route of administration
Spain	VETOQUINOL ESPECIALIDADES VETERINARIAS, S.A. A. Fuencarral Alcobendas km 15 700 Edificio Europa I Portal 3 2º5 28108 Alcobendas (Madrid) Spain	TYLUCIL 200 mg/ml SOLUCIÓN INYECTABLE	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs	IM slow IV (cattle)
Spain	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium	PHARMASIN 200 MG/ML SOLUCIÓN INYECTABLE PARA BOVINO OVINO CAPRINO Y PO	Tylosin	Solution for injection	200,000 IU/ml	Cattle Sheep Goats Pigs	IM slow IV (cattle)
Spain	Biovet JSC, 39 Petar Rakov Str. 4550 Peshtera Bulgaria	TYLAXEN 200 MG/ML SOLUCIÓN INYECTABLE PARA BOVINO OVINO CAPRINO Y PORC	Tylosin	Solution for injection	200,000 IU/ml	Cattle sheep Goats Pigs	IM slow IV (cattle)
Sweden	Vetoquinol Scandinavia AB Box 9 265 21 Åstorp Sweden	Tylucyl	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs	IM slow IV (cattle)
United Kingdom	Cross Vetpharm Group Ltd. Broomhill Road, Tallaght Dublin 24 Ireland	Bilovet 200 mg/ml Solution for Injection for Cattle and Pigs	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs	IM

Member State EU/EEA	Applicant/Marketing authorisation holder	Name	INN	Pharmaceutical form	Strength	Animal species	Route of administration
United Kingdom	Eli Lilly & Company Ltd Elanco Animal Health Priestley Road Basingstoke Hampshire RG24 9NL United Kingdom	Tylan 200, 200 mg/ml Solution for Injection	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs	IM
United Kingdom	Vetoquinol UK Ltd Vetoquinol House Great Slade Buckingham Industrial Park Buckingham MK18 1PA United Kingdom	Tylucyl 200 mg/ml solution for injection for cattle and pigs	Tylosin	Solution for injection	200,000 IU/ml	Cattle Pigs	IM slow IV (cattle)

Annex II

Scientific conclusions and grounds for amendment of the summary of product characteristics, labelling and package leaflet

Overall summary of the scientific evaluation of veterinary medicinal products containing tylosin that are administered parenterally and intended for the treatment of bovine mastitis caused by *Mycoplasma* spp. (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.

Finland noted that there are veterinary medicinal products containing tylosin that are administered parenterally and intended for the treatment of bovine mastitis caused by *Mycoplasma* spp. (or *Mycoplasma bovis*) which are currently authorised or pending authorisations in the European Union.

Mastitis caused by *M. bovis* differs in several ways from infections caused by the majority of more common mastitis pathogens (e.g. *Streptococcus* spp., *Staphylococcus* spp.). Often more than one quarter is affected and there is a marked drop in milk production. The pathogen is highly contagious and causes severe economic losses.

Finland noted that in the current scientific literature there is no support for the indication 'bovine mastitis caused by *Mycoplasma bovis*', but instead it is widely stated that there are no antimicrobial treatment options for bovine mastitis caused by mycoplasma.

Finland considered that ineffective treatment of mycoplasma mastitis with tylosin presents a serious concern to animal and human health as it delays the correct diagnosis, enables spread of the pathogen to other cows, impedes efficient/prudent control measures and increases risk for the development of antimicrobial resistance due to unnecessary use of antimicrobials.

Therefore, on 22 June 2016, Finland initiated a referral procedure under Article 35 of Directive 2001/82/EC, for veterinary medicinal products containing tylosin that are administered parenterally and intended for the treatment of bovine mastitis caused by *Mycoplasma* spp. The Committee for Medicinal Products for Veterinary Use (CVMP) was requested to consider the available data and the current scientific knowledge, and to provide its opinion on whether the indication 'bovine mastitis caused by *Mycoplasma* spp.' should be granted, maintained, varied or removed from the product information of the aforementioned products.

2. Discussion of data available

The use of tylosin as a veterinary medicine has been discussed in the CVMP reflection paper on the use of macrolides, lincosamides and streptogramins (MLS) in food-producing animals in the European Union: development of resistance and impact on human and animal health (EMA/CVMP/SAGAM/741087/2009)[1]. The Committee concluded that indications for use should preferably be restricted to those for which efficacy has been proven and general indications without a solid clinical basis should be avoided. In case of old products where data are sparse indications should be reviewed and revised, based on the current scientific knowledge, where appropriate.

[1] CVMP reflection paper on the use of macrolides, lincosamides and streptogramins (MLS) in food-producing animals in the European Union: development of resistance and impact on human and animal health (EMA/CVMP/SAGAM/741087/2009) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/11/WC500118230.pdf

In this procedure none of the concerned applicants/marketing authorisation holders provided data in support of the use of parenterally administered tylosin in the treatment of bovine mastitis caused by *Mycoplasma* spp. The marketing authorisation holder for the reference medicinal product 'Tylan 200 mg/ml', Elanco Animal Health, agreed with the concerns raised and concluded that there is a lack of reliable pre-clinical and clinical data in support of the respective indication. Hence, this marketing authorisation holder suggested a deletion of *Mycoplasma* spp. from the bovine mastitis indications for the concerned tylosin injectable products in the European Union.

Mycoplasma spp. causes a variety of infections including respiratory disease, otitis media, arthritis and mastitis in cattle worldwide. The major pathogen among the genera is *Mycoplasma bovis* that was first isolated from bovine mastitis in the USA in the 1960s. Since then it has spread to cattle worldwide and is known to cause severe economic losses in the herds affected.

Mastitis caused by *M. bovis* differs in several ways from infections caused by the majority of the more common mastitis pathogens (e.g. *Streptococcus* spp., *Staphylococcus* spp.). *M. bovis* is a highly contagious udder pathogen which typically causes mastitis that affects several quarters as it is capable of hematologic dissemination. The clinical signs vary but the milk loss is usually significant. Infected cows may remain externally normal with few clinical signs, even in severe cases. Affected milk may seem normal but it may also be purulent and/or have abnormal and discoloured secretions. In addition to the spread to other quarters, hematologic dissemination of mycoplasma to other parts of the body, e.g. joints, respiratory tract and ears, is possible. Mycoplasma is also easily spread via infected milk or milking equipment; thus, undetected or inefficiently treated mastitis in a cow may eventually lead to multiple infections in animals of different ages.

Mycoplasmas do not grow on conventional media; this hampers the diagnosis. Special media and atmosphere are required and the incubation period is long (7-10 days). For the same reasons sensitivity testing of *Mycoplasma* spp. is difficult. Internationally agreed methodology on sensitivity testing was not available at the time when tylosin was first authorised for veterinary use and there is none to date.

Current technologies such as Polymerase Chain Reaction (PCR) have enabled significantly quicker identification of *M. bovis*. The assay time has been reduced to hours as opposed to almost two weeks needed for the conventional culture. Screening of bulk tank milk can be used to detect infection in the herd and by pooled and/or individual sampling the carrier animals and the new infections are further tracked down.

Despite the improved diagnostic technologies, a major challenge in the diagnosis of mycoplasma mastitis (and in assessing success of antimicrobial treatment) remains that the pathogen may be shed intermittently in the milk of infected cows.

In 1977 Jasper [2] described natural resolution of the disease as unpredictable and recognised the danger of intermittently shedding cows. These findings have since been verified. In the study by Biddle *et al*., 2003[3], milk samples were collected daily for 28 days from 10 *Mycoplasma* spp. infected dairy cows and directly plated on mycoplasma agar to evaluate shedding patterns. 29% of the composite samples (81/280) and 43% of the quarter milk samples (433/1008) did not yield growth of Mycoplasma. The authors concluded that the risk of misdiagnosis is increased if multiple milk samples are not tested. A negative cultivation result after treatment could, before, have been falsely interpreted as bacteriological cure although at present it is known merely to be a characteristic of the infection.

[2] Jasper 1977. Mycoplasma and mycoplasma mastitis; JAVMA 1977 Vol. 170 No.10: 1167-1171
[3] Biddle MK, Fox LK, Hancock D 2003. Patterns of mycoplasma shedding in the milk of dairy cows with intramammary mycoplasma infection. J Am Vet Med Association 2003, 223 (8) 1163-1166

Jasper was also one of the first to question the efficacy of antimicrobials in the treatment of mycoplasma mastitis. He reported testing various antimicrobials, including tylosin. Details of the treatment experiments are scarce, but altogether he described the results as unrewarding. The proportion of cows that were found to be *M. bovis* positive after 5 days of tylosin treatment (3g/cow/day i.m.) was as high as 53% (8/15) (Jasper (1977)). The dose 3 g/cow/day is within the dose range widely authorised in Europe i.e. 4-10 mg/kg/day i.m.

A thorough literature search to find new data on the efficacy of tylosin in the treatment of mycoplasma mastitis revealed no original studies. Instead several comprehensive review articles dealing with mycoplasma mastitis have been published (Pfützner and Sachse (1996)[4], Nicholas and Ayling (2003)[5], Gonzalez and Wilson (2003)[6], Maunsell *et al.* (2011)[7], Fox (2012)[8], Nicholas *et al*. (2016)[9]). The common view shared in these reviews is that mycoplasma mastitis is untreatable or unresponsive to antimicrobial treatment and that quick identification of infected animals is crucial to prevent the spread of the pathogen in the herd.

3. Benefit-risk assessment

Introduction

The aim of the referral procedure was to consider the available data and current scientific knowledge regarding the efficacy of parenterally administered tylosin formulations authorised for the treatment of bovine mastitis caused by *Mycoplasma* spp..

Benefit assessment

No pre-clinical or clinical data in support of the indication were provided from the applicants/marketing authorisation holders and no benefits of the use on tylosin in treatment of mastitis caused by *Mycoplasma* spp. have been identified. These veterinary medicinal products are also indicated for the treatment of several other diseases including respiratory and gastrointestinal infections, but these indications fall outside the scope of this referral procedure.

Risk assessment

Tylosin belongs to macrolides which have been classified as critically important antimicrobials both in veterinary and human medicine. It is generally accepted that all use of antimicrobials increases the risk of antimicrobial resistance and thus to minimise the risk of transmission of those resistance to the public and animals all unnecessary use should be carefully avoided.

M. bovis is a highly contagious udder pathogen that is easily spread. It is a major problem for milk production and animal welfare in the herds affected, and causes severe economic losses. In addition to mastitis *Mycoplasma* spp. causes respiratory infections, arthritis and otitis (media) both in young and old cattle. Inefficient treatment of mastitis caused by *Mycoplasma* spp. with tylosin delays the correct diagnosis, impedes efficient control measures and enables the spread of the pathogen to other animals of the herd thus risking animal health and welfare along with increasing the need for antimicrobial treatment and development of antimicrobial resistance.

[4] Pfützner H. and Sachse K. 1996. *Mycoplasma* bovis as an agent of mastitis, pneumonia, arthritis and genital disorders in cattle. Rev. sci. tech. Off. int. Epiz. 1996, 15(4), 1477-1494
[5] Nicholas RAJ and Ayling R 2003. *Mycoplasma* bovis: disease, diagnosis and control; Res. Vet. Sci. 2003: 74: 105-112
[6] Gonzalez RN and Wilson DJ 2003. Mycoplasma mastitis in dairy herds; Vet Clin North Am Food Anim Pract 2003: 19(1):199-221
[7] Maunsell FP, Woolums AR, Francoz D, Rosenbuch RF, Step DL, Wilson DJ, Janzen ED 2011. ACVIM Consensus Statement: *Mycoplasma* bovis infections in cattle; J Vet Intern Med; 2011: 25:772-783
[8] Fox LK 2012. Mycoplasma mastitis: causes, transmission and control. Vet Clin North Am Food Anim Pract 2012; 28: 225-37
[9] Nicholas RAJ, Fox LK, Lysnyansky I 2016. Mycoplasma mastitis in cattle: To cull or not to cull. A review. Vet Journal 2016 (2016) 142-147

Monitoring the lack of efficacy is a part of the veterinary pharmacovigilance system. However, it is difficult, if not impossible, to assess the true level of lack of efficacy of tylosin in the treatment of 'bovine mastitis caused by *Mycoplasma* spp.' based solely on the pharmacovigilance data as it is highly likely that such adverse events for antimicrobials are very seldom reported.

Risk management or mitigation measures

The Committee considered that all references to indications 'bovine mastitis caused by *Mycoplasma* spp.' or 'bovine mastitis caused by *Mycoplasma bovis*' should be deleted from the product information for veterinary medicinal products containing tylosin that are administered parenterally.

As the aforementioned indications have been included in the product information of these veterinary medicinal products for many years, the Committee considered that information on the removal of the indication should be given, thus the following warning sentence should be added to the product information: *'The efficacy data do not support the use of tylosin for the treatment of bovine mastitis caused by Mycoplasma spp.'.*

Evaluation and conclusions on the benefit-risk balance

On the basis of the available information the Committee considered that the treatment of bovine mastitis caused by *Mycoplasma* spp. with veterinary medicinal products containing tylosin that are administered parenterally is not effective. Furthermore, the Committee concluded that inefficient antimicrobial treatment with tylosin delays the correct diagnosis, impedes efficient control measures and enables the spread of the pathogen thus risking animal welfare, causing severe economic losses and a risk of increased antimicrobial use and resistance.

Provided that the indications 'bovine mastitis caused by *Mycoplasma* spp.' or 'bovine mastitis caused by *Mycoplasma bovis*' are deleted from the indication of parenteral tylosin products, the Committee considered that the benefit-risk of these products could continue to be regarded as positive.

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

Whereas

- in the absence of pre-clinical or clinical data and in light of the current scientific knowledge the CVMP considered that the treatment of bovine mastitis caused by *Mycoplasma* spp. with veterinary medicinal products containing tylosin that are administered parenterally is not effective;
- the CVMP considered that inefficient antimicrobial treatment of bovine mastitis caused by *Mycoplasma* spp. with tylosin delays the correct diagnosis, impedes efficient control measures and enables the spread of the pathogen thus risking animal health and welfare, causing severe economic loss and increasing the risk of antimicrobial resistance due to increased need for antimicrobial treatment. Consequently the CVMP concluded that the indications 'bovine mastitis caused by *Mycoplasma* spp.' or 'bovine mastitis caused by *Mycoplasma bovis*' can no longer be maintained;

the CVMP has recommended the variation of the marketing authorisations for veterinary medicinal products containing tylosin that are administered parenterally and intended for the treatment of bovine mastitis caused by *Mycoplasma* spp. (see Annex I) in order to amend the summary of product characteristics, labelling and package leaflet in line with recommended changes in the product information as set out in Annex III. Furthermore, this indication should not be granted for the pending marketing authorisation applications (see Annex I).

Annex III

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

Summary of product characteristics

4.2 Indication(s) for use

Delete, where applicable, the indication 'bovine mastitis caused by *Mycoplasma* spp.'. In cases where the indication for a particular product specifies the mastitis pathogen as *Mycoplasma bovis*, the indication should also be deleted.

Add, to all products:

4.5 Special precautions for use

Special precautions for use in animals

The efficacy data do not support the use of tylosin for the treatment of bovine mastitis caused by *Mycoplasma* spp.

4.9 Amounts to be administered and administration route

Delete, where applicable, any specific dosing recommendation related to 'bovine mastitis caused by *Mycoplasma* spp.'. In cases where the indication for a particular product specifies the mastitis pathogen as *Mycoplasma bovis*, the dosing instruction should also be deleted.

5.1 Pharmacodynamic properties

Delete, where applicable, any references to 'bovine mastitis caused by *Mycoplasma* spp. or *Mycoplasma bovis'*.

Labelling:

Delete, where applicable, any references to 'bovine mastitis caused by *Mycoplasma* spp. or *Mycoplasma bovis'*.

Package leaflet:

4. INDICATION(S)

Delete, where applicable, the indication 'bovine mastitis caused by *Mycoplasma* spp.'. In cases where the indication for a particular product specifies the mastitis pathogen as *Mycoplasma bovis*, the indication should also be deleted.

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

Delete, where applicable, any specific dosing recommendation related to 'bovine mastitis caused by *Mycoplasma* spp.'. In cases where the indication for a particular product specifies the mastitis pathogen as *Mycoplasma bovis*, the dosing instruction should also be deleted.

Add, to all products:

12. SPECIAL WARNING(S)

Special precautions for use in animals:
The efficacy data do not support the use of tylosin for the treatment of bovine mastitis caused by *Mycoplasma* spp.