Annex I

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

Member State EU / EEA	Applicant / marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Austria	Bayer Austria GmbH, Lerchenfelder Guertel 9-11 1160 Wien Austria	Baytril 100 mg/ml - Lösung zum Eingeben für Hühner und Puten	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Austria	Krka d.d. Novo mesto, Šmarjeska cesta 6 8501 Novo Mesto Slovenia	Enrox 100 mg/ml Lösung zum Eingeben für Hühner und Puten	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens (broilers, broiler breeders, replacement chickens), turkeys
Austria	Pro Zoon Pharma GmbH, Karl Schoenherr Strasse 3 4600 Wels Austria	Enrozid TWS 100 mg/ml Lösung zum Eingeben für Hühner und Puten	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chicken and turkeys
Belgium	Bayer SA-NV J.E. Mommaertslaan 14 1831 Diegem (Machelen) Belgium	Baytril 10 %	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Belgium	Laboratorios Karizoo S.A., Pol. Ind. La Borda, Mas Pujades 11-12, 08140 Caldes de Montbui, Barcelona Spain	Enro-K 10 %	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Belgium	Eurovet Animal Health BV Handelsweg 25 5531 AE Bladel The Netherlands	Enroshort 100 mg/ml	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Belgium	Vetpharma Animal Health S.L., Les Corts 23, 08028 Barcelona Spain	Enroveto 100 mg/ml	Enrofloxacin	100 mg/ml	Concentrate for oral solution	Oral	Chickens and turkeys
Belgium	Krka d.d. Novo mesto, Šmarjeska cesta 6 8501 Novo Mesto Slovenia	Enroxil 100 mg/ml	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys

Member State EU / EEA	Applicant / marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Belgium	S.P. VETERINARIA, S.A. Ctra. Reus - Vinyols Km 4,1 Riudoms 43330 (Tarragona) Spain	Floxamax 100 mg/ml	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Belgium	Global Vet Health S.L. C/Capcanes, 12-bajos Poligono Agro-Reus 43206-Reus Tarragona Spain	Quinoflox 100 mg/ml	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and rabbits
Belgium	HIPRA LABORATORIOS Avda. La Selva 135, 17170 Amer (Girona) Spain	Spectron 100 mg/ml	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Belgium	Vetpharma Animal Health S.L., Les Corts 23, 08028 Barcelona Spain	Unisol 100mg/ml	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Belgium	aniMedica GmbH, Im Südfeld 9, 48308 Senden-Bosensell Germany	Enrotron 100 mg/ml	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Bulgaria	VET - PARTNERS Ltd. 25 Ivan Asen II Str. 4270 Parvomay Bulgaria	Полистар Енро	Enrofloxacin	100 mg/ml	Oral solution	Oral	Poultry
Bulgaria	Ceva Santé Animale, 10 avenue de La Ballastière, 33500 Libourne France	Квиноекс -10	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Bulgaria	Ceva Santé Animale, 10 avenue de La Ballastière, 33500 Libourne France	Квинокол орален разтвор	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys

Member State EU / EEA	Applicant / marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Bulgaria	Laboratorios Syva, s.a.u, Avenue Parroco Pablo Diez 49-57, 24010 Leon, Spain	Сиваквинол 10% орал	Enrofloxacin	100 mg/ml	Oral solution	Oral	Broilers
Bulgaria	Asklep Farma Lyulin 7, bl. 711, mag. 3 Sofia 1324 Bulgaria	Роксацин БГ орален	Enrofloxacin	100 mg/ml	Oral solution	Oral	Broilers
Bulgaria	Farma vet Ltd. 40 Otec Paisii Str. Shumen 9700 Bulgaria	Енрофлоксацин 10% разтвор	Enrofloxacin	100 mg/ml	Oral solution	Oral	Broilers
Bulgaria	Bayer Animal Health GmbH, 51368 Leverkusen, Germany	Байтрил 10% перорален разтвор	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Bulgaria	Global Vet Health S.L. C/Capcanes, 12-bajos Poligono Agro-Reus 43206-Reus Tarragona Spain	Флоксацин 100 mg/ml концентрат за орален разтвор за пилета и пуйки	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Bulgaria	Interchemie Werken De Adelaar BV Metaalweg 8 5804 CG Venray The Netherlands	Интерфлокс орален	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Cyprus	Bayer Animal Health GmbH 51368 Leverkusen Germany	Baytril oral solution 10% for chickens (broilers and breeders) and turkeys	Enrofloxacin	10%	Solution for oral use	Oral	Chickens (broilers and breeders), turkeys
Cyprus	Bayer Animal Health GmbH 51368 Leverkusen Germany	Baytril oral solution 0.5%	Enrofloxacin	0,5%	Solution for oral use	Oral	Broilers, rearing poultry, turkeys

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Cyprus	Laboratorios Karizoo S.A., Pol. Ind. La Borda, Mas Pujades 11-12, 08140 Caldes de Montbui, Barcelona Spain	K-flox 100 mg/ml oral solution for broilers and rabbits	Enrofloxacin	100 mg/ml	Solution for oral use	Oral	Chickens and rabbits
Cyprus	Global Vet Health S.L. C/Capcanes, 12-bajos Poligono Agro-Reus 43206-Reus Tarragona Spain	Floxacin 100 mg concentrated solution for oral solution for chickens and turkeys	Enrofloxacin	100 mg/ml	Solution for oral use	Oral	Chickens and turkeys
Czech Republic	Laboratorios Karizoo S.A., Pol. Ind. La Borda, Mas Pujades 11-12, 08140 Caldes de Montbui, Barcelona Spain	Enro-K 10% (w/v) perorální roztok	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chicken - broilers and turkey
Czech Republic	Vétoquinol s.r.o., Zámečnická 411, 288 02 Nymburk Czech Republic	ENROBIOFLOX 100 mg/ml perorální roztok	Enrofloxacin	100 mg/ml	Oral solution	Oral	Broiler chicken, non-ruminating calves and pigs
Czech Republic	INTERSIGN Pechačkova 5, 150 00 Prague 5 Czech Republic	ENROFLOXAN 100 mg/ml perorální roztok	Enrofloxacin	100 mg/ml	Oral solution	Oral	Broiler chicken, non-ruminating calves and pigs
Czech Republic	Pharmagal spol. s.r.o., Murgašova 5, 949 01 Nitra Slovak Republic	ENROGAL 100 mg/ml perorální roztok	Enrofloxacin	100 mg/ml	Oral solution	Oral	Pigs, calves, chicken (broilers), turkeys
Czech Republic	Krka d.d. Novo mesto, Šmarjeska cesta 6 8501 Novo Mesto Slovenia	Enroxil 100 mg/ml, perorální roztok	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys

Member State EU/EEA	Applicant/marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Czech Republic	Global Vet Health S.L. C/Capcanes, 12-bajos Poligono Agro-Reus 43206-Reus Tarragona Spain	FLOXACIN 100 mg/ml, koncentrát pro přípravu perorálního roztoku pro kura domácího a krůty	Enrofloxacin	100 mg/ml	Concentrate for oral solution	Oral	Chickens and turkeys
Czech Republic	Ceva Animal Health Slovakia, spol s.r.o., Račianska 77, 831 02 Bratislava, Slovak Republic	QUINOEX 100 mg/ml perorální roztok	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chicken broilers, turkey
Czech Republic	Laboratorios Calier S.A., C/Barcelones, 26 (Pla del Ramassa), 08520 Les Franqueses del Valles, Barcelona Spain	ROXACIN 100 mg/ml perorální roztok	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chicken broilers
Czech Republic	Laboratorios Hipra S.A. Avda. La Selva 135, 17170 - Amer (Girona) Spain	SPECTRON 100 mg/ml roztok pro podání v pitné vodě pro kuřata a krůty	Enrofloxacin	100 mg/ml	Solution for use in drinking water	Oral	Chickens and turkeys
Czech Republic	Vetpharma Animal Health S.L., Les Corts 23, 08028 Barcelona Spain	UNISOL 100 mg/ml perorální roztok pro podání v pitné vodě pro kuřata a krůt	Enrofloxacin	100 mg/ml	Solution for use in drinking water	Oral	Chicken - broilers and turkey
Denmark	aniMedica GmbH, Im Südfeld 9, 48308 Senden-Bosensell Germany	Enrotron	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Denmark	Bayer Animal Health GmbH, 51368 Leverkusen, Germany	Baytril Vet	Enrofloxacin	100 mg/ml	Oral solution	Oral	Poultry, non egglayers
Estonia	Ceva Santé Animale, 10 avenue de La Ballastière, 33500 Libourne France	Quinoflox	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys

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Estonia	Industrial Veterinaria S.A. Esmeralda, 19. 08950 Espluges de Llobregat, Barcelona Spain	Ganadexil Enrofloxacina	Enrofloxacin	100 mg/ml	Oral solution	Oral	Broiler
Estonia	Vetoquinol Biowet Sp. z.o.o., ul. Kosynierów Gdynskich 13-14, 66-400 Gorzów Wlkp., Poland	Enrobioflox 10%	Enrofloxacin	100 mg/ml	Oral solution	Oral	Cattle (calves), pigs, chicken (broilers), cats, dogs
Estonia	Interchemie werken "De Adelaar" Eesti AS, Vanapere tee 14, Pringi 74001 Viimsi, Harjumaa, Estonia	Interflox Oral	Enrofloxacin	100 mg/ml	Oral solution	Oral	Poultry
France	Bayer Sante 220 Avenue de la Recherche 59120 Loos France	BAYTRIL 10 % solution buvable	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens, turkeys and rabbits
France	Virbac 1ere Avenue 2065 M L I D 06516 Carros Cedex Spain	TENOTRYL 10 % solution buvable	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
France	Vetpharma Animal Health S.L., Les Corts 23, 08028 Barcelona Spain	LANFLOX 100 MG/ML solution pour utilisation dans l'eau de boisson pour poulets et dindes	Enrofloxacin	100 mg/ml	Solution for use in drinking water	Oral	Chickens and turkeys

Member State EU/EEA	Applicant/marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
France	Laboratorios Karizoo S.A., Pol. Ind. La Borda, Mas Pujades 11-12, 08140 Caldes de Montbui, Barcelona Spain	KARIFLOX 10 % solution buvable pour poulets et dindes	Enrofloxacin	100 mg/ml	Solution for use in drinking water	Oral	Chickens and turkeys
France	Ceva Santé Animale, 10 avenue de La Ballastière, 33500 Libourne France	QUINOFLOX 10% solution buvable	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
France	Sogeval 200 Avenue De Mayenne Zone Industrielle Des Touches 53000 Laval France	ENROVAL 10 % solution buvable pour volailles	Enrofloxacin	100 mg/ml	Solution for use in drinking water	Oral	Chickens (broilers, replacement chickens, broiler breeders) and turkeys
France	Laboratorios Hipra S.A. Avda. La Selva 135, 17170 - Amer (Girona) Spain	SPECTRON 100 MG/ML solution pour utilisation dans l'eau de boisson pour poulets et dindes	Enrofloxacin	100 mg/ml	Solution for use in drinking water	Oral	Chickens and turkeys
France	Global Vet Health S.L. C/Capcanes, 12-bajos Poligono Agro-Reus 43206-Reus Tarragona Spain	NYOFLOX 100 MG/ML solution pour administration dans l'eau de boisson pour poulets et lapins	Enrofloxacin	100 mg/ml	Solution for use in drinking water	Oral	Chickens (broilers, replacement chickens, broiler breeders) and rabbits
Germany	Bayer Vital GmbH Kaiser-Wilhelm-Allee 51373 Leverkusen Germany	Baytril 10%	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Germany	Vetpharma Animal Health S.L., Les Corts 23, 08028 Barcelona Spain	Lanflox 100 mg/ml Lösung zum Eingeben über das Trinkwasser für Hühner und Puten	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys

Member State EU/EEA	Applicant/marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Germany	aniMedica GmbH, Im Südfeld 9, 48308 Senden-Bosensell Germany	Enrotron 100 mg/ml oral solution for chicken and turkeys	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Germany	Laboratorios Hipra S.A. Avda. La Selva 135, 17170 - Amer (Girona) Spain	Spectron	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Germany	Global Vet Health S.L. C/Capcanes, 12-bajos Poligono Agro-Reus 43206-Reus Tarragona Spain	Quinoflox	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chicken (broilers, broiler parent animals, pullets), rabbit
Germany	Eurovet Animal Health BV Handelsweg 25 5531 AE Bladel The Netherlands	Enro-Sleecol	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Germany	Laboratorios Karizoo S.A., Pol. Ind. La Borda, Mas Pujades 11-12, 08140 Caldes de Montbui, Barcelona Spain	Enro-K 10%	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Germany	Vetpharma Animal Health S.L., Les Corts 23, 08028 Barcelona Spain	Unisol 100 mg/ml Lösung zum Eingeben über das Trinkwasser für Hühner und Puten	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Germany	bioptivet Tierarzneimittel GmbH & Co. Im Landwehrwinkel 22 59073 Hamm Germany	Enrobioflox 100 mg/ml Lösung	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys

Member State EU/EEA	Applicant/marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Germany	bioptivet Tierarzneimittel GmbH & Co. Im Landwehrwinkel 22 59073 Hamm Germany	Enroflox 100 mg/ml	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Greece	Bayer Animal Health GmbH, 51368 Leverkusen, Germany	BAYTRIL 10%	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chicken - broilers and turkey
Greece	Bayer Animal Health GmbH, 51368 Leverkusen, Germany	BAYTRIL 0,5	Enrofloxacin	5 mg/ml	Oral solution	Oral	Chicken - broilers and turkey
Greece	VIRBAC SA, 13e Rue LID BP 27 06511 Carros cedex France	FLOXATRIL	Enrofloxacin	100 mg/m	Oral solution	Oral	Chicken - broilers and turkey
Greece	S.P. VETERINARIA, S.A. Ctra. Reus - Vinyols Km 4,1 Riudoms 43330 (Tarragona) Spain	ENROFLOXACIN 10%	Enrofloxacin	100 mg/m	Oral solution	Oral	Chicken - broilers and turkey
Greece	Laboratorios Karizoo S.A., Pol. Ind. La Borda, Mas Pujades 11-12, 08140 Caldes de Montbui, Barcelona Spain	FLEXIN	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chicken - broilers and turkey
Greece	Vetpharma Animal Health S.L., Les Corts 23, 08028 Barcelona Spain	LEVOFLOK	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chicken - broilers and rabbits
Greece	Laboratorios Karizoo S.A., Pol. Ind. La Borda, Mas Pujades 11-12, 08140 Caldes de Montbui, Barcelona Spain	AMIPLUS	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chicken - broilers and rabbits

Member State EU/EEA	Applicant/marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Greece	Laboratorios Hipra S.A. Avda. La Selva 135, 17170 - Amer (Girona) Spain	SPECTRON	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chicken - broilers and turkey
Greece	Laboratorios Maymo, S.A., Via Augusta 302, 08017 Barcelona Spain	QUIMIOCOLI	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chicken broiler
Hungary	Bayer Hungária Kft, Alkotás u. 50. 1123 Budapest Hungary	Baytril 10% belsőleges oldat	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Hungary	Vetoquinol Biowet Sp. z.o.o., ul. Kosynierów Gdynskich 13-14, 66-400 Gorzów Wlkp., Poland	Enrobioflox 10% belsőleges oldat	Enrofloxacin	100 mg/ml	Oral solution	Oral	Swine, cattle (calves), broiler chickens, dogs, cats
Hungary	Lavet Pharmaceuticals Ltd., Ottó u. 14., 1161 Budapest, Hungary	Enrocin 10% oldat	Enrofloxacin	100 mg/ml	Concentrate for oral solution	Oral	Chickens and turkeys
Hungary	DIVASA - FARMAVIC, S.A. Ctra Sant Hipolit Km 71 08503 Gurb-Vic Barcelona Spain	Enrovet 10% belsőleges oldat	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens
Hungary	VMD Állatgyógyászati Kft. Közraktár u. 22/b. 1093 Budapest Hungary	Enroveto-20 belsőleges oldat	Enrofloxacin	200 mg/ml	Concentrate for oral solution	Oral	Chickens, pigs and turkeys
Hungary	Krka d.d. Novo mesto, Šmarjeska cesta 6 8501 Novo Mesto Slovenia	Enroxil 10% belsőleges oldat	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys

Member State EU/EEA	Applicant/marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Hungary	Global Vet Health S.L. C/Capcanes, 12-bajos Poligono Agro-Reus 43206-Reus Tarragona Spain	Floxacin 100 mg/ml koncentrátum belsőleges oldathoz házityúk és pulyka részére	Enrofloxacin	100 mg/ml	Concentrate for oral solution	Oral	Chickens and turkeys
Hungary	Dunavet-B Zrt. Dolgos u. 2., 1126 Budapest, Hungary	Ganadexil Enrofloxacina belsőleges oldat	Enrofloxacin	100 mg/ml	Oral solution	Oral	Broiler chickens
Hungary	Laboratorios Karizoo S.A., Pol. Ind. La Borda, Mas Pujades 11-12, 08140 Caldes de Montbui, Barcelona Spain	Kariflox 10% belsőleges oldat házityúk és pulyka részére	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Hungary	Vetpharma Animal Health S.L., Les Corts 23, 08028 Barcelona Spain	LANFLOX 100 mg/ml oldat ivóvízbe keveréshez házityúk és pulyka részére	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Hungary	TolnAgro Kft. Rákóczi u. 146. 7100 Szekszárd, Hungary	Neoflox 10% belsőleges oldat házityúk (brojler csirke) és házinyúl számára	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chicken - broilers and rabbits
Hungary	Novimed Kft., Kiss Ernő u. 3. P+P Kereskedőház 1046 Budapest, Hungary	Novicen Flox belsőleges oldat	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens
Hungary	CEVA-Phylaxia Zrt. Szállás u. 5. 1107 Budapest, Hungary	Quinoex 10 belsőleges oldat	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys

Member State EU/EEA	Applicant/marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Hungary	CEVA-Phylaxia Zrt. Szállás u. 5. 1107 Budapest, Hungary	QUINOFLOX 100 mg/ml belsőleges oldat	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Hungary	Laboratorios Hipra S.A. Avda. La Selva 135, 17170 - Amer (Girona) Spain	Spectron 100 mg/ml belsőleges oldat csirkék és pulykák részére	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Hungary	Laboratorios Syva, s.a.u, Avenue Parroco Pablo Diez 49-57, 24010 Leon, Spain	Syvaquinol 10% belsőleges oldat	Enrofloxacin	100 mg/ml	Oral solution	Oral	Broiler chickens
Ireland	Bayer Limited, The Atrium, Blackthorn Road, Dublin 18 Ireland	Baytril 10% Oral Solution	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Ireland	Krka d.d. Novo mesto, Šmarjeska cesta 6 8501 Novo Mesto Slovenia	Enrox Oral Solution 100 mg/ml	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens (broilers, broiler breeders, replacement chickens), turkeys
Ireland	Universal Farma, S.L., Gran Via Carlos III, 98-7a, 08028 Barcelona Spain	Lanflox 100 mg/ml Oral Solution	Enrofloxacin	10 mg/ml	Oral solution	Oral	Chickens and turkeys
Ireland	Universal Farma, S.L., Gran Via Carlos III, 98-7a, 08028 Barcelona Spain	Unisol 10% Oral Solution	Enrofloxacin	10 mg/ml	Oral solution	Oral	Chickens and turkeys
Ireland	Laboratorios Karizoo S.A., Pol. Ind. La Borda, Mas Pujades 11-12, 08140 Caldes de Montbui, Barcelona Spain	ENRO-K 10% Oral Solution	Enrofloxacin	10 mg/ml	Oral solution	Oral	Chickens and turkeys

Member State EU/EEA	Applicant/marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Ireland	Laboratorios Karizoo S.A., Pol. Ind. La Borda, Mas Pujades 11-12, 08140 Caldes de Montbui, Barcelona Spain	Kariflox 10% Oral Solution for Chickens and Turkeys	Enrofloxacin	10 mg/ml	Oral solution	Oral	Chickens and turkeys
Ireland	S.P. VETERINARIA, S.A. Ctra. Reus - Vinyols Km 4,1 Riudoms 43330 (Tarragona) Spain	Floxamax Enrofloxacin 10% Concentrate for Oral	Enrofloxacin	10 mg/ml	Oral solution	Oral	Chickens and turkeys
Ireland	Laboratorios Hipra S.A. Avda. La Selva 135, 17170 - Amer (Girona) Spain	Spectron 100 mg/ml Solution for use in Drinking Water for Chickens and Turkeys	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Ireland	Eurovet Animal Health BV Handelsweg 25 5531 AE Bladel The Netherlands	Enro-Sleecol 100 mg/ml oral solution for chickens and turkeys	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Ireland	aniMedica GmbH, Im Südfeld 9, 48308 Senden-Bosensell Germany	Enrotron	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Ireland	HCS bvba, H. Kennisstraat 53, 2650 Edegem, Belgium	Enrofloxacin HCS 100 mg/ml oral solution for chickens and turkeys	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Italy	Laboratorios Hipra S.A. Avda. La Selva 135, 17170 - Amer (Girona) Spain	Spectron 100 mg/ml concentrate for oral solution	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Italy	Vetpharma Animal Health S.L., Les Corts 23, 08028 Barcelona Spain	Unisol 10% oral solution	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys

Member State EU/EEA	Applicant/marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Italy	Ceva Santé Animale, 10 avenue de La Ballastière, 33500 Libourne France	Cevaflox 100 mg/ml oral solution	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Italy	DOX-AL Italia S.p.A. Largo Donegani 2 20121 Milano Italy	Floxadox	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens, turkeys, guinea fowl, ducks, pheasant, quails, rabbits
Italy	Virbac SA Rue 13eme Rue 06511 Carros Cedex, France	Floxatril	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Italy	Global Vet Health S.L. C/Capcanes, 12-bajos Poligono Agro-Reus 43206-Reus Tarragona Spain	Quinoflox 100 mg/ml solution for use in drinking water, chicken and rabbits	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens, rabbits
Italy	Vetpharma Animal Health S.L., Les Corts 23, 08028 Barcelona Spain	Levoflok 100 mg/ml	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens, rabbits
Italy	Laboratorios Karizoo S.A., Pol. Ind. La Borda, Mas Pujades 11-12, 08140 Caldes de Montbui, Barcelona Spain	K-Flox oral solution for broilers and rabbits	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens, rabbits
Italy	S.P. VETERINARIA, S.A. Ctra. Reus - Vinyols Km 4,1 Riudoms 43330 (Tarragona) Spain	Floxavex	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Italy	Bayer Viale Certosa 130 20156 Milano Italy	Baytril 10% O.L.	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens, turkeys, rabbits

Member State EU / EEA	Applicant / marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Latvia	Krka d.d. Novo mesto, Šmarjeska cesta 6 8501 Novo Mesto Slovenia	Enroxil	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Latvia	Laboratorios Hipra S.A. Avda. La Selva 135, 17170 - Amer (Girona) Spain	Spectron	Enrofloxacin	100 mg/ml	Solution for use in drinking water	Oral	Chickens and turkeys
Latvia	Vet Line SIA Mazā Rāmavas 2, Valdlauči, Ķekavas novads, Latvia	Interflox Oral	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Latvia	Ceva Santé Animale, 10 avenue de La Ballastière, 33500 Libourne France	Quinoflox	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Latvia	Laboratorios Calier S.A., C/Barcelones 26 (Pla del Ramassa), 08520 Les Franqueses del Valles, Barcelona Spain	Roxacin	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens
Latvia	Vetoquinol Biowet Sp. z.o.o., ul. Kosynierów Gdynskich 13-14, 66-400 Gorzów Wlkp., Poland	Enrobioflox 10%	Enrofloxacin	100 mg/ml	Oral solution	Oral	Calves, pigs, dogs, cats, chickens (broilers), pigeons
Lithuania	CENAVISA, S.A., Cami Pedra Estela s/n, 43205 Reus (Tarragona) Spain	E-FLOX, geriamasis tirpalas	Enrofloxacin	100 mg/ml	Oral solution	Oral	Broiler chickens

Member State EU/EEA	Applicant/marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Lithuania	Vetoquinol Biowet Sp. z.o.o., ul. Kosynierów Gdynskich 13-14, 66-400 Gorzów Wlkp., Poland	ENROBIOFLOX 10%, geriamasis tirpalas	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chicken, cattle, swine, pigeons, dogs and cats
Lithuania	Lavet Pharmaceuticals Ltd., Ottó u. 14., 1161 Budapest, Hungary	ENROCIN 10%, geriamasis tirpalas	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Lithuania	PPHU "INEX" Partnership, ul. Bialostocka 12, 11-500 Giżycko Poland	ENROFLOXAN 10%, geriamasis tirpalas	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chicken, turkey, pigeons, cattle, swine, dogs and cats
Lithuania	Krka d.d. Novo mesto, Šmarjeska cesta 6 8501 Novo Mesto Slovenia	ENROXIL 100 mg/ml geriamasis tirpalas paukščiams	Enrofloxacin	100 mg/ml	Oral solution	Oral	Poultry
Lithuania	Ceva Santé Animale, 10 avenue de La Ballastière, 33500 Libourne France	QUINOFLOX 100 mg/ml geriamasis tirpalas	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Lithuania	Laboratorios Hipra S.A. Avda. La Selva 135, 17170 - Amer (Girona) Spain	SPECTRON 100 mg/ml tirpalas girdyti su geriamuoju vandeniu vištoms ir kalakutams	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Luxembourg	Bayer Belgium J.E. Mommaertslaan 14 B-1831 Diegem (Machelen) Belgium	Baytril 10% solution orale	Enrofloxacin	10 g/100ml	Oral solution	Oral	Chickens and turkeys

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Luxembourg	Global Vet Health S.L. C/Capcanes, 12-bajos Poligono Agro-Reus 43206-Reus Tarragona Spain	Floxacin 100 mg/ml solution orale pour poulets et dindes	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Luxembourg	Krka d.d. Novo mesto, Šmarjeska cesta 6 8501 Novo Mesto Slovenia	Enroxil 100 mg/ml pour poulets et dindes	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Malta	Industrial Veterinaria S.A. Esmeralda, 19. 08950 Espluges de Llobregat, Barcelona Spain	Ganadexil Enrofloxacino	Enrofloxacin	100 mg/ml	Oral solution	Oral	Broilers
Malta	Laboratorios Syva, s.a.u, Avenue Parroco Pablo Diez 49-57, 24010 Leon, Spain	Syvaquinol 10% oral	Enrofloxacin	100 mg/ml	Oral solution	Oral	Poultry
Malta	S.P. VETERINARIA, S.A. Ctra. Reus - Vinyols Km 4,1 Riudoms 43330 (Tarragona) Spain	Floxavex Oral solution	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Malta	Laboratorios Hipra S.A. Avda. La Selva 135, 17170 - Amer (Girona) Spain	Hipralona Enro-S	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Malta	Aerden L V.M.D Hoge Mauw 900 2370 Arendonk Belgium	Enroveto-20	Enrofloxacin	200 mg/ml	Oral solution	Oral	Chickens and turkeys
Malta	Romvac Co.S.A, 7 Soseaua Centurii, Voluntari, IF-077190 Romania	Enrofloxarom 10% solution	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys

Member State EU / EEA	Applicant / marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Malta	Pharmagal spol. s r.o., Murgašova 5, 949 01 Nitra, Slovakia	Enrogal oral solution	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Netherlands	Bayer B.V. Animal Health Division Energieweg 1 3641 RT Mijdrecht The Netherlands	Baytril 10% orale oplossing	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Netherlands	Krka d.d. Novo mesto, Šmarjeska cesta 6 8501 Novo Mesto Slovenia	Enrox 100 mg/ml orale oplossing	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Netherlands	Laboratorios Karizoo S.A., Pol. Ind. La Borda, Mas Pujades 11-12, 08140 Caldes de Montbui, Barcelona Spain	Kariflox 10% orale oplossing	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Netherlands	Vetpharma Animal Health S.L., Les Corts 23, 08028 Barcelona Spain	Lanflox 100 mg/ml orale oplossing	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Netherlands	S.P. VETERINARIA, S.A. Ctra. Reus - Vinyols Km 4,1 Riudoms 43330 (Tarragona) Spain	Floxamax 10% orale oplossing	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Netherlands	aniMedica GmbH, Im Südfeld 9, 48308 Senden-Bosensell Germany	Enrotron 100 mg/ml orale oplossing	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys

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Poland	Przedsiębiorstwo Farmaceutyczne Okoniewscy "Vetos-Farma" Sp. z o.o., ul. Dzierżoniowska 21, 58-260 Bielawa Poland	Enrofloksacyna 10% płyn, enrofloksacyna 100 mg/ml roztwór doustny dla kur i indyków	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Poland	Biowet Puławy Sp. z o.o. ul. Arciucha 2, 24-100 Puławy Poland	Enflocyna Sol, 50 mg/ml, roztwór doustny dla bydła, świń, psów, kur, indyków i gołębi	Enrofloxacin	50 mg/ml	Oral solution	Oral	Cattle, pig, dog, chicken, turkey and pigeon
Poland	Biofaktor Sp. z o.o., ul. Czysta 4, 96-100 Skierniewice, Poland	Enrofloxan 10% roztwór, enrofloksacyna 100 mg/ml roztwór do podawania w wodzie do picia dla świń, kur i gołębi	Enrofloxacin	100 mg/ml	Oral solution for use in drinking water	Oral	Pig, chicken (broilers and laying hens) and pigeon
Poland	Laboratorios Calier S.A., C/Barcelones, 26 (Pla del Ramassa), 08520 Les Franqueses del Valles, Barcelona Spain	Roxacin 10% oral solution, enrofloksacyna 100 mg/ml, roztwór doustny dla kur	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chicken
Poland	Przedsiębiorstwo Wielobranżowe VET-AGRO Sp. z o.o., ul. Gliniana 32, 20-616 Lublin, Poland	Enrocin 10% Oral, enrofloksacyna 100 mg/ml, roztwór doustny dla kur i gołębi	Enrofloxacin	10 g/100 ml	Oral solution	Oral	Chicken and pigeon
Poland	Drwalewskie Zakłady Przemysłu Bioweterynaryjnego S.A. ul. Grójecka 6, 05-651 Drwalew, Poland	ENROFLOKSACYNA 10%, enrofloksacyna 100 mg/ml roztwór doustny dla kur, indyków i gołębi	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chicken, turkey and pigeon

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Poland	Vetoquinol Biowet Sp. z.o.o., ul. Kosynierów Gdynskich 13-14, 66-400 Gorzów Wlkp., Poland	Enrobioflox 10%, 100 mg/ml, roztwór doustny dla kur, bydła, świń, psów, kotów i gołębi	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chicken, cattle, pig, dog, cat and pigeon
Poland	Scan Vet Poland Sp. z o.o. Skiereszowo, ul. Kiszkowska 9, 62-200 Gniezno Poland	Scanoflox 10% Oral	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys (broilers); pigeons not intended for human consumption
Poland	Ceva Santé Animale, 10 avenue de La Ballastière, 33500 Libourne France	Quinoex-10, 100 mg/ml roztwór doustny dla kur i indyków	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Poland	Vetpharma Animal Health S.L., Les Corts 23, 08028 Barcelona Spain	Unisol 10% roztwór doustny do podania w wodzie do picia dla kurcząt i indyków	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Poland	Laboratorios Karizoo S.A., Pol. Ind. La Borda, Mas Pujades 11-12, 08140 Caldes de Montbui, Barcelona Spain	ENRO-K roztwór doustny	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Poland	MEDIVET S.A., ul. Szkolna 17, 63-100 Śrem Poland	MEDOXIL ORAL 100 mg/ml roztwór doustny dla kur i królików	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and rabbits
Poland	Global Vet Health S.L. C/Capcanes, 12-bajos Poligono Agro-Reus 43206-Reus Tarragona Spain	Floxacin 100 mg/ml koncentrat do sporządzania roztworu doustnego dla kur i indyków	Enrofloxacin	100 mg/ml	Concentrate for oral solution	Oral	Chickens and turkeys

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Poland	Laboratorios Hipra S.A. Avda. La Selva 135, 17170 - Amer (Girona) Spain	Spectron 100 mg/ml roztwór do podawania w wodzie do picia dla kurcząt i indyków	Enrofloxacin	100 mg/ml	Solution for use in drinking water	Oral	Chickens and turkeys
Poland	Global Vet Health S.L. C/Capcanes, 12-bajos Poligono Agro-Reus 43206-Reus Tarragona Spain	Quinoflox	Enrofloxacin	100 mg/ml	Solution for use in drinking water	Oral	Chicken (broilers, replacement chickens, broiler breeders), rabbit
Poland	Krka d.d. Novo mesto, Šmarjeska cesta 6 8501 Novo Mesto Slovenia	Enroxil 10% Oral	Enrofloxacin	100 mg/ml	Solution for use in drinking water	Oral	Chicken
Portugal	Global Vet Health S.L. C/Capcanes, 12-bajos Poligono Agro-Reus 43206-Reus Tarragona Spain	Quinoflox 100 mg/ml solução para administração na água de bebida para frangos e coelhos	Enrofloxacin	100 mg/ml	Concentrate for oral solution for use in drinking water	Oral	Chickens (broilers, replacement chickens, broiler breeders) and rabbits
Portugal	Vetpharma Animal Health S.L., Les Corts 23, 08028 Barcelona Spain	Levoflok 100 mg/ml solução oral para frangos de carne e coelhos (niflox)	Enrofloxacin	100 mg/ml	Oral solution to be administered in drinking water	Oral	Chicken - broilers and rabbits
Portugal	Laboratorios Karizoo S.A., Pol. Ind. La Borda, Mas Pujades 11-12, 08140 Caldes de Montbui, Barcelona Spain	K-Flok 100 mg/ml solução oral para frangos de carne e coelhos	Enrofloxacin	100 mg/ml	Oral solution to be administered in drinking water	Oral	Chicken - broilers and rabbits

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Portugal	VETLIMA - Soc. distribuidora de produtos agro-pecuários, LDA Av. 5 de Outubro, 35-3º Esq. 1050-047 Lisboa Portugal	Vetaflox 100 mg/ml solução oral para frangos de engorda e coelhos	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chicken - broilers and rabbits
Portugal	Prodivet-Zn, Nutrição e Comércio de Produtos Químicos, Farmacêuticos e Cosméticos, SA Av. Infante D. Henrique nº333 H 3º Piso Esc. 41 1800-282 Lisboa Portugal	Prodirox 100 mg/ml solução oral para frangos e coelhos	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chicken - broilers and rabbits
Portugal	ESTEVE FARMA, LDA Av. Do Forte 3 - Edifício Suécia II, Piso 4A 2794-044 Carnaxide Portugal	ALSIR 100 mg/ml solução oral para frangos, galinhas e perus	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Portugal	Bayer Portugal S.A. Rua Quinta do Pinheiro 5 2794-003 Carnaxide Portugal	Baytril 10% sol. oral	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens
Portugal	Calier Portugal, S.A Centro Empresarial Sintra Estoril II, Ed. C, R. Pé do Mouro Estrada de Albarraque 2710-335 Sintra Portugal	Roxacin oral, enrofloxacina 100 g/l solução oral	Enrofloxacin	100 g/ 1L	Oral solution.	Oral	Chickens (broilers)
Portugal	Representagro – Representaçoes LDA Estrada da Lapa 1, 2665-540 Venda do Pinheiro, Portugal	COLMYC-P solução oral 10% para frangos de carne	Enrofloxacin	10 g/100ml	Oral solution	Oral	Broilers

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Portugal	CENAVISA, S.A., Cami Pedra Estela s/n, 43205 Reus (Tarragona) Spain	ACROLIN 10 solução oral para frangos de carne	Enrofloxacin	100 mg/ml	Oral solution	Oral	Broilers
Portugal	Global Vet Health S.L. C/Capcanes, 12-bajos Poligono Agro-Reus 43206-Reus Tarragona Spain	Floxacin 100 mg/ml concentrado para solução oral, para frangos e perús	Enrofloxacin	100 mg/ml	Concentrate for oral solution	Oral	Chickens and turkeys
Romania	INVESA C/ Esmeralda 19-21 08950 Esplugues de Llobregat, Barcelona Spain	Ganadexil Enrofloxacina	Enrofloxacin	100 mg/ml	Oral solution	Oral	Poultry
Romania	S.C. Romvac Company S.A. Şos. Centurii, nr. 7, Voluntari Romania	Enrofloxarom 10%	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Romania	S.C. CRIDA PHARM S.R.L. Str. Stadionului nr. 1, Oltenita Romania	Enroflox lich. 10%	Enrofloxacin	100 mg/g	Oral solution	Oral	Poultry and pigs
Romania	Bayer Animal Health GmbH, 51368 Leverkusen, Germany	Baytril 10%	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Romania	DIVASA - FARMAVIC, S.A. Ctra Sant Hipolit Km 71 08503 Gurb-Vic Barcelona Spain	Enrovet 10%	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Romania	Krka d.d. Novo mesto, Šmarjeska cesta 6 8501 Novo Mesto Slovenia	Enroxil 10%	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys

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Romania	Laboratorios Syva, s.a.u, Avenue Parroco Pablo Diez 49-57, 24010 Leon Spain	Syvaquinol 10%	Enrofloxacin	100 mg/ml	Oral solution	Oral	Poultry
Romania	Lavet Pharmaceuticals Ltd., Ottó u. 14., 1161 Budapest, Hungary	Enrocin 10%	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Romania	Hipra Laboratorios Avda. La Selva, 135, 17170 Amer (Girona) Spain	Hipralona Enro S	Enrofloxacin	100 mg/ml	Oral solution	Oral	Poultry (chicken)
Romania	S.C.MARAVET SRL 9 Europa, Baia Mare Romania	Anka-floxacin 10%	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Romania	UNIVERSAL PHARMA Gran Via Carlos III 98-7a 08028-Barcelona Spain	Lanflox 100 mg/ml	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Romania	CEVA SANTE ANIMALE ZI Très le Bois - BP 372 22603 Loudeac Cedex France	Quinoex 10	Enrofloxacin	100 mg/ml	Oral solution	Oral	Poultry (broiler chickens, breeder hens, turkeys, breeder turkeys)
Romania	DELOS IMPEX' 96 SRL Str. Horia, Cloşca şi Crişan, nr. 81, Otopeni, Jud. Ilfov, Romania	Enrodem 10%	Enrofloxacin	100 mg/ml	Oral solution	Oral	Poultry, pigs
Romania	Global Vet Health S.L. C/Capcanes, 12-bajos Poligono Agro-Reus 43206-Reus Tarragona Spain	Quinoflox 100 mg/ml	Enrofloxacin	100 mg/ml	Oral solution	Oral	Poultry, rabbits

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Romania	Vetoquinol Biowet Sp. z.o.o., ul. Kosynierów Gdynskich 13-14, 66-400 Gorzów Wlkp., Poland	Enrobioflox 10%	Enrofloxacin	100 mg/ml	Oral solution	Oral	Poultry (broilers), bovine (calves), pigs
Romania	Pasteur - Filiala Filipesti SRL Str. Principala nr. 944 Filipestii de Padure, Jud. Prahova, Romania	Enrofloxacina 10%	Enrofloxacin	100 mg/ml	Oral solution	Oral	Calves, lambs, kids, piglets, poultry, dogs, cats
Romania	Global Vet Health S.L. C/Capcanes, 12-bajos Poligono Agro-Reus 43206-Reus Tarragona Spain	Floxacin 100 mg/ml	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Slovakia	Pharmagal spol. s r.o., Murgašova 5, 949 01 Nitra, Slovakia	Enrogal 100 mg/ml perorálny roztok	Enrofloxacin	100 mg/ml	Oral solution for use in drinking water	Oral	Pigs, calves, lambs, kids, poultry (chicken and turkey)
Slovakia	Krka d.d. Novo mesto, Šmarjeska cesta 6 8501 Novo Mesto Slovenia	Enroxil 10 % sol. ad us.vet.	Enrofloxacin	100 mg/ml	Oral solution for use in drinking water	Oral	Chickens and turkeys
Slovakia	Ceva Animal Health Slovakia, spol s r.o., Račianska 77, 831 02 Bratislava, Slovakia	Quinoex 100 mg/ml perorálny roztok	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Slovakia	Laboratorios Calier S.A., C/Barcelones, 26 (Pla del Ramassa), 08520 Les Franqueses del Valles, Barcelona Spain	Roxacin 100 mg/ml perorálny roztok	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chicken

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Slovakia	Laboratorios Hipra S.A. Avda. La Selva 135, 17170 - Amer (Girona) Spain	Spectron 100 mg/ml roytok na použitie v pitnej vode pre kurčatá a morkz	Enrofloxacin	100 mg/ml	Solution for use in drinking water	Oral	Chickens and turkeys
Slovakia	Vetpharma Animal Health S.L., Les Corts 23, 08028 Barcelona Spain	Unisol 100 mg/ml perorálny roztok na použitie v pitnej vode pre kurčatá a morky	Enrofloxacin	100 mg	Oral solution	Oral	Chickens and turkeys
Slovenia	Bayer d.o.o., Bravničarjeva 13 Ljubljana Slovenia	BAYTRIL 10 % peroralna raztopina	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Slovenia	Krka d.d. Novo mesto, Šmarjeska cesta 6 8501 Novo Mesto Slovenia	ENROX 100 mg/ml peroralna raztopina	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Slovenia	Krka d.d. Novo mesto, Šmarjeska cesta 6 8501 Novo Mesto Slovenia	ENROXIL 100 mg/ml peroralna raztopina za perutnino	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Slovenia	GENERA SI d.o.o., Dunajska 51, 1000 Ljubljana Slovenia	VETOFLOK 10% peroralna raztopina	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Slovenia	Ceva Santé Animale, 10 avenue de La Ballastière, 33500 Libourne France	QUINOFLOX 100 mg/ml peroralna raztopina	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Spain	Laboratorios Ovejero, S.A. Ctra León - Vilecha nº 30, 24192 León Spain	QUINOVET F	Enrofloxacin	100 mg/ml	Oral solution to be administered via drinking water	Oral	Chickens and turkeys

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Spain	Labiana Life Sciences, S.A. C/ Venus, 26 Can Parellada Industrial 08228 Tarrassa Spain	KIN-O-FLOX	Enrofloxacin	100 g/1l	Oral solution	Oral	Poultry (broilers)
Spain	MEVET S.A.U. Polígono Industrial El Segre, P. 410. 25191 Lérida Spain	ENROVALL ORAL	Enrofloxacin	100 mg/ml	Oral solution to be administered via drinking water	Oral	Chickens (broilers)
Spain	Laboratorios Calier S.A., C/Barcelones, 26 (Pla del Ramassa), 08520 Les Franqueses del Valles, Barcelona Spain	ROXACIN SOLUCION ORAL	Enrofloxacin	100 mg/ml	Oral solution to be administered via drinking water	Oral	Chickens (broilers)
Spain	Laboratorio JAER. C/Barcelona 411. 08620 Sant Vicenc del Horts, Barcelona Spain	SORANOX	Enrofloxacin	100 mg/ml	Oral solution to be administered via drinking water	Oral	Chickens and turkeys
Spain	DIVASA - FARMAVIC, S.A. Ctra Sant Hipolit Km 71 08503 Gurb-Vic Barcelona Spain	ENROVET 10%	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
Spain	POLICHEM, S.A. Ctra Reus- Cambrils, Km 3. 43206 Reus. Tarragona Spain	POLISTAR	Enrofloxacin	100 g/l	Oral solution to be administered via drinking water	Oral	Chickens (broilers)
Spain	Industrial Veterinaria S.A. Esmeralda, 19. 08950 Espluges de Llobregat, Barcelona Spain	FENUTIN	Enrofloxacin	100 mg/ml	Oral solution to be administered via drinking water	Oral	Chickens (broilers)

Member State EU/EEA	Applicant/marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Spain	CHEMO IBÉRICA, S.A. Gran Vía Carlos III 98 - 7a, 08028 Barcelona Spain	ENROFLOXACINO CHEMO 100 mg/ml	Enrofloxacin	100 mg/ml	Oral solution to be administered via drinking water	Oral	Chickens (broilers)
Spain	Laboratorios Karizoo S.A., Pol. Ind. La Borda, Mas Pujades, 11-12, 08140 Caldes de Montbui, Barcelona Spain	CONFLOX 100 mg/ml solucion oral para pollos	Enrofloxacin	100 mg/ml	Oral solution to be administered via drinking water	Oral	Chickens (broilers)
Spain	Industrial Veterinaria S.A. Esmeralda, 19 08950 Espluges de Llobregat, Barcelona Spain	Ganadexil enrofloxacino solucion oral	Enrofloxacin	100 mg/ml	Oral solution to be administered via drinking water	Oral	Chicken - broilers and rabbits
Spain	Laboratorios Karizoo S.A., Pol. Ind. La Borda, Mas Pujades 11-12, 08140 Caldes de Montbui, Barcelona Spain	K-FLOX 100 mg/ml solucion oral para pollos y conejos	Enrofloxacin	100 mg/ml	Oral solution to be administered via drinking water	Oral	Chicken - broilers and rabbits
Spain	Universal Farma, S.L., Gran Via Carlos III 98 - 7a, 08028 Barcelona Spain	Enrofloxacino Universal 100 mg/ml solucion oral para pollos y conejos	Enrofloxacin	100 mg/ml	Oral solution to be administered via drinking water	Oral	Chicken - broilers and rabbits
Spain	S.P. VETERINARIA, S.A. Ctra. Reus - Vinyols Km 4,1 Riudoms 43330 (Tarragona) Spain	FLOXAVEX 100 mg/ml concentrado para solucion oral pollos y pavos	Enrofloxacin	10 % w/v	Concentrate for oral solution	Oral	Chickens and turkeys
Spain	Global Vet Health S.L. C/Capcanes, 12-bajos Poligono Agro-Reus 43206-Reus Tarragona Spain	FLOXACIN 100 mg/ml concentrado para solucion oral pollos y pavos	Enrofloxacin	100 mg/ml	Concentrate for oral solution	Oral	Chickens and turkeys

Member State EU/EEA	Applicant/marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Spain	Global Vet Health S.L. C/Capcanes, 12-bajos Poligono Agro-Reus 43206-Reus Tarragona Spain	AQUAFLOX 100 mg/ml solucion para administracion en agua de bebida	Enrofloxacin	100 mg/ml	Solution for use in drinking water.	Oral	Chickens (broilers, replacement chickens, broiler breeders) and rabbits
Spain	Laboratorios Syva, s.a.u, Avenue Parroco Pablo Diez 49-57, 24010 Leon, Spain	SYVAQUINOL 10% oral	Enrofloxacin	100 mg/ml	Oral solution	Oral	Poultry (broilers)
Spain	S.P. VETERINARIA, S.A. Ctra. Reus - Vinyols Km 4,1 Riudoms 43330 (Tarragona) Spain	COLMYC-C	Enrofloxacin	100 mg/ml	Oral solution to be administered via drinking water	Oral	Poultry (broilers and fattened turkeys), rabbits
Spain	Laboratorios Hipra S.A. Avda. La Selva 135, 17170 - Amer (Girona) Spain	HIPRALONA ENRO-S	Enrofloxacin	100 mg/ml	Oral solution to be administered via drinking water	Oral	Poultry (broilers and fattened turkeys), rabbits
Spain	Laboratorios Maymo, S.A., Via Augusta 302, 08017 Barcelona Spain	QUIMIOCOLI	Enrofloxacin	10 g/100 ml	Oral solution	Oral	Poultry (broilers)
Spain	LABORATORIOS E INDUSTRIAS IVEN, S.A. C/Luis I 56 28031 Madrid Spain	FLOXACIVEN	Enrofloxacin	10 g/100ml	Oral solution	Oral	Poultry (broilers)
Spain	LABORATORIOS DR ESTEVE Avda. Madre de Déu de Montserrat 221 08041 Barcelona Spain	ALSIR 10% solucion oral	Enrofloxacin	10 g/100 ml	Oral solution	Oral	Poultry (broilers, replacement chickens, broiler breeders and turkeys)

Member State EU/EEA	Applicant/marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Spain	CENAVISA, S.A., Cami Pedra Estela s/n, 43205 Reus (Tarragona) Spain	FLOXICEN	Enrofloxacin	100 mg/ml	Oral solution	Oral	Poultry (broilers)
Spain	Laboratorios Serra Pamies, S.A. Crta de Castellvell, 24 43206 Reus (Tarragona) Spain	E-FLOX solucion oral	Enrofloxacin	100 mg/ml	Oral solution to be administered via drinking water	Oral	Poultry (broilers)
Spain	CEVA SALUD ANIMAL, Carabela La Niña 12, 5ª 08017 Barcelona Spain	QUINOEX-10	Enrofloxacin	100 mg/ml	Oral solution	Oral	Poultry (broilers and broiler breeders)
Sweden	Bayer Animal Health GmbH, 51368 Leverkusen, Germany	Baytril vet.	Enrofloxacin	100 mg/ml	Solution for use in water	Oral	Poultry
Sweden	aniMedica GmbH, Im Südfeld 9, 48308 Senden-Bosensell Germany	Enrotron	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
United Kingdom	Bayer plc Animal Health Division Bayer House Strawberry Hill Newbury RG14 1JA Berkshire United Kingdom	Baytril 10% Oral Solution	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
United Kingdom	Krka d.d. Novo mesto, Šmarjeska cesta 6 8501 Novo Mesto Slovenia	Enroxil 100 mg/ml Oral Solution for Chickens and Turkeys	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys
United Kingdom	Vetpharma Animal Health S.L., Les Corts 23, 08028 Barcelona Spain	Lanflox 100 mg/ml Solution for Use in Drinking Water for Chickens and Turkeys	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys

Member State EU/EEA	Applicant/marketing authorisation holder	Product name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
United Kingdom	Global Vet Health S.L. C/Capcanes, 12-bajos Poligono Agro-Reus 43206-Reus Tarragona Spain	Quinoflox 100 mg/ml Solution for Use in Drinking Water, Chicken and Rabbits	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens Rabbits
United Kingdom	Vetpharma Animal Health S.L., Les Corts 23, 08028 Barcelona Spain	Unisol 100 mg/ml Oral Solution for use in Drinking Water for Chickens and Turkeys	Enrofloxacin	100 mg/ml	Oral solution	Oral	Chickens and turkeys

Annex II

Scientific conclusions and grounds for amendment of the summaries of product characteristics, labelling and package leaflets

Overall summary of the scientific evaluation of all veterinary medicinal products containing enrofloxacin to be administered via the drinking water to chickens and/or turkeys *(see Annex I)*

1. Introduction

Enrofloxacin is a synthetic chemotherapeutic agent from the class of the fluoroquinolone carboxylic acid derivatives. It has antibacterial activity against a broad spectrum of Gram-negative and Gram-positive bacteria. Its bactericidal activity inhibits the bacterial DNA-gyrase. Enrofloxacin is for veterinary use only. Fluoroquinolones are recognised as veterinary critically important antimicrobials in the treatment of colibacillosis septicaemia and chronic respiratory disease in poultry.

Veterinary medicinal products as oral solutions contain 50 mg, 100 mg or 200 mg enrofloxacin per ml for use in drinking water. All products are administered at the dose of 10 mg enrofloxacin per kg body weight (bw).

Following a referral procedure (EMEA/V/A/067) under Article 34 of Directive 2001/82/EC, the full product information of the 'pioneer' product 'Baytril 10% Oral Solution' and it associated names was harmonised with a Commission Decision of 8 October 2012[1].

During the above mentioned Article 34 referral procedure for Baytril 10% oral solution and its associated names it became apparent that some of the indications for use in the target species chickens and turkeys were not consistent with the principles of responsible use of antimicrobial veterinary medicinal products and therefore such indications were removed from the harmonised product information. In addition the CVMP concluded that there is insufficient data to optimise the dose regimen for treatment of *Escherichia coli* in chickens and/or turkeys.

The United Kingdom also noted that the withdrawal periods for oral solutions containing enrofloxacin vary across Member States from 3-15 days for chickens and 3-13 days for turkeys, therefore on 18 October 2012, the United Kingdom presented to the European Medicines Agency a referral notification under Article 35 of Directive 2001/82/EC for all veterinary medicinal products containing enrofloxacin to be administered via the drinking water to chickens and/or turkeys. The Committee for Medicinal Products for Veterinary Use (CVMP) was requested to consider the indications, dosage regimens and withdrawal periods for chickens and turkeys in order to ensure consumer safety, efficacious treatment in chickens and turkeys, as well as lower the risk of development of antimicrobial resistance to enrofloxacin.

2. Discussion

Efficacy issues

Chickens

Mycoplasma spp

Eleven references were submitted, two of which were dated after 2000, in support of the indication for *Mycoplasma* spp. The majority of studies used an experimental inoculation with *M.gallisepticum*. They show that 10 mg/kg bw enrofloxacin was efficacious in reducing mortality and morbidity and that there was reduction in pathogen re-isolation for up to 4 weeks after inoculation. One study also demonstrated that continuous administration of the product at 10 mg/kg bw was better than pulsed

[1] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/veterinary/referrals/Baytril_10/vet_referral_000065.jsp&mid=WC0b01ac05805c5170

administration of the same dose rate. The most recent report (Reinhardt et al 2005)[2] demonstrated that, even with treatment with enrofloxacin at 10 mg/kg bw, the pathogen was not eradicated and when birds were stressed at up to 3 months after the initial inoculation, *M.gallisepticum* was reactivated.

Under field conditions, *Mycoplasma* is typically part of a mixed infection, therefore it can be difficult to demonstrate field efficacy for this indication. Once infected, birds may remain carriers, and although antibiotics may alleviate clinical signs and lesions, they do not eliminate infection. Control programmes aim to eliminate infection from breeding stock.

Mycoplasma spp are rarely included in surveillance or monitoring schemes and evidence of widespread resistance in the EU or lack of efficacy of the dose in the treatment of mycoplasmosis is hard to find. Two references were provided showing that in 1993, the Minimum Inhibitory Concentration (MIC) of enrofloxacin to *M.gallisepticum* isolates was 0.0125-0.1 µg/ml and for *M.synoviae* it was 0.0125-0.8 µg/ml, and in 1997, MIC for *M.gallisepticum* isolates was 0.025-1.0 µg/ml and for *M.synoviae* it was 0.05-0.5 µg/ml. Based on the Clinical Laboratory and Standards Institute (CLSI) resistance breakpoint of ≥2 µg/ml, one report shows that the upper range of MICs of *M.synoviae* increased further to 2/4 µg/ml in 2008 in The Netherlands with an 11.7% resistance noted. Although methods cannot be directly compared, there is evidence of reduced susceptibility emerging over time. It should be noted that levels of enrofloxacin in the lungs of chickens have been consistently reported as 0.88 µg/g after chickens have been dosed with enrofloxacin at 10 mg/kg bw. This would indicate that suitable levels are not reached in lung tissue for efficacy against *Mycoplasma* spp with an MIC of ≥1 µg/ml.

Although there are some deficiencies in individual clinical studies, sufficient data have been presented to support the indications for *M.synoviae* and *M.gallisepticum* in chickens. The data do not conclusively justify the proposed dose rate against the named mycoplasma species. Although there is some evidence of resistance development in *Mycoplasma*, these organisms are rarely included in surveillance schemes and evidence of widespread resistance in the EU or lack of efficacy of the dose is hard to find. Therefore, a warning in Section 4.5 of the Summaries of Products Characteristics (SPCs) that resistance has been identified in *M.synoviae* in the EU should be added to highlight the risk. A further warning in section 4.4 of the SPCs should be added also to advise that treatment of mycoplasma infections may not eradicate the organism.

A.paragallinarum

Two studies were submitted to support the indication for *A.paragallinarum*, one using an experimental infection and one field study. Dose rates less than 8.3 mg/kg bw were highly effective and the MIC study indicated that *A.paragallinarium* is highly susceptible to enrofloxacin. Although both studies had been conducted approximately 25 years ago, there are sufficient data to support the indication for *A.paragallinarium* at the proposed dose rate. Alternative therapies include amoxicillin, erythromycin, tetracyclines and sulphonamides, although resistance which may be plasmid-borne has been reported to aminoglycosides and macrolides in Asia. Therefore, there is justification to have a second-line treatment available.

P.multocida

One field study was submitted to support the indication of *P.multocida* using an inclusion rate of 50 ppm. Susceptibility tests with isolates outside of the EU were submitted. These showed that there is a gradual increase in MIC and resistance over the last 10 years. The one reference conducted in the EU

[2] Reinhardt A.K., Gautier-Bouchardon A.V., Gicquel-Bruneau M., Kobisch M., and Kempf I. (2005) Persistence of Mycoplasma gallisepticum in chickens after treatment with enrofloxacin without development of resistance. Vet. Microbiol. 106: 129-372.

agreed with these conclusions, although the MIC_{90} remained low at 0.03 µg/ml, range 0.008 -2 µg/ml (Wallman et al, 2007)[3]. Taking account of the overall data, the indication for the treatment of *P.multocida* in chickens and turkeys is justified at a dose of 10 mg/kg bw for 3-5 days. Alternative treatments include amoxicillin, tetracyclines, macrolides and sulphonamides. A report by Sellyei *et al,* 2009[4], advised that although *P.multocida* isolates are susceptible to most widely used antimicrobials, remarkable resistance was detected to sulphonamides, tetracyclines, first generation quinolones and aminoglycosides. In addition, *P.multocida* causes acute, serious and highly contagious disease in poultry, therefore there is a justification for having a second line treatment available for this pathogen.

E.coli

A considerable number of studies and references have been submitted to support the indication of *E.coli*. All but four studies were conducted with an experimental infection of *E.coli*. The studies were mainly conducted between 1985 and 1998 and did not conclusively show optimum efficacy with a dose rate of 10 mg/kg bw. The MIC of the challenge strain was 0.06 µg/ml, where reported. Dose rates up to 35.4 mg/kg in young broilers showed optimum reduction in mortality and reduction in *E.coli* re-isolation rate. Field studies conducted in 1997-1998 showed that an inclusion rate of 50 ppm reduced clinical signs but the pathogen was not eliminated. A further field study conducted in the EU demonstrated that dose rates up to 20.6 mg/kg bw again controlled signs but did not eliminate the pathogen. The field studies are more than 20 years old and are limited in their reporting. Another study demonstrated that a dose rate of 12.52 mg/kg bw administered for 3 days controlled signs of disease but did not eliminate the pathogen.

Two studies conducted in 1997 and 2002 both demonstrated that when birds were infected with *E.coli* with reduced susceptibility, MIC=0.5 µg/ml, the efficacy of 10 mg/kg enrofloxacin was reduced – clinical signs were less well controlled and in one study mortality was approximately 43%.

In a study from 2010 an experimental infection of *E.coli* did not acquire resistance from a pre-inoculated multi-resistant *E.coli*. The study did show that one *E.coli* isolate acquired resistance from the commensal flora of the chicken.

Fluoroquinolones are recognised as veterinary critically important antimicrobials in the treatment of colibacillosis septicaemia and chronic respiratory disease in poultry with few effective alternatives, therefore the indication should be maintained. However, from the data submitted it is not possible to determine an optimum dose rate to treat *E.coli* infection in chickens.

Turkeys

Three references were provided to justify that the pharmacokinetics of enrofloxacin in turkeys is very similar to that of chickens. The data are sparse but show that lung levels and plasma Cmax are similar, while AUC is greater in turkeys.

Mycoplasma spp

Two experimental studies and one field study were submitted to support the indication of *Mycoplasma* spp in turkeys. These studies were conducted at least 25 years ago. The field study replicated the situation that would be encountered – a mixed infection which included *Mycoplasma* spp. The studies showed that a dose of 10 mg/kg bw for 5 days controlled clinical signs in the field but only reduced re-

[3] Wallmann J., Schröer U., Kaspar H. (2007) Quantitative resistance level (MIC) of bacterial pathoges (Escherchia coli, Pasteurella multocida, Pseudomonas aeroginosa, Salmonella sp., Staphylococcus aureus) isolated from chickens and turkeys: National resistance monitoring by the BVL 2004/2005

[4] Sellyei B Varga Z Szentesi-Samu K Kaszanyitzky E Magyar T (2009) Antimicrobial susceptibility of Pasteurella multocida isolated from swine and poultry Acta Vet Hung 57 (3): 357-67

isolation rate; however, in severe experimental infections, dose rates of 35 and 66 mg/kg bw reduced mortality and the severity of the pathological findings.

There are adequate data to support the indication of *Mycoplasma* spp in turkeys, based on the fact that they are considered a minor species and extrapolation can be made from the data in chickens.

P.multocida

Four experimental studies which used a variety of different doses were submitted in support of the indication for *P.multocida* in turkeys. Dose rates from as low as 1.5 mg/kg bw up to dose rates of 13.02 mg/kg bw were successful in controlling mortality and morbidity. Taking account of all the data, the indication for the treatment of *P.multocida* in turkeys is acceptable at a dose of 10 mg/kg bw for 3-5 days.

E.coli

Two experimental and two field studies were submitted in support of the indication for *E.coli*. The field studies were old and poor methods and reporting mean that the results cannot be considered supportive of the dose rate. In the more recent laboratory study (2007) which simulated field conditions, turkeys were administered enrofloxacin at 10 mg/kg bw for 5 days, but the re-isolation rate was not investigated. This dose rate controlled the signs of disease. The 2009 experimental study (using a susceptible *E.coli* isolate) showed that a daily dose of 10 mg/kg bw for 5 days was more effective at controlling disease and reducing *E.coli* re-isolation compared to the total dose (50 mg/kg bw) administered over a 20 hours period when *E.coli* was detected in the trachea 4 days after the onset of treatment.

Although the data provided are not sufficient to conclusively support the dosing regimen, taking into consideration the fact that colibacillosis is a very common disease in turkeys and the importance of fluoroquinolones in its treatment, it is agreed that the indication and dose regimen should remain in the SPCs of the products concerned.

Antimicrobial resistance in target pathogens

In Europe, several antimicrobials are authorised for treatment of colibacillosis in chickens and turkeys (apramycin, chlortetracycline, colistin, difloxacin, doxycycline and sulphadiazine + trimethoprim), but the widespread multidrug resistance of pathogenic *E.coli* has led to the extensive use of enrofloxacin. Usually resistance to fluoroquinolones arises spontaneously because of point mutations that result in amino acid substitutions within the topoisomeerase subunits gyrA, gyrB, parC or parE, a decreased expression of outer membrane porins, or an overexpression of multidrug efflux pumps.

MIC data were provided for enrofloxacin against target pathogens (*E.coli*, *P. multocida, M. gallisepticum, M. synoviae*) isolated from respiratory tract infections or septicaemia in poultry. The data presented show that the MICs of *E.coli* have increased over the last 20 years and the approved dose regimen may no longer be optimal.

Resistance rates in *E.coli* from chickens and turkeys are reported as low in the study by Wallman 2007, where a clinical breakpoint of ≥ 2 mg/l was used and resistance was determined as up to 4.6% in isolates from 2004-2005. However according to the EFSA/ECDC report (2012)[5] resistance to ciprofloxacin in indicator *E.coli* isolates taken from chickens is described as moderate to high at a rate of 47%. It has to be borne in mind that this resistance rate is based on epidemiological cut-off values

[5] European Food Safety Authority and European Centre for Disease Prevention and Control; The European Union Summary Report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2010. EFSA Journal 2012; 10(3):2598 [233 pp.] doi:10.2903/j.efsa.2012.2598. Available online at www.efsa.europa.eu/efsajournal

for non-pathogenic strains. The paper by de Jong et al[6], 2012, quotes data from the EASSA collected from EU countries. Clinical resistance of *E.coli* in chickens to ciprofloxacin was 1.9% in 1999-2000 and increased through 2002-2003 to 5.9% in 2005-2006. The paper states that the high values for 2005-2006 were due to the high level of resistance in Spain (24%), which was not included in reports for 1999-2000. In this paper, clinical resistance was assessed against the CLSI break-point for ciprofloxacin of ≥4 mg/l. Rates of decreased susceptibility of *E. coli* to ciprofloxacin (based on an epidemiological cut-off of 0.06 mg/l) were 19.3% in 1999-2000 and 33.5% in 2005-2006.

The susceptibility of *E.coli* isolated predominantly from Germany as part of the GermVet 2008[7] and 2009[8] and Germap 2010[9] resistance monitoring during 2004-2009 was provided. Isolates were from cases of respiratory tract infections or septicaemia of poultry. The CLSI breakpoint of ≥2 mg/l was used. In total, approximately 2000 isolates from broilers, turkeys and layers showed that the overall MIC range was 0.015-≥32 µg/ml, with up to 8.7% resistance. MIC_{90} was determined as 0.5 µg/ml in most references.

In a recent study from Italy, Russo *et al.* (2012)[10] found that 30.34% of eighty-nine APEC (avian pathogenic *E. coli*) isolates from turkeys were classified as resistant to enrofloxacin and 40.45% as intermediately resistant with a breakpoint of 2 µg/ml.

Enrofloxacin is associated with a concentration-dependent bactericidal action and therefore $AUC_{0\text{-}24h}$/MIC and C_{max}/MIC ratios are considered indicators of efficacy. It has been postulated that $AUC_{0\text{-}24h}$/MIC and C_{max}/MIC ratios of >100 and >8, respectively, are predictive of clinical outcome for fluoroquinolones.

When administered continuously in drinking water (based on a daily dose of 10 mg/kg bw), steady-state plasma concentrations (C_{ss}) for enrofloxacin were 0.33 ± 0.04 µg/ml in turkeys and 0.56 ± 0.13 µg/ml in chickens. Given the inter-individual variability surrounding C_{ss} values and the fact that several studies quoted MIC_{90} values for enrofloxacin against *E. coli* of 0.5-1 µg/ml, it seems that plasma concentrations greater than the MIC would not be achieved in all individuals against all isolates.

A comprehensive PK/PD analysis was provided. This showed that when enrofloxacin is dosed as a single oral dose of 10 mg/kg bw against a less susceptible *E.coli* isolate with MIC of 0.5 µg/ml, in chickens, AUC/MIC was 28.8 and in turkeys AUC/MIC was 32.2. When site of infection lung levels of enrofloxacin of 0.84 µg/g are considered, against the same pathogen, C_{max}/MIC is far below the clinically predictive value of 8.

A study by Haritova *et al* (2011)[11] demonstrated that when *E.coli* O78/H12 infected chickens (MIC 0.01 µg/ml) were treated with either 10 mg/kg bw or 50 mg/kg bw enrofloxacin for 3 days, both dose

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[6] de Jong A, Stephan B, Silley P.(2012).Fluoroquinolone resistance in E coli and Salmonella from healthy livestock and poultry in the EU. Journal of Applied Microbiology, 112: 239-245.

[7] GermVet (2008) Kaspar H., Römer A., Steinacker U., Mankertz J., Gowik P., Dombrowski S., Banspach N.; Berichte zur Resistenzmonitoringstudie 2008, Resistenzsituation bei klinisch wichtigen tierpathogenen Bakterien Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL). ISBN 978-3-0348-0422-6
http://www.bvl.bund.de/SharedDocs/Downloads/09_Untersuchungen/Archiv_berichte_Resistenzmonitoring/Bericht_Resistenzmonitoring_2008.pdf?__blob=publicationFile&v=3

[8] GermVet (2009) Kaspar H., Römer A., Steinacker U., Mankertz J., Gowik P., Dombrowski S., Banspach N.; Berichte zur Resistenzmonitoringstudie 2009, Resistenzsituation bei klinisch wichtigen tierpathogenen Bakterien Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL). ISBN 978-3-0348-0504-9.
http://www.bvl.bund.de/SharedDocs/Downloads/09_Untersuchungen/Bericht_Resistenzmonitoring_2009.pdf?__blob=publicationFile&v=2

[9] GERMAP (2010) Antibiotika-Resistenz und –Verbrauch Bericht über den Antibiotikaverbrauch und die Verbreitung von Antibiotikaresistenzen in der Human- und Veterinärmedizin in Deutschland. Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL). ISBN 978-3-00-031622-7.
http://www.bvl.bund.de/SharedDocs/Downloads/08_PresseInfothek/Germap_2010.pdf?__blob=publicationFile&v=2.

[10] Russo, E., Lucatello, L., Giovanardi, D., Cagnardi, P., Ortali, G., Di Leva, V., Montesissa, C. (2012). Approved medication of water with enrofloxacin to treat turkey colibacillosis: Assessment of efficacy using a PK/PD approach. Vet Microbiol, 161, 206-212.

[11] Haritova, A., V. Urumova, M. Lutckanov, V. Petrov, and L. Lashev. 2011. Pharmacokinetic-pharmacodynamic indices of enrofloxacin in Escherichia coli O78/H12 infected chickens. Food and Chemical Toxicology 49:1530-1536

rates controlled clinical signs, but at up to 25 days after infection, the pathogen was still re-isolated from the spleen in the 50 mg/kg bw group compared with re-isolation from the lungs, liver, heart and spleen in the 10 mg/kg bw group. In a previous study, the Minimal Bactericidal Concentration (MBC) of 0.06 µg/ml and mutant prevention concentrations (MPC) of 4 µg/ml were determined for this O78/H12 pathogenic strain. There is a wide mutant selection window between 0.06 and 4 µg/ml which supports the fact that the pathogenic strain could not be eradicated after treatment with even a high dose of enrofloxacin.

Apart from mutant selection windows, other features of enrofloxacin also promote the selection of resistant strains. For example, approximately 25-35% of enrofloxacin, at any given timepoint, is metabolized to ciprofloxcacin, resulting in subtherapeutic concentrations of ciprofloxacin, that could select for resistant strains, as well as cross-resistance.

A recent study from Russo *et al* (2012) used modern techniques of measuring plasma levels after pulsed administration of enrofloxacin in drinking water to turkeys at 10 mg/kg bw. Cmax was determined as approximately 0.67 µg/ml in healthy birds and 0.54 µg/ml in sick birds infected with APEC, and AUC_{0-24} as 7.4 mg/h/l in healthy birds and 7.7 mg/h/l in sick birds. The MIC_{50} and MIC_{90} values of the *E coli* isolates were 1 and 32 mg/L, respectively, which results in Cmax/MIC and AUC/MIC parameters considerably below the breakpoints for fluoroquinolones.

The method of antimicrobial administration via the drinking water increases the resistance selection pressure due to variability in intake and therefore pharmacokinetics across the population. In order to recommend a dosage regimen, the population variability and the impact of disease on pharmacokinetic parameters needed to be investigated. Clinical response is also affected by pharmacodynamic variability (host response, population distribution of MIC values for the target pathogen). Toutain, 2006[12], advises that the optimal dosage regimen for antibiotics should be a "population dosage regimen" aimed to ensure appropriate exposure of most (90%) of the animals in a given population and, as far as possible, limit the under-exposure of some individuals to the drug and hence limit the risk of emergence of resistance.

In addition, PK/PD concepts have recently been developed that use the hypothesis of the mutant selection window in order to elaborate a dosing regimen that can limit the emergence of resistant organisms (Drlica & Zhao, 2007)[13].

It is therefore proposed that a new dosing regimen should be elaborated that takes into account the evolution of the susceptibility profile of *E. coli* since enrofloxacin was first authorised in poultry and new PK/PD concepts aimed at limiting development of resistance in target pathogens.

Antimicrobial resistance in food borne bacteria

The active metabolite of enrofloxacin, ciprofloxacin, is categorised as a critically important antibiotic for use in human medicine.

A comprehensive review of data regarding resistance in *E.coli, Salmonella* sp and *Campylobacter* spp (bacteria of concern to human health) from poultry from EU Member States isolated during 2002-2009 was provided.

E.coli

[12] Population PK and PK/PD investigations and Monte Carlo simulations for a rational dose regimen. Toutain PL. *J Vet Pharmacol Ther.* 2006 (29) Suppl 1, 19-21.

[13] Drlica, K., and X. Zhao. 2007. Mutant selection window hypothesis updated. Clinical Infectious Diseases 44:681-688.

Data collected from EU surveillance programmes showed that levels of resistance in *E.coli* to enrofloxacin varied from 0-47% depending on the EU Member State from which the isolates were sourced. Decreased susceptibility varied from approximately 10-50%. According to the EFSA summary report, 2010[14], the level of resistance (defined by epidemiological cut-off values) to ciprofloxacin in indicator (commensal) *E.coli* isolates from broiler chickens was 29%.

In a recent study from Italy, Russo *et al.* (2012) found that 30.34% of eighty-nine APEC (avian pathogenic *E. coli*) isolates from turkeys were classified as resistant to enrofloxacin and 40.45% as intermediately resistant with a breakpoint of 2 µg/ml. Although APEC is generally considered to be non-pathogenic in man, there is evidence that some strains may constitute a potential zoonotic risk.

From the public health perspective, the main concern in regards to *E.coli* is the potential to transfer resistance genes from commensal *E.coli* in poultry to potentially pathogenic bacterial strains in man. The issue of *E.coli* is changing with evidence of poultry ESBL *E. coli* (CTX-M1) in processed meat products and increasing human prevalence of ESBL CTX-M1 infections. It is currently unknown if enrofloxacin usage is associated with CTX-M1 selection and shedding, but ESBL *E. coli* can also be resistant to fluoroquinolones.

Salmonella spp

The data submitted demonstrate that the *Salmonella* control programmes implemented over the last 20 years have reduced the prevalence of non-typhoidal *Salmonella* in poultry. In the strains that were isolated, resistance to ciprofloxacin was absent. Reduced susceptibility has been detected (11.3-49.4%) for years, based on a breakpoint of ≥4 µg/ml and a non-wild type MIC of ≥0.12 µg/ml. According to the EFSA summary report, 2010, 24% of *Salmonella* spp isolates from breeding, layer and broiler flocks were resistant (defined by epidemiological cut-off values) to ciprofloxacin. The Joint ECDC/EFSA/EMA scientific opinion[15] identified resistance to fluoroquinolones in salmonella of major concern for public health as ciprofloxacin is the antimicrobial of choice for treatment of severe or invasive *Salmonella* infections in humans. In October 2012, following an Article 34 referral procedure for Baytril 10% Oral Solution (EMEA/V/A/067) the indication for treatment of salmonella infections has been removed from the SPC due to the lack of support for the dosing regimen, especially in regards to elimination of infection, and EU legislation in regards to national control programmes for the control of salmonella in poultry that state that antimicrobials should not be used except in exceptional circumstances (Regulation EC 1177/2006). Consequently it is concluded that *Salmonella* as a target pathogen should be removed also from the SPCs of all products concerned by this referral procedure.

Campylobacter

According to the EFSA summary report, 2010, the level of resistance (defined by epidemiological cut-off values) to ciprofloxacin in *Campylobacter jejuni* isolates from broiler chickens was 47%, although there is variability between Member States.

In a review by Luangtongkum et al (2009)[16], it has been reported that a steady increase in fluoroquinolone-resistance among *Campylobacter* isolates has also been observed in many EU Member States and 17-99% of *Campylobacter* strains isolated from humans and animals in this region were resistant to fluoroquinolones with the highest resistance levels reported in Spain.

[14] European Food Safety Authority and European Centre for Disease Prevention and Control; The European Union Summary Report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2010. EFSA Journal 2012; 10(3):2598 [233 pp.] doi:10.2903/j.efsa.2012.2598. Available online at www.efsa.europa.eu/efsajournal
[15] Joint Opinion on antimicrobial resistance focused on zoonotic infections. EFSA Journal 2009; 7(11):1372. - http://www.efsa.europa.eu/en/scdocs/doc/1372.pdf
[16] Luangtongkum T, Jeon B, Han J, Plummer P, Logue CM, Zhang Q (2009) Antibiotic resistance in Campylobacter: emergence, transmission and persistence. Future Microbiol Mar;4(2):189-200

This review states that multiple studies have demonstrated the rapid development of fluoroquinolone resistant mutants in chickens originally infected with fluoroquinolone-susceptible *C.jejuni*, but treated with enrofloxacin. The mutant population continues to persist even after removal of the selection pressure as fluoroquinolone resistance mediated by gyrA mutations can be stably maintained in *Campylobacter* and possess an enhanced fitness. There has been much debate as to whether quinolone resistant *Campylobacter* infection is associated with adverse human health consequences. The study by Evans at al (2009)[17] concluded that in the UK humans infected with fluoroquinolone-resistant *Campylobacter* did not suffer a more severe disease than those infected with susceptible *Campylobacter* even when use of antimicrobials is taken into account, however the authors did not state if there was any impact on specific vulnerable sub-groups.

CVMP considered the impact of infections with fluoroquinolone-resistant foodborne bacteria on human health due to use of fluoroquinolones in food-producing animals in the EU in a CVMP Public Statement (2007)[18]. The recommendations were carried forward to the CVMP Strategy 2011-2015 and were addressed in the previous Article 35 referral for all veterinary medicinal products for food producing species containing quinolones and/or fluoroquinolones as active substances (EMEA/V/A/049)[19] and in the current referral.

Target species safety

Tolerance data from 2009 show that at doses of 300 and 600 mg enrofloxacin /kg bw administered once or for 5 days to 21 day old broiler chickens, diarrhoea and abnormal behaviour such as reluctance to move, reduced motor activity and disturbed coordination of movement were seen. No abnormal findings were present according to palpation of the examined joints and articular cartilage surface. Quantitative histopathological evaluation revealed no substantial changes in examined articular cartilages in birds treated with doses up to 100 mg/kg bw/day. Dose dependent abnormalities were observed in the total index of lesions of femoral head, femoral condyles and tibial condyles in birds receiving ≥50 mg/kg bw/day for 5 days. A margin of at least five times the recommended dose was safe.

A further study by the same authors determined that treatment with a therapeutic dose of enrofloxacin for a prolonged duration (up to 35 days) to 21 day old broiler chickens did not cause arthropathy in growing chickens and toxicity is not caused by cumulative effects.

These data provide information regarding the possible implications of a change of dose regimen on target species safety.

Withdrawal periods

Both proprietary and published data were provided to form a picture of the depletion of residues from edible tissues resulting from treatment with enrofloxacin-containing, orally-administered veterinary

[17] Evans MR, Northey G, Sarvotham TS, Rigby CJ, Hopkins AL, Thomas DR (2009)
Short-term and medium-term clinical outcomes of quinolone-resistant Campylobacter infection.
Clinical Infectious Diseases 48, 1500-1506.
[15] Smith KE Besser JM Hedberg CW Leano FT Bender JB Wicklund JH Johnson BP Moore KA Osterholm MT and the investigation team (1999) Quinolone resistant Campylobacter jejuni infections in Minnesota 1992-1998. The New England Journal of Medicine 340 (20) 1525-32
[16] Nelson JM Smith KE Vugia DJ Rabatsky-Her T Segler SD Kassenborg HD Zansky SM Joyce K Marano N Hoekstra RM Angulo FJ Prolonged diarrhea due to ciprofloxacin-resistant Campylobacter infection (2004) J Infect Dis 190 (6) 1150
[17] Engberg J Neimann J Moller Nielsen E Moller Aarestrup F Fussing V Quinolone resistant Campylobacter infections: Risk factors and clinical consequences (2004) Emerg Infect dis 10 (6) 1056-1063
[18] CVMP Public statement on the use of (fluoro)quinolones in food-producing animals in the European Union: development of resistance and impact on human and animal health (2007) (EMEA/CVMP/SAGAM/184651/2005) - http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2009/10/WC500005152.pdf
[18] Helms M Simonsen J Olsen KEP Molbak K (2005) Adverse health events associated with antimicrobial drug resistance in Campylobacter species: a registry- based cohort study J Infect Dis 191 (9) 1570
[19] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/veterinary/referrals/Quinolones_containing_medicinal_products/vet_referral_000039.jsp&mid=WC0b01ac05805c5170

medicinal products given at a dose of 10 mg/kg bw/day for 5 consecutive days to chickens and turkeys. In both species, the available data are rather variable in both quality and outcome.

Many of the studies submitted did not conform to current guidance, in that some MAHs provided only summaries of the data that they hold, and did not provide the details of the analytical method(s) used, the method validation data, nor data to demonstrate the stability of the analytes in the various matrices during storage between sampling and analysis, or during sample processing. These omissions add to the uncertainties that also arise due to the variability in the results of the submitted studies. Other MAHs however, did supply these data, and as such, the studies provided by these companies provide more reliable information on which to base a conclusion on the length of the meat withdrawal periods.

Although the studies provided are not considered to be of equal reliability, the CVMP attempted a 'pooled' statistical analysis of all the data provided by all of the studies submitted and found that this method could not be applied, because the statistical parameters (defined by the Bartlett, Shapiro-Wilk and ANOVA (lack of fit) tests) showed a significant deviation from normality ($p < 0.01$), i.e. the data were not normally distributed and showed no homogeneity of variance. The data were too variable to be analysed in this way because the studies were not sufficiently similar and the influence of some aspects of study design could not be taken into account when interpreting the findings. These aspects include:

- Breed of bird used in the study; faster-growing or slower-growing; different metabolism;
- Size and weight of the birds used in the studies varied considerably, and did not correlate to the calculated length of the WP from each study;
- The method of administration; some studies used gavage administration (which improves the accuracy of the dose, but also (potentially) affects the metabolic profile of the substance, since this is in effect a bolus dose, rather than a continuous dose), some studies used drinking water administration, as specified in the SPCs (which could lead to more variable results due to some birds drinking more medicated water than others, but is more representative of what would happen 'in the field');
- Correction factors based on the determined accuracy of the analytical method have been used in some cases and not in others;
- Most of the studies provided were not reported to current standards, omitting raw data, analytical method validation data and storage stability data.

The CVMP also considered the possibility that there were significant formulation differences between the products that might account for the variability in metabolism and depletion due to potential bioavailability differences; however, the formulations of all the products concerned are very similar, containing similar excipients. All products are aqueous solutions and contain a solubilising agent, such as potassium hydroxide or acetic acid, a preservative such as benzyl alcohol, and are made up to volume with water; thus there are no indications that formulation differences can account for the variability seen between the studies provided.

The variability of the data leads to estimates of the withdrawal period for chickens ranging between 4 and 8 days and between 4 and 13 days for turkeys, depending on the individual study. The Committee agreed that the most conservative withdrawal periods, derived from the better conducted and reported studies, should be established i.e. 7 days for chickens and 13 days for turkeys. The bibliographic data are also supportive of the longer withdrawal periods. This proposal would ensure the safety of consumers of meat and offal taken from chickens and turkeys treated with the veterinary medicinal

products containing enrofloxacin for administration via drinking water to chickens and turkeys at the recommended dose of 10 mg/kg bw/day for 5 consecutive days.

3. Benefit-risk assessment

Adequate data have been submitted to support indications for *M.gallisepticum, M.synoviae, A.paragallinarium, P.multocida* and *E.coli* in chickens and *M.gallisepticum, M.synoviae, P.multocida* and *E.coli* in turkeys.

The indication for treatment of salmonella infections should be removed from the SPCs due to the lack of support for the dosing regimen, especially in regards to elimination of infection, and EU legislation in regards to national control programmes for the control of salmonella in poultry that state that antimicrobials should not be used except in exceptional circumstances (Regulation EC 1177/2006).

A risk has been identified regarding an insufficient dose rate against target pathogens, in particular *E.coli*, in both chickens and turkeys. It has been shown that both MICs and resistance are increasing within the EU. The current dosing regimen for *E. coli* infections is not considered to be optimised in terms of efficacy or limiting the development of resistance in this target pathogen. Therefore in order to take into account the evolution of the susceptibility profiles of *E.coli* since enrofloxacin was first authorised in poultry, and new PK/PD concepts, a population PK/PD analysis is needed to optimise the dosing regimen.

The withdrawal periods should be set 7 days for chickens and 13 days for turkeys to ensure consumer safety at the recommended dose of 10 mg/kg bw/day for 5 consecutive days

The overall benefit-risk balance for the veterinary medicinal products containing enrofloxacin to be administered via the drinking water to chickens and/or turkeys (see annex I) is deemed positive subject to the recommended changes in the product information (see annex III) and, in view of the need to obtain further data in order fully to address the public health issues that have given rise to this referral procedure, subject to the imposition of conditions affecting the Marketing Authorisations (see annex IV).

The evaluation of data generated in fulfilment of these conditions should be undertaken by CVMP in the interests of maintaining the harmonised EU approach achieved by this referral procedure, and given the EU-wide importance of achieving an optimal dose regimen for this range of products. The CVMP's conclusion on the benefit-risk balance will be revisited in line with the provisions in these conditions.

Grounds for amendment of the summaries of product characteristics, labelling and package leaflets

Whereas:

- on the basis of the available data, the CVMP considered that indications for *M.gallisepticum, M.synoviae, A.paragallinarium, P.multocida* and *E.coli* in chickens and *M.gallisepticum, M.synoviae, P.multocida* and *E.coli* in turkeys should be maintained;
- due to the lack of support for the dosing regimen, especially in regards to elimination of infection, and EU legislation in regards to national control programmes for the control of salmonella in poultry that state that antimicrobials should not be used except in exceptional circumstances (Regulation EC 1177/2006), the CVMP considered that the indication for treatment of salmonella infections should be removed from the SPCs;

- on the basis of the available data, the CVMP considered that the current dosing regimen for *E. coli* infections is not optimised in terms of efficacy or limiting the development of resistance in this target pathogen;
- the CVMP considered that in order to take into account the evolution of the susceptibility profiles of *E.coli* since enrofloxacin was first authorised in poultry, and new PK/PD concepts, the dosing regimen should be optimised for efficacy and to limit the potential for further development of resistance in target pathogens;
- on the basis of the available residue depletion data in chickens and turkeys, the CVMP considered that withdrawal periods of 7 days for chicken meat and offal and 13 days for turkeys meat and offal were safe;
- the CVMP considered that the overall benefit-risk balance is positive for the veterinary medicinal products containing enrofloxacin to be administered via the drinking water to chickens and/or turkeys (see annex I), subject to amendments in the product information and conditions on the marketing authorisations;

the CVMP has recommended the variations of the marketing authorisations for the veterinary medicinal products containing enrofloxacin to be administered via the drinking water to chickens and/or turkeys (see annex I of the opinion) in order to amend the summaries of product characteristics, labelling and package leaflets as set out in annex III.

The conditions of the Marketing Authorisations are described in annex IV.

Annex III

Amendments in the relevant sections of the summaries of product characteristics, labelling and package leaflets

Summary of product characteristics

Add, to all products and delete the existing text:

4.2 Indications for use, specifying the target species

Treatment of infections caused by the following bacteria susceptible to enrofloxacin:

Chickens

Mycoplasma gallisepticum,
Mycoplasma synoviae,
Avibacterium paragallinarum,
Pasteurella multocida,
Escherichia coli.

Turkey

Mycoplasma gallisepticum,
Mycoplasma synoviae,
Pasteurella multocida,
Escherichia coli.

Add, to all products:

4.3 Contraindications

Do not use for prophylaxis.
Do not use when resistance/ cross-resistance to (fluoro)quinolones is known to occur in the flock intended for treatment.
……..

Add, to all products:

4.4 Special warnings for each target species

……..
Treatment of *Mycoplasma spp* infections may not eradicate the organism.

Add, to all products:

4.5 Special precautions for use

Special precautions for use in animals

Since enrofloxacin was first authorised for use in poultry, there has been widespread reduction in susceptibility of *E.coli* to fluoroquinolones and emergence of resistant organisms. Resistance has also been reported in *Mycoplasma synoviae* in the EU.

Add, to all products and delete the existing text:

4.9 Amount(s) to be administered and administration route

Chickens and turkeys

10 mg enrofloxacin/kg bodyweight per day for 3-5 consecutive days.

Treatment for 3-5 consecutive days; for 5 consecutive days in mixed infections and chronic progressive forms. If no clinical improvement is achieved within 2-3 days, alternative antimicrobial therapy should be considered based on susceptibility testing.

Amend where applicable:

4.11 Withdrawal period(s)

Chickens: Meat and offal: 7 days.
Turkeys: Meat and offal: 13 days.

Not authorised for use in birds producing eggs for human consumption.
Do not administer to layer replacement birds within 14 days of coming into lay.

Add, to all products and amend where applicable:

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: quinolone and quinoxaline antibacterials, fluoroquinolones.
ATCvet Code: QJ01MA90.

5.1 Pharmacodynamic properties

Antibacterial spectrum

Enrofloxacin is active against many Gram-negative bacteria, against Gram-positive bacteria and *Mycoplasma* spp.

In vitro susceptibility has been shown in strains of (i) Gram-negative species such as *Escherichia coli*, *Pasteurella multocida* and *Avibacterium* (*Haemophilus*) *paragallinarum* and (ii) *Mycoplasma gallisepticum* and *Mycoplasma synoviae*. (See section 4.5)

Types and mechanisms of resistance.

Resistance to fluoroquinolones has been reported to arise from five sources, (i) point mutations in the genes encoding for DNA gyrase and/or topoisomerase IV leading to alterations of the respective enzyme, (ii) alterations of drug permeability in Gram-negative bacteria, (iii) efflux mechanisms, (iv) plasmid mediated resistance and (v) gyrase protecting proteins. All mechanisms lead to a reduced susceptibility of the bacteria to fluoroquinolones. Cross-resistance within the fluoroquinolone class of antimicrobials is common.

Labelling:

Amend where applicable:

8. WITHDRAWAL PERIOD

Chickens: Meat and offal: 7 days.
Turkeys: Meat and offal: 13 days.
Not authorised for use in birds producing eggs for human consumption.
Do not administer to layer replacement birds within 14 days of coming into lay.

Package leaflet:

Add, to all products and delete the existing text:

4. INDICATIONS

Treatment of infections caused by the following bacteria susceptible to enrofloxacin:

Chickens

Mycoplasma gallisepticum,
Mycoplasma synoviae,
Avibacterium paragallinarum,
Pasteurella multocida,
Escherichia coli.

Turkey

Mycoplasma gallisepticum,
Mycoplasma synoviae,
Pasteurella multocida,
Escherichia coli.

Add, to all products:

5. CONTRAINDICATIONS

Do not use for prophylaxis.
Do not use when resistance/ cross-resistance to (fluoro)quinolones is known to occur in the flock intended for treatment.

……..

Add, to all products and delete the existing text:

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

Chickens and turkeys

10 mg enrofloxacin/kg bodyweight per day for 3-5 consecutive days.

Treatment for 3-5 consecutive days; for 5 consecutive days in mixed infections and chronic progressive forms. If no clinical improvement is achieved within 2-3 days, alternative antimicrobial therapy should be considered based on susceptibility testing.

Amend where applicable:

10. WITHDRAWAL PERIOD

Chickens: Meat and offal: 7 days.
Turkeys: Meat and offal: 13 days.
Not authorised for use in birds producing eggs for human consumption.
Do not administer to layer replacement birds within 14 days of coming into lay.

Add, to all products:

12. SPECIAL WARNINGS

Since enrofloxacin was first authorised for use in poultry, there has been widespread reduction in susceptibility of *E.coli* to fluoroquinolones and emergence of resistant organisms. Resistance has also been reported in *Mycoplasma synoviae* in the EU.

……..

Annex IV

Conditions of the marketing authorisations

The following conditions should be fulfilled by all marketing authorisation holders (see annex I):

- Taking into account the decreases in the susceptibility profiles of *E. coli* observed in EU surveillance from the time enrofloxacin was first authorised in poultry species, a dosing regimen should be elaborated based on new studies that encompass the current susceptibility of *E. coli* and new PK/PD concepts aimed at limiting the development of resistance for the target pathogens.

  In this regard, turkeys are recognised as being a minor species.

- The marketing authorisation holders should also provide scientific justification/s that this new dosing regimen will be effective for the treatment of the remaining target pathogens in the SPC.

- Where there is a change to the dose regimen for chickens and/or turkeys, then adequate withdrawal periods should be established, according to current guidelines; a revised environmental risk assessment should also be provided; furthermore any potential effects on user and target species safety should be reviewed. If the withdrawal period for turkeys is extrapolated from residues studies in chickens, then an additional safety factor should be added to take into account the evidence from previous residues studies that demonstrated that the depletion of enrofloxacin is slower in turkeys than chickens.

- A new overall benefit-risk should be provided for the products for the treatment of respiratory disease in chickens and turkeys.

The abovementioned data should be provided to the CVMP for assessment not later than 3 years after the Commission Decision on this referral procedure.