Annex I

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

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Bulgaria	Farma vet Ltd. 40 Otec Paisii str. Shumen Bulgaria	Колитетравит / COLI – TETRAVIT	Oxytetracycline hydrochloride Colistin sulphate	5.0 g 3 500 000 UI	Oral solution	Chickens and pigs	Oral administration
Bulgaria	COOPHAVET S.A.S. B.P. 7 Saint Herblon 44153 ANCENIS Cedex France	Колисултрикс/ COLISULTRIX	Trimethoprim Colistin sulphate	3.75 g 50 MIU	Oral powder	Chickens, rabbits, pigs, calves and lambs	Oral administration
Croatia	Arnika Veterina d.o.o. Vodovodna 20a 10000 Zagreb Croatia	COLISULTRIX	Trimethoprim Colistin sulphate	3.75 g 50 MIU	Oral powder	Calves, lambs, kids, piglets, poultry and rabbits	Oral
Croatia	Ceva Santé Animale 10 Avenue de la Ballastière 33500 Libourne France	QUINOCOL	Enrofloxacin Colistin sulphate	100 g 41.67 g	Oral solution	Chicken, turkey	Oral
Cyprus	FATRO S.p.A. Via Emilia, 285 40064 Ozzano Emilia (Bologna) Italy	BACOLAM powder for oral solution for calves, sheep, goats, pigs, foals, chickens, turkeys (excluding layers)	Amoxicillin trihydrate Colistin sulphate	100 mg 500,000 I.U.	Powder for oral solution	Calves, sheep, goats, pigs, foals, chickens, turkeys (excluding layers)	Administer the dose subdivided into two administrations each day, dissolved in drinking water or in milk.

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Cyprus	Vetoquinol Italia S.R.L Via Piana, 265 47032 Bertinoro Italy	ZEMAMIX premix for medicated feedingstuff for pigs	Amoxicillin trihydrate Colistin sulphate	11.48 g 4.00 g	Premix for medicated feedingstuff	Pigs	Premix for medicated feedingstuff in insoluble powder, to be administered orally properly mixed in solid feed.
Czech Republic	LAVET Pharmaceuticals Ltd. Ottó u.14 1161 Budapest Hungary	AMOXYCOL plv.sol.	Amoxicillin trihydrate Colistin sulphate	640 mg/g 3 200 000 IU/g	Powder for oral solution for use in drinking water or in feed	Pigs, chicken (broilers)	Oral
Czech Republic	COOPHAVET S.A.S. B.P. 7 Saint Herblon 44153 ANCENIS Cedex France	BELCOSPIRA ORAL prášek pro přípravu perorálního roztoku	Colistin sulphate Spiramycin adipate	500 000 IU 650 000 IU	Powder for oral solution	Calves, piglets, foals, chicken	Oral
Czech Republic	COOPHAVET S.A.S. B.P. 7 Saint Herblon 44153 ANCENIS Cedex France	COLISULTRIX plv. sol.	Trimethoprim Colistin sulphate	37.5 mg 500 000 IU/g	Powder for oral solution	Chicken	Oral

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Czech Republic	Industria Italiana Integratori Trei S.p.A. Via Corassori, 62 41100 Modena Italy	MICROAMOX COLI premix pro medikaci krmiva	Amoxicillin trihydrate Colistin sulphate	100 mg/g 600 000 IU/g	Premix for medicated feed	Pigs	Oral
France	MERIAL 29 avenue Tony Garnier 69007 LYON France	BELCOSPIRA ORAL	Colistin sulphate Spiramycin adipate	500 000 IU/g 650 000 IU/g	Powder for oral use	Cattle, pigs, poultry	Oral use
France	LABORATOIRES BIOVE 3 Rue de Lorraine 62510 Arques France	COLAMPI B	Ampicillin trihydrate Colistin sulphate	25 mg/g 0.075 MIU/g	Powder for oral use	Pigs, calves	Oral use
France	LABORATOIRES BIOVE 3 Rue de Lorraine 62510 Arques France	COLAMPI O	Ampicillin trihydrate Colistin sulphate	1 g/tablet 1 MIU/ tablet	Tablet	Calves	Oral use
France	VETOQUINOL Magny Vernois 70200 Lure France	COLIDIARYL	Colistin sulphate Erythromycin estolate	83 400 IU/g 16 600 IU/g	Powder for oral use	Lamb, goat, piglets, foals, calves	Oral use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
France	MERIAL 29 avenue Tony Garnier 69007 LYON France	COLISULTRIX POUDRE	Colistin sulphate Trimethoprim	500 000 IU/g 37.5 mg/g	Powder for oral use	Lamb, goat, rabbits, pigs, calves, poultry	Oral use
France	VIRBAC 1ere Avenue 2065m L.I.D. 06516 Carros Cedex France	ENTEROGEL 30	Colistin sulphate Scopolamine Sulfaguanidine	10.5 MIU/ syringe 0.216 g/ syringe 4.2 g/ syringe	Oral paste	Foals, calves	Oral use
France	VIRBAC 1ere Avenue 2065m L.I.D. 06516 Carros Cedex France	INTESTIVO	Colistin sulphate Sulfaguanidine	2.5 MIU/ tablet 1 g/tablet	Tablet	Lamb, goat, calve	Oral use
France	MERIAL 29 avenue Tony Garnier 69007 LYON France	N.P. 8	Colistin sulphate Neomycin sulfate	300 000 IU/g 60 000 IU/g	Powder for oral use	Lamb, goat, rabbits, pigs, calves, poultry	Oral use
France	QALIAN 34 rue Jean Monnet ZI D'Etiché BP20341 49503 Segré Cedex France	OXYCOLI	Colistin sulphate Oxytetracycline hydrochloride	200 000 IU/g 0.07 g/g	Premix for medicated feed	Pigs, calves	Oral use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
France	Ceva Santé Animale 10 Avenue de la Ballastière 33500 Libourne France	PHADILACT	Ampicillin trihydrate Colistin sulphate	5.00 mg/g 1 000 000 IU/g	Powder for oral use	Lamb, goat, calves, poultry	Oral use
France	QALIAN 34 rue Jean Monnet ZI D'Etiché BP20341 49503 Segré Cedex France	PREMELANGE MEDICAMENTEUX CS FRANVET	Colistin sulphate Sulfadimethoxine	700 000 IU/g 210 mg/g	Premix	Lamb, calves	Oral use
France	VETOQUINOL Magny Vernois 70200 Lure France	SEPTOTRYL-COLISTINE	Colistin sulphate Sulfamethoxypyridazine	2 MIU/ tablet 1 g/tablet	Tablet	Lamb, dogs, foals, calves	Oral use
Hungary	Lavet Gyógyszergyártó Kft. Ottó u. 14 1161 Budapest Hungary	Amoxycol por belsőleges oldathoz A.U.V.	Amoxicillin trihydrate Colistin sulphate	640.0 mg/g 133.3 mg/g	Powder for oral solution	Pigs, chickens	In drinking water use
Hungary	Industria Italiana Integratori Trei S.p.A. Viale Corassori, 62 41100 Modena Italy	BETAMICYN gyógypremix sertések részére A.U.V.	Amoxicillin trihydrate Colistin sulphate	100 g/kg 600 MIU/kg	Premix for medicated feeding stuff	Pigs	In feed use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Hungary	Rhone Vet Kft. Petőfi u. 9. 2053 Herceghalom Hungary	Colisutrix belsőleges por	Trimethoprim Colistin sulphate	3.75 g/100 g 50 MIU/100 g	Powder for oral solution	Cattle (calves), sheep (lambs), pigs and chickens, rabbit, goat	In drinking water use
Italy	Fatro S.p.a. Via Emilia, 285 40064 Ozzano Emilia Italy	COMBOMIX	Amoxicillin trihydrate Colistin sulphate	115 mg/g 40 mg/g	Premix for medicated feeding stuff	Pigs, chickens (other than laying hens in lay)	Oral
Italy	Industria Italiana Integratori Trei S.P.A. Via Affarosa, 4 42010 - Rio Saliceto Italy	BETAMICYN	Amoxicillin trihydrate Colistin sulphate	100 g/kg 600 MIU/kg	Premix for medicated feeding stuff	Pigs	Oral
Italy	Doxal Italia S.p.a. largo Donegani 2 20121 - Milano Italy	CLOVER BMP	Amoxicillin trihydrate Colistin sulphate	115 g/kg 40 g/kg	Premix for medicated feeding stuff	Pigs	Oral
Italy	Industria Italiana Integratori Trei S.P.A. Via Affarosa, 4 42010 - Rio Saliceto Italy	DUOBAN	Doxycycline hyclate Colistin sulphate	60 mg/g 1 200 000 UI/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	Virbac S.r.l. Via Caldera 21 20153 Milano Italy	DUALMIX	Amoxicillin trihydrate Colistin sulphate	115 mg/g 4 mg/g (20 000 UI/mg)	Premix for medicated feeding stuff	Pigs, chickens (except hens producing eggs for human consumption)	Oral
Italy	Fatro S.p.a. Via Emilia, 285 40064 Ozzano Emilia Italy	BACOLAM	Amoxicillin trihydrate Colistin sulphate	500 mg/g 2 500 000 IU/g	Powder for oral solution	Calves, sheep and goats, pigs, ponies, chickens, turkeys (excluding hens)	Oral
Italy	Intervet Productions S.r.l. Via Nettunense, km 20,300 04011 - Aprilia Italy	NADASIN	Amoxicillin trihydrate Colistin sulphate	500 mg/g 200 mg/g	Oral powder for use in drinking water or liquid feed	Calves, pigs, chickens (other than laying hens), turkeys	Oral
Italy	Vetoquinol Italia S.r.l. Via Piana, 265 47032 Bertinoro Italy	NEOMIX COMPLEX	Neomycin sulfate Colistin sulphate	200 mg/g 20 000 IU/g	Oral powder, for use in drinking water or liquid feed	Calves, piglets, broilers and turkeys	Oral
Italy	Vétoquinol Italia S.r.l. Via Piana 265 47032 Bertinoro Italy	ZEMAMIX	Amoxicillin trihydrate Colistin sulphate	100 mg/g 40 mg/g	Oral powder	Pigs	Oral use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Italy	Virbac S.r.l. Via Caldera 21 20153 Milano Italy	STABOX COLI	Amoxicillin trihydrate Colistin sulphate	100 mg/g 800 000 IU/g	Premix for medicated feeding	Pigs, chickens (except hens producing eggs for human consumption)	Oral
Latvia	Ceva Santé Animale 10 Avenue de la Ballastière 33500 Libourne France	Quinocol Oral Solution	Enrofloxacin Colistin sulphate	100 g 41.67 g	Solution for oral use	Chicken, turkeys	Oral use
Lithuania	Lavet Pharmaceuticals Ltd. Ottó u. 14. H-1161 Budapest Hungary	AMOXYCOL, geriamieji milteliai	Amoxicillin trihydrate Colistin sulphate	640 mg/ml 3 200 000 IU/ml	Water soluble oral solution	Pig, chicken	Oral
Lithuania	COOPHAVET S.A.S. B.P. 7 Saint Herblon 44153 ANCENIS Cedex France	COLISULTRIX, geriamieji milteliai	Trimethoprim Colistin sulphate	3.75 g/100 g 50 MIU/100 g	Oral powder	Calves, lamb, kid, piglets, poultry and rabbits	Oral
Lithuania	COOPHAVET S.A.S. B.P. 7 Saint Herblon 44153 ANCENIS Cedex France	BELCOSPIRA ORAL, geriamieji milteliai	Spiramycin adipate Colistin sulphate	65 MIU/100 g 50 MIU/100 g	Oral powder	Calves, lamb, kid, foals, piglets, poultry and rabbits.	Oral

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Luxembourg	VETOQUINOL Magny Vernois 70200 Lure France	COLIDIARYL	Erythromycin estolate Colistin sulphate	83 400 UI/g 16 600 UI/g	Powder for oral use	Lamb, goat, piglets, foals, calves	Oral use
Luxembourg	VETOQUINOL Magny Vernois 70200 Lure France	SEPTOTRYL-COLISTINE	Colistin sulphate Sulfamethoxypyridazine	2 MIU/tablet 1 g/tablet	Tablet	Lamb, dogs, foals, calves	Oral use
Netherlands	Dopharma B.V. Zalmweg 24 4941 VX Raamsdonksveer The Netherlands	AMOXY-COL WSP	Amoxicillin trihydrate Colistin sulphate	150 mg/g 500 000 IU/g	Powder for oral use via drinking water	Pigs	Oral, via drinking water
Poland	Dopharma B.V. Zalmweg 24 4941 VX Raamsdonksveer The Netherlands	Amoxy-col WSP	Amoxicillin trihydrate Colistin sulphate	150 mg/g 500 000 IU/g	Powder for oral solution	Pigs	Oral use
Poland	Fatro S.p.A. Via Emilia 285-40064 Ozzano Emilia Italy	Bacolam	Amoxicillin trihydrate Colistin sulphate	100 mg/g 500 000 IU/g	Powder for administration in drinking water or milk	Cattle, chickens, pigs	Oral use
Poland	SkanVet Poland Sp. z o.o. Skiereszewo, ul. Kiszkowska 9 62-200 Gniezno Poland	Colamox 3200/640	Amoxicillin trihydrate Colistin sulphate	640 mg/g 3 200 000 IU/g	Powder for oral solution	Chicken, pigs	Oral use

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Poland	Drwalewskie Zakłady Przemysłu Bioweterynaryjnego S.A ul. Grójecka 6 05-651 Drwalew Poland	Spiracol AD	Spiramycin adipate Colistin sulphate	100 000 IU/g 130 000 IU/g	Powder for use in drinking water	Cattle, chickens, pigs	Oral use
Portugal	DIVASA FARMAVIC DE PORTUGAL Produtos e Equipamentos Veterinários, Lda. Praceta Jaime Cortesão, Nº 1 – R/C Loja Esq. 2625-170 Póvoa de Santa Iria Portugal	NUTRIVET TOTAL, pó para suspensão oral, para vitelos e cordeiros	Ampicillin trihydrate Colistin sulphate	0.7 g 1 500 000 IU	Powder for oral suspension for administration in drinking water	Calves and lambs	Oral
Portugal	VETLIMA-Sociedade Distribuidora de Produtos Agro-Pecuários, S.A. Centro Empresarial da Rainha, Lote 27 2050-501 Vila Nova da Rainha Portugal	COLIMIX (116 g/kg /40 g/kg), pré-mistura medicamentosa para alimento medicamentoso para suínos	Amoxicillin trihydrate Colistin sulphate	116 g/kg 40 g/kg	Premix for medicated feeding stuff	Pigs	Oral

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Portugal	Fatro S.p.A Via Emilia Nº 285 Ozzano Emilia Italy	Premaxol, 100 mg/g + 40 mg/g de pré-mistura medicamentosa para alimento medicamentoso para suínos, frangos e galinhas (excepto poedeiras)	Amoxicillin trihydrate Colistin sulphate	100 mg/g 40 mg/g	Premix for medicated feeding stuff	Pigs and chickens (except laying)	Oral
Romania	Industria Italiana Integratori Trei S.p.A Viale Corassori, 62 41100 Modena Italy	DUOBAN	Doxycycline hyclate Colistin sulphate	60 mg/g 1 200 000 IU/g	Premix	Pigs	Mixed in feeding stuffs
Romania	Industria Italiana Integratori Trei S.p.A Viale Corassori, 62 41100 Modena Italy	MICROAMOX COLI	Amoxicillin trihydrate Colistin sulphate	100 mg/g 600 000 IU/g	Premix	Pigs	Mixed in feeding stuffs
Romania	COOPHAVET SAS Herblon 44150 Ancenis France	COLISULTRIX	Trimethoprim Colistin sulphate	37.5 mg 500 000 IU	Powder for oral solution	Calves, lambs, kids, pigs, rabbits and poultry	Oral administration in drinking water or liquid feed

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Romania	SC ROMVAC COMPANY SA Sos. Centurii nr.7 077194 Voluntari Romania	GALIPROTECT C	Oxytetracycline hydrochloride Colistin sulphate	12 mg/tablet 5 mg/tablet	Tablets	Poultry (grouse and web-footed)	Oral administration individually
Romania	Lavet Pharmecuticals LTD. Otto u.14. H-1161 Budapest Hungary	AMOXYCOL	Amoxicillin trihydrate Colistin sulphate	640 mg/g 3 200 000 IU/g	Powder for oral solution	Pigs, chickens	Oral administration in drinking water
Slovakia	Pharmagal spol. s.r.o. Murgašova 5 949 01 Nitra Slovakia	Amikol perorálny prášok	Amoxicillin trihydrate Colistin sulphate	57.5 mg/g 8.1 mg/g	Oral powder	Pig, calves, poultry (chicken, turkey), pigeon	Oral administration, after incorporation into the feed
Slovakia	Pharmagal spol. s.r.o. Murgašova 5 949 01 Nitra Slovakia	Amikol premix na medikáciu krmiva	Amoxicillin trihydrate Colistin sulphate	57.5 mg/g 200 000 IU/g	Premix for medicated feeding stuff	Pig	Oral administration, after incorporation into the feed
Slovakia	Pharmagal spol. s.r.o. Murgašova 5 949 01 Nitra Slovakia	Amikol-S prášok na perorálny roztok	Amoxicillin trihydrate Colistin sulphate	575 mg/g 81 mg/g	Powder for oral solution	Pig, calves, poultry (chicken, turkey), pigeon	Oral administration via drinking water

Member State EU/EEA	Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Slovakia	Pharmagal spol. s.r.o. Murgašova 5 949 01 Nitra Slovakia	SUTRICOL prášok na perorálny roztok	Colistin sulphate Sulfadimidine sodium Trimethoprim	300 000 IU/g 50 mg/g 12.5 mg/g	Powder for oral solution	Broiler chicken, pig, rabbit, calve	Oral administration via drinking water
Slovakia	Pharmagal spol. s.r.o. Murgašova 5 949 01 Nitra Slovakia	TETRAKOL prášok na perorálny roztok	Chlortetracycline hydrochloride Colistin sulphate	120 mg/g 120 000 IU/g	Powder for oral solution	Pig, calves, poultry (chicken)	Oral administration via drinking water
Spain	CENAVISA, S.A. Camí Pedra Estela s/n. Reus (Tarragona) 43205 Spain	TRISOL	Ampicillin trihydrate Colistin sulphate	200 mg/g 1 025 000 IU/g	Oral powder	Lambs	In drinking water use
Spain	LABORATORIOS MAYMO, S.A. Via Augusta, 302. Barcelona 08017 Spain	COLIPHUR 100 000/1 200 000 UI/ml solución para administración en agua de bebida	Neomycin sulfate Colistin sulphate	100 000 IU/ml 1 200 000 IU/ml	Solution for use in drinking water	Pig for fattening	In drinking water use

Annex II

Scientific conclusions and grounds for the withdrawal of the marketing authorisations

Overall summary of the scientific evaluation of all veterinary medicinal products containing colistin in combination with other antimicrobial substances to be administered orally (see Annex I)

1. Introduction

Colistin is a cationic, multicomponent lipopeptide antibacterial agent produced by cultures of *Bacillus polymyxa* var. *colistinus*. In veterinary medicine, it is used typically as the sulphate salt for oral preparations and as the methanesulphonate for parenteral administration. It belongs to the polymyxin therapeutic class and is identical to polymyxin E. Colistin is used for the treatment and prevention of diseases caused by sensitive bacteria (e.g. *Escherichia coli*) in pigs, poultry, rabbits, cattle, sheep and goats. Combinations of colistin with other antimicrobials are available for group treatments of gastro-intestinal and respiratory infections in food-producing animals in some European Member States. There are also products available for parenteral, intramammary and intrauterine administration, which are not within the scope of this referral. Colistin is also used in human medicine.

In the light of the increase in bacterial resistance to antimicrobial substances, discussions are ongoing in the EU and on an international level on how to contain and minimise this phenomenon for the benefit of human and animal health. Following a request from the European Commission, in July 2013 the CVMP and CHMP adopted scientific advice and detailed considerations on colistin[1]. This advice critically reviewed information on the use of colistin in food-producing animals in the EU, its effect on the development of resistance to this category of antimicrobial agents in bacterial species that are of importance for human and animal health, and the possible impact on human and animal health.

On the status of colistin as a critically important antimicrobial in human medicine, the advice stated:

"Transfer of resistance either on mobile genetic elements (such as plasmids) between bacteria or from animals to humans has not been reported."

"However, severe nosocomial infections due to multidrug-resistant (MDR) Gram-negative bacteria now account for high morbidity and mortality in man. Colistin is therefore nowadays a last resort drug in human medicine in the context of treatment of infections caused by MDR Pseudomonas aeruginosa, Acinetobacter baumannii and Enterobacteriaceae (Escherichia coli, Klebsiella pneumoniae), for which mortality can be extremely high."

Regarding combinations of colistin with other antimicrobials the advice indicates that "*The marketing authorisations for these products should be reviewed and unless sound justification can be provided that the combination is in line with responsible use principles, combination products should be withdrawn."*

Considering the significant number of products containing colistin authorised in the EU it was considered appropriate to follow a stepwise approach based on risk for the revision of summary of the product characteristics of products containing colistin. In view of the information available in the reports of the EMA European Surveillance of Veterinary Antimicrobial Consumption[2] on sales of

[1] Request for scientific advice on the impact on public health and animal health of the use of antibiotics in animals, answer to the first request from the European Commission (EMA/363834/2013)
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/07/WC500146812.pdf

Use of colistin products in animals within the European Union: development of resistance and possible impact on human and animal health (EMA/755938/2012)
http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/07/WC500146813.pdf

[2] European Medicines Agency, European Surveillance of Veterinary Antimicrobial Consumption. Sales of veterinary antimicrobial agents in 26 EU/EEA countries in 2012. Fourth ESVAC report.

antimicrobials, the number of marketing authorisations per pharmaceutical form/route of administration and types of use, the products containing colistin only and administered orally (group treatment) were considered a priority.

In May 2014 the European Commission initiated a referral procedure under Article 35 of Directive 2001/82/EC for all veterinary medicinal products containing colistin as sole active substance for oral administration to food-producing species (EMEA/V/A/106). The procedure was concluded and on 16 March 2015 the European Commission adopted a Decision[3] restricting the indications, target species, and duration of treatment of the concerned products, as well as adding prudent use warnings to the product information.

In the aforementioned Commission Decision it is stated that in line with the agreed stepwise approach "*The combinations of colistin with another antimicrobial substance and the non-oral administration of products containing colistin may be addressed as a next step following the completion of this referral procedure.*"

In view of the concerns above and in line with the aforementioned recommendations from the EMA/CVMP/CHMP scientific advice to the European Commission, as a second step, the Committee was requested to review the marketing authorisations of all veterinary medicinal products containing colistin in combination with other antimicrobial substances for oral administration to food-producing species in order to ensure responsible use of the substance in protecting animal health and limiting the possibility of future risk to public health.

2. Discussion of data available

Introduction

The bactericidal effect of colistin (and polymyxin B) is the result of an interaction with divalent cations of the outer bacterial membrane, which causes a disruption of the cell structure, leakage of the cell contents and thereby cell lysis[4]. The broad-spectrum activity of colistin against Gram-negative bacteria involves binding to lipid A, the anchor for lipopolysaccharide and the main constituent of the outer membrane of many bacteria[5]. Polymyxins are active particularly against a wide range of species of Gram-negative bacilli (e.g. *E. coli*, *Salmonella spp*. and *P. aeruginosa*), including those displaying carbapenem resistance, as well as certain *Mycobacterium spp*. Polymyxins have no clinically useful activity against Gram-positive bacteria, Gram-negative cocci, anaerobes and Mollicutes including *Mycoplasma spp*.[6]. In addition, colistin lacks therapeutic activity against inherently resistant species, including the genera *Serratia*, *Stenotrophomonas* and *Proteus*[7].

Colistin has been used since the 1950s both in human and veterinary medicine[8]. For food-producing animals in the EU/EEA today, field studies have shown that it is used primarily for pigs including group treatments and prevention of diarrhoea caused by *E. coli* and *Salmonella spp*., as first-choice

---

http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/10/WC500175671.pdf

[3] Commission Decision concerning, in the framework of Article 35 of Directive 2001/82/EC of the European Parliament and of the Council, the marketing authorisations for all veterinary medicinal products containing "Colistin" to be administered orally ((2015)1916 of 16/03/2015)
http://ec.europa.eu/health/documents/community-register/html/vo25478.htm

[4] Lim LM *et al*. 2010 Resurgence of colistin: a review of resistance, toxicity, pharmacodynamics, and dosing. *Pharmacotherapy* **30**:1279–91.

[5] Gales AC *et al*. 2011 Contemporary activity of colistin and polymyxin B against a worldwide collection of Gram-negative pathogens: results from the SENTRY Antimicrobial Surveillance Program (2006–09). *J Antimicrob Chemother* **66**:2070–4.

[6] Falagas ME *et al*. 2005 Colistin: the revival of polymyxins for the management of multidrug-resistant Gram-negative bacterial infections. *Clin InfectDis* **40**:1333–41.

[7] Pogue JM *et al*. 2011 Revisiting 'older' antimicrobials in the era of multidrug resistance. *Pharmacotherapy* **31**:912–21.

[8] Koyama Y *et al*. 1950 A new antibiotic 'colistin' produced by spore-forming soil bacteria. *J Antibiot (Tokyo)* **3**:457–8.

treatment for neonatal diarrhoea caused by *E. coli* in piglets[9] and veal calves[10] as well as for the therapy of mild colibacillosis in poultry[11]. In relation to the total weight of animals 'at risk' of treatment across 26 EU/EEA countries for which veterinary sales data were available[12], polymyxins were the fifth most sold group of antimicrobials (6%), after tetracyclines (37%), penicillins (24%), sulfonamides (10%) and macrolides (7%). The vast majority of consumption of polymyxins in food-producing animals is accounted for by colistin administered orally, in a variety of different formulations (e.g. premix, powder, oral solutions). Sales of combination products with colistin represented less than 10% of the overall sales of colistin (ESVAC, unpublished data).

A recent global increase in Gram-negative bacteria in human medicine that are multidrug-resistant (MDR), extensively drug-resistant (XDR) and pandrug-resistant (PDR)[13] has forced clinicians to re-introduce toxic systemic colistin treatment in the form of its less toxic inactive prodrug, colistin methanesulfonate, as a last-resort antimicrobial for infections with such bacteria, which are frequently the cause of healthcare-associated infections[14]. Human infections with such highly resistant bacteria are associated with higher patient morbidity and mortality, higher costs and longer length of hospital stay[15]. Thus, colistin has re-emerged as a last-resort therapeutic option to treat infections due to MDR, XDR and PDR, lactose-fermenting and non-fermenting Gram-negative bacilli, including *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Due to colistin's new status as critically important in human medicine, the public health impact of the current or future use of colistin products in animals needs to be re-assessed at this time. This was supported by a recent EU commissioned *ad hoc* expert group on antimicrobial resistance (AMEG) as well as a recent Article 35 referral procedure on veterinary medicinal products containing colistin as sole active substance to be administered orally. This is a very different situation in Europe since colistin has traditionally only been used in veterinary medicine and not critically important for human health.

Previous CVMP conclusions applicable to colistin combination products

In the above mentioned Article 35 referral procedure (EMEA/V/A/106) for all veterinary medicinal products containing colistin as sole active substance for oral administration to food-producing species, the CVMP reached certain conclusions (described below) on some indications, dosages and target species, which would also apply to colistin combination products.

In the present procedure no data or evidence was presented for the indication of salmonellosis in any target species. Specific control programmes for salmonellosis in food-producing animals have been implemented in EU countries. Following the Article 35 referral procedure for veterinary medicinal products containing colistin as sole active substance (EMEA/V/A/106), colistin is no longer recommended for treatment of gastrointestinal infections caused by *Salmonella* spp. due to a negative benefit-risk assessment. The same applies for *Salmonella spp*. indications for colistin combination products. The risk to public health identified is that treatment of clinical or subclinical *Salmonella* infections with the objective to reduce the number of bacteria can interfere with EU control

[9] Callens B *et al*. 2012 Prophylactic and metaphylactic antimicrobial use in Belgian fattening pig herds. *Prev Vet Med* **106**:53–62.
[10] Pardon B *et al*. 2012 Prospective study on quantitative and qualitative antimicrobial and anti-inflammatory drug use in white veal calves. *J Antimicrob Chemother* **67**:1027–38.
[11] Kempf I *et al*. 2013 What do we know about resistance to colistin in Enterobacteriaceae in avian and pig production in Europe? *Int J Antimicrob Agents* **42**:379–83.
[12] European Medicines Agency, European Surveillance of Veterinary Antimicrobial Consumption, 2015. 'Sales of veterinary antimicrobial agents in 26 EU/EEA countries in 2013'. Fifth ESVAC report. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2015/10/WC500195687.pdf
[13] Magiorakos AP *et al*. 2012 Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* **18**:268–81.
[14] Nation RL and Li J 2009 Colistin in the 21st century. *Curr Opin Infect Dis* **22**:535–43.
[15] Cosgrove SE 2006 The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. *Clin InfectDis* **42**:S82–9.

programmes[16] and thus compromises public health and food safety. Also, some *Salmonella* subtypes have reduced sensitivity to colistin. A recent paper identified another risk of colistin products and *Salmonella spp*.[17]. Specifically, in EU countries with known higher consumptions of colistin products, minimum inhibitory concentration (MIC) distributions were higher for *Salmonella spp.* isolates from pigs and chickens with up to 77% classified as resistant. *Salmonella* spp. with elevated MICs to colistin could constitute a risk to public health.

Also, the previous Article 35 referral procedure confirmed a dose of 100,000 IU colistin per kg body weight daily for calves, lambs and pigs, and a dose of 75,000 IU colistin per kg body weight daily in poultry for 3–5 consecutive days. Additionally, it was agreed that the suggested dose of 50,000 IU per kg body weight twice daily was reasonable. In the present Article 35 referral, several colistin combinations veterinary medicinal products were identified with colistin doses of below 50,000 IU per kg body weight. No clinical studies or justification was given for the under-dosing which could constitute a risk to public health by promoting colistin resistant bacteria.

Some of the products included in the scope of this referral procedure are indicated for use in foals. Gastrointestinal infection caused by *E. coli* (colibacillosis) is not a recognised clinical disease in foals or adult horses. Colibacillosis is not a term used in equine medicine, but a term used for pigs, poultry and ruminants. Colibacillosis is defined as an infection of the colon by Enterobacteriaceae, especially *E. coli*, resulting in a disease manifestation, typically diarrhoea and other manifestations in poultry. *E. coli* septicaemia is a recognised disease in neonatal foals that can be sometimes be expressed as diarrhoea, among other symptoms. The current scientific literature does not support the use of colistin combination products in foals as its use could disrupt the gastrointestinal microflora balance, leading to a well-recognised fatal antimicrobial-associated colitis, typically associated with *Clostridium difficile*. Thus, the use of colistin in foals is considered to present a serious risk in relation to target animal safety and foals cannot be supported as a target animal species for colistin combination products. The risk identified by maintaining this indication is that it promotes the treatment of an unknown clinical disease, leading to treatment failures because the true cause (e.g. viral, other bacteria, protozoans, parasites) is unaffected by colistin combination treatments. Treatment failures could compromise foal health in these cases. The same conclusion was reached in the recent Article 35 referral procedure on oral colistin monotherapy products.

Justification of colistin combination products

Proprietary data, scientific references and expert reports were provided in this Article 35 referral procedure in support of some indications of some of the products included in the scope of the procedure. In addition, the MAHs were asked to justify the benefits of using a colistin combination product over the use of monotherapy for the treatment of the respective conditions, particularly taking into account the CVMP guideline on pharmaceutical fixed combination products[18] (EMEA/CVMP/83804/2005).

For non-gastrointestinal indications there are concerns of lack of justification for colistin combination products. This is for the reason that colistin is not absorbed from the gastrointestinal tract after oral administration and thus does not contribute to the overall therapeutic efficacy for these indications. No valid therapeutic principles could be identified for non-gastrointestinal indications and hence the combination offers no advantage over its active substances when used as single substance products,

[16] Commission Regulation (EC) No 1177/2006 of 1 August 2006 implementing Regulation (EC) No 2160/2003 of the European Parliament and of the Council as regards requirements for the use of specific control methods in the framework of the national programmes for the control of salmonella in poultry http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32006R1177&from=en

[17] de Jong A *et al*. 2012 Pan-European monitoring of susceptibility to human-use antimicrobial agents in enteric bacteria isolated from healthy food-producing animals. *J Antimicrob Chemother* **67**: 638–651

[18] CVMP guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004645.pdf

as described in the CVMP guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005). The end result is an unnecessary use of colistin. Given the recent critical importance of colistin in human medicine, then veterinary use can only be justified under prudent use principles, which is not the case for colistin combinations products for non-gastrointestinal indications. This is especially a concern for certain colistin combination products (e.g. colistin and neomycin or colistin and oxytetracycline) where both active substances are not absorbed but yet the products are currently authorised with non-gastrointestinal tract indications.

For gastrointestinal indications, there are also concerns if colistin combinations products are necessary over monotherapy. For example, the current status for relevant Gram-negative gastrointestinal pathogens (e.g. *E. coli*) in the EU is that MICs to colistin are very low and colistin colonic concentrations are very high (e.g. 20 times more than the MIC) such that a monotherapy product could suffice for these indications. Most clinical studies provided in this Article 35 referral procedure demonstrated that monotherapy products shared the same efficacy as colistin combination products. Arguments for polymicrobial infections were mostly theoretical and only discussed by MAHs in relation to respiratory and skin indications. As stated previously, this has no clinical relevance for colistin combination products, since colistin is not absorbed from the gastrointestinal tract and thus will never participate in combating polymicrobial infections in other target tissues. Polymicrobial gastrointestinal infections were not identified by the MAHs for the animal species and indications listed for their products. Concurrent *E. coli* related gastrointestinal diseases (e.g. septicaemia) were identified by MAHs as occurring as complications from the original gastrointestinal disease through either direct systemic spread or immunosuppression. No specific clinical studies were provided for invasive *E. coli* secondary to gastrointestinal disease. Thus, it is unknown if a combination product provides an added value over a monotherapy product for this indication. Also, it is unclear whether at the time of systemic complications from colibacillosis the main clinical disease is still the gastrointestinal disease or the systemic complications. No specific reasons could be identified for the need of a colistin combination product for food-producing animals in the EU with either an improvement of activity (synergistic or additive activity), or broadening of the activity spectrum. Therefore, the CVMP concluded that no gastrointestinal indications could be supported for colistin combination products.

In vitro antimicrobial synergy was identified by several MAHs and backed up by scientific publications, based on both a reduction of the MIC for target pathogens in the presence of the colistin combination and a reduction in the fractional inhibitory concentration index. However, these *in vitro* studies are unreliable because the major problem with using *in vitro* susceptibility methods for establishing efficacy of colistin combinations against bacteria is that the accuracy of the different techniques available such as broth microdilution, agar dilution, and Etest is questionable because of the cationic properties of colistin[19]. Current European Committee on Antimicrobial Susceptibility Testing clinical breakpoints for Enterobacteriaceae are under revision because of these issues. The disk diffusion test is applied routinely worldwide yet is seldom reliable due to the inability of colistin to regularly diffuse in the agar and produce a consistent concentration gradient. This means that with the lack of international standard techniques for colistin susceptibility testing no agreed standards exist for *in vitro* synergy evaluation for colistin combinations. No published data is available that has identified the mechanism by which synergism could occur for colistin combinations. Also, the clinical relevance of synergy with colistin combinations is highly doubtful for the reason that colonic concentrations of colistin alone are so much higher than the MIC (e.g. 20 times more than the MIC) for *E. coli* and other bacteria, as a monotherapy, hence there is no clinical added value for an *in vitro* synergy of colistin combinations. Concepts of colistin combination synergy are more relevant in human medicine since low doses of colistin are injected parenterally with other antimicrobials in order to avoid toxicity.

[19] Lo-Ten-Foe JR *et al*. 2007 Comparative evaluation of the VITEK 2, disk diffusion, Etest, broth microdilution,and agar dilution susceptibility testing methods for colistin in clinical isolates, including heteroresistant *Enterobacter cloacae* and *Acinetobacter baumannii* strains. *Antimicrob Agents Chemother* **51**:3726–30.

In conclusion, colistin combination products are intended to address different clinical needs to monotherapy products. These additional clinical needs can include a broader spectrum of antimicrobial coverage in the body to either extend antimicrobial coverage to the rest of the body as well as the gastrointestinal tract (e.g. gastrointestinal infection plus septicaemia), or extra antimicrobial coverage within the gastrointestinal tract due to extenuating circumstances (e.g. antimicrobial resistance or polymicrobial infections). On these points, no convincing data were provided by the MAHs, in terms of clinical trials or other scientifically acceptable studies, as to clinical scenarios where colistin combination products are essential for food-producing animals in the EU compared to monotherapy products.

3. Benefit-risk assessment

Benefit assessment

Veterinary medicinal products containing colistin in combination with other antimicrobial substances to be administered orally to food-producing species represent commonly used antimicrobials in veterinary medicine. In production animals, stresses in neonates and such related to weaning lead to dysbacteriosis and *E. coli* diarrhoea, which appear clinically similar. More virulent strains resulting in more severe disease can further lead to septicaemia and/or immunosuppression with the result of either multi-organ disease or polymicrobial infections. Colistin combination products are seen to serve a role for these more complex production-related diseases and clinical studies are available for some combinations, which demonstrated efficacy for some conditions. Additionally, pharmacovigilance data have revealed no reports of lack of efficacy for colistin combination products.

Several scientific reports and EU surveillance data[17,20] have demonstrated continued very low level of resistance to colistin in food-producing animals, as well as reduced levels of resistance to several other antimicrobials used in colistin combination products, despite the wide use of these products in the EU for some years.

Risk assessment

A substantial change has occurred over the last five years regarding the importance of colistin in human and veterinary medicine – from a molecule used only in veterinary medicine, colistin has become a critically important molecule in human medicine. With the renewed use of colistin use in human medicine, particularly as a last-resort therapeutic option to treat infections due to multidrug-resistant (MDR), extensively drug-resistant (XDR) and pandrug-resistant (PDR), lactose-fermenting and non-fermenting Gram-negative bacilli, including *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, then there are potential public health concerns with continued veterinary use of the substance. Until recently it was felt the public health concerns were small due to the known characteristics of colistin resistance identified in veterinary medicine, including that these colistin-resistant bacteria are rare, possess only non-transferable genetic elements to other bacteria and are unstable, meaning colistin-resistant bacteria do not persist. Historically, this instability of polymyxin resistance, and the absence of horizontal gene transfer of these mutations, was thought to reduce the risk of rapid spread of resistance to colistin[21]. However, it is important to note that stable resistance at the subclinical level (heteroresistance) can remain undetected by conventional culture/sensitivity techniques[22]. Biofilms are protective layers around bacteria that are formed, for example, in the

[20] Catry, B *et al.* 2015 Use of colistin-containing products within the European Union and European Economic Area (EU/EEA): development of resistance in animals and possible impact on human and animal health. *International Journal of Antimicrobial Agents* **46(3)**: 297 – 306.
[21] Landman D *et al*. 2008 Polymyxins revisited. *Clin Micro-biol Rev* **21**:449–65.
[22] Snitkin ES *et al*. 2013 Genomic insights into the fate of colistin resistance and *Acinetobacter baumannii* during patient treatment. *Genome Res* **23**:1155–62.

digestive tract as mucosal biofilm communities[23]. Until recently, polymyxin resistance had involved only chromosomal mutations but had never been reported via horizontal gene transfer. During a routine surveillance project on antimicrobial resistance in commensal *E. coli* from food animals in China, polymyxin resistance was shown to be singularly due to the plasmid-mediated *mcr-1* gene[24]. Furthermore, this *mcr-1* carriage in *E. coli* isolates was also found in 78 (15%) of 523 samples of raw meat products and 166 (21%) of 804 animals sampled during 2011–14. This emergence of *MCR-1* in animals and human-related bacteria heralds the breach of the last group of antibiotics, polymyxins, by plasmid-mediated transferable resistance. Since the discovery in China, *MCR-1* plasmid-mediated colistin resistance has been reported in a number of countries worldwide. Thus, it is no longer the case that colistin-resistant bacteria in animals are unrelated to public health and the example found in China does demonstrate that transferable *mcr-1* gene colistin resistance can occur in food animals and meat products and potentially constitute a public health risk.

The use of combination products represents a risk of unnecessary use of colistin in cases where no additional benefit has been shown over the use of one substance alone.

Quality, target animal safety, user safety, environmental risk and residues were not assessed in this referral procedure.

Risk management or mitigation measures

In light of the renewed use of colistin use in human medicine and its critical importance for public health then it is essential to ensure prudent use of the substance in veterinary medicine in order to avoid an increase in the development of antimicrobial resistance. In a previous Article 35 referral procedure for all veterinary medicinal products containing colistin to be administered orally the Committee agreed a harmonised indication, a limitation of the duration of treatment up to 7 days and warning sentences on prudent use.

The same considerations taken for the colistin monotherapy products also apply to products containing colistin in combination with other antimicrobial substances. Indications for prevention and prophylaxis can no longer be justified. No proprietary data or valid justifications could be provided in support of prevention and prophylaxis claims. Also, no proprietary data or valid justifications could be provided in support of *Salmonella spp*. indications. Gastrointestinal infection caused by *E. coli* (colibacillosis) is not a recognised clinical disease in foals or adult horses and no data were provided to support the use of colistin in foals, therefore this target species should be removed. Non-gastrointestinal indications are considered an unnecessary use of colistin as the substance does not contribute to any therapeutic effect of other organs infected with bacterial infections. In this context, colistin combination products are not utilised under prudent use principles nor fulfil the criteria outlined in the fixed combinations guideline for the approval of these products.

Based on the information provided by MAHs, including proprietary data, scientific references and expert reports, a possible risk mitigation measure considered in this Article 35 referral was to further limit the use of colistin combination products to treatment of individual animals only and remove presentations of products intended for group treatment.

However, concerns were raised whether gastrointestinal indications for colistin combinations products are justified when it would be more prudent to use a monotherapy product. Currently the status for relevant Gram-negative gastrointestinal pathogens (e.g. *E. coli*) in the EU is that MICs of colistin are very low and colistin colonic concentrations are very high (e.g. 20 times above the MIC) such that a monotherapy product will suffice for these indications. In most clinical studies provided in this Article

[23] Fite A *et al*. 2013 Longitudinal analyses of gut mucosal microbiotas in ulcerative colitis in relation to patient age and disease severity and duration. *J Clin Microbiol* **51**:849–56.
[24] Liu YY *et al*. 2015 Emergence of plasmid-mediated colistin resistance mechanism *MCR-1* in animals and human beings in China: a microbiological and molecular biological study. *Lancet* **16(2)**:161-8

35 referral procedure monotherapy products demonstrated the same efficacy as colistin combination products. No specific reasons could be identified for the need of a colistin combination product for food-producing animals in the EU with either an improvement of activity (synergistic or additive activity), or broadening of the activity spectrum. The CVMP considered that the end result of using colistin combination products instead of monotherapy is an unnecessary use of colistin.

While in cases involving other substances used in veterinary medicine there were still therapeutic options for human medicine, in this case any potential food-chain related contributions to colistin resistance in human medicine would lead to no therapeutic options for human infections against MDR, XDR and PDR bacteria. As even a limited use of colistin combinations products is deemed to lead to unnecessary use of colistin and could potentially contribute to the development of antimicrobial resistance, the measures discussed above were not considered sufficient to mitigate the identified risk. This combined with the lack of quality clinical studies and of other credible evidence to confirm the added value of colistin combination products over monotherapy, combined with lack of compliance with prudent use principles and the CVMP guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005), leads to the conclusion that there is no valid justification for the use of colistin combination products in veterinary medicine.

Evaluation and conclusions on the benefit-risk balance

In this procedure the CVMP was requested to review the marketing authorisations of all veterinary medicinal products containing colistin in combination with other antimicrobial substances for oral administration to food-producing species in order to ensure responsible use of the substance in protecting animal health and limiting the possibility of future risk to public health.

It is recognised that colistin combination products could be efficacious for the treatment and metaphylaxis of gastrointestinal diseases caused by *E. coli* susceptible to both active substances in piglets, poultry, neonatal calves and lambs, provided the dose and duration of treatment are adjusted according to those previously recommended by CVMP. However, no benefit could be demonstrated of using colistin combination products over monotherapy and no feasible risk mitigation measures could be identified to address the identified potential risk for human health, as even a limited use of colistin combination products was considered an unnecessary use of colistin.

Having considered all data submitted in writing, the CVMP concluded that the benefit-risk balance for all veterinary medicinal products containing colistin in combination with other antimicrobial substances to be administered orally to food-producing species is negative, due to a lack of clinical relevance and in view of over-exposure of colistin that could pose a potential risk to animal and human health from an acceleration of the occurrence of colistin resistance.

Therefore, the CVMP recommended the withdrawal of the marketing authorisations for all veterinary medicinal products containing colistin in combination with other antimicrobial substances to be administered orally.

Grounds for withdrawal of the marketing authorisations

Whereas

- the CVMP considered that no convincing data were provided by the MAHs, in terms of clinical trials or other scientifically acceptable studies, as to clinical scenarios where colistin combination products are essential for food-producing animals in the EU compared to monotherapy products;
- the CVMP considered that even a limited use of colistin combinations products is deemed to lead to unnecessary use of colistin and could potentially contribute to the development of antimicrobial resistance;

- the CVMP considered that the development of antimicrobial resistance to colistin is considered a risk for human health as colistin is also used as a last resort treatment in human medicine in the context of treatment of specific highly drug-resistant bacterial infections;
- the CVMP concluded that the benefit-risk assessment for all veterinary medicinal products containing colistin in combination with other antimicrobial substances to be administered orally is negative and that the products could pose a potential risk to human health;

the CVMP has recommended the withdrawal of the marketing authorisations for all veterinary medicinal products containing colistin in combination with other antimicrobial substances to be administered orally as referred in Annex I.