Annex I

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

Member State EU/EEA	Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Austria	Ceva Sante Animale La Ballastière - BP 126 33501 Libourne France	Altresyn 4 mg/ml Lösung zum Eingeben für Schweine	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Austria	Intervet GmbH Siemensstraße 107 1210 Wien Austria	Regumate Equine 2.2 mg/ml Lösung zum Eingeben für Pferde	Altrenogest	2.2 mg/ml	Oral solution	Horses	Oral
Austria	Virbac SA 1'ere Avenue 2065 m – LID 06516 Carros Cedex France	Virbagest 4 mg/ml, Lösung zum Eingeben für Schweine (Jungsauen)	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Austria	aniMedica GmbH Im Südfeld 9 48308 Senden-Boesensell Germany	Suifertil 4 mg/ml Lösung zum Eingeben für Schweine	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Belgium	Ceva Santé Animale N.V. Metrologielaan 6 1130 Brussel Belgium	Altresyn 4 mg/ml	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Belgium	MSD Animal Health BVBA Lynx Binnenhof 5 1200 Brussel Belgium	Regumate 4 mg/ml	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral

Member State EU/EEA	Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Belgium	MSD Animal Health BVBA Lynx Binnenhof 5 1200 Brussel Belgium	Regumate Equine 2,2 mg/ml	Altrenogest	2.2 mg/ml	Oral solution	Horses	Oral
Belgium	Virbac S.A. 1ère avenue 2065 m - LID 06516 Carros Cedex France	Virbagest 4 mg/ml	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Bulgaria	Ceva Animal Health Bulgaria, ul. Elemag 26, vh. B, et. 1, apt. 1 Sofia 1113 Bulgaria	АЛТРЕЗИН 4 мг/мл разтвор за перорално приложение/ ALTRESYN 4 mg/ml oral solution	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Bulgaria	Virbac S.A. 1ère avenue 2065 m – LID 06516 Carros Cedex France	ВИРБАГЕСТ 4 мг/мл перорален разтвор за прасета/ VIRBAGEST 4 mg/ml oral solution for pigs	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Cyprus	Ceva Sante Animale Z.I. La Ballastiere 33500 Libourne France	ALTRESYN 4MG/ML ORAL SOLUTION FOR PIGS	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral

Member State EU/EEA	Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Cyprus	Virbac S.A. 1ère avenue 2065 m – LID 06516 Carros Cedex France	VIRBAGEST 4MG/ML, ORAL SOLUTION FOR PIGS	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Czech republic	Ceva Animal Health Slovakia, s. r. o. Račianska 77 831 02 Bratislava Slovak Republic	ALTRESYN 4 mg/ml perorální roztok	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Czech republic	Intervet International B.V. Wim de Korverstraat 35 5831 AN Boxmeer The Netherlands	Regumate Equine 2,2 mg/ml perorální roztok pro koně	Altrenogest	2.2 mg/ml	Oral solution	Horses	Oral
Czech republic	Intervet International B.V. Wim de Korverstraat 35 5831 AN Boxmeer The Netherlands	Regumate Porcine 4 mg/ml perorální roztok	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Czech republic	Virbac S.A. 1ère avenue 2065 m - LID 06516 Carros Cedex France	VIRBAGEST 4 mg/ml perorální roztok pro prasata	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral

Member State EU / EEA	Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Denmark	Intervet Danmark A/S. Postbox 66, Lautrupbjerg 2 DK-2750 Ballerup Denmark	Regumate Equine	Altrenogest	2.2 mg/ml	Oral solution	Horses	Oral
Denmark	Ceva Animal Health A/S, Ladegårdsvej 2 DK-7100 Vejle Denmark	Altresyn	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Estonia	Ceva Sante Animale ZI La Ballastiere 33500 Libourne France	Altresyn	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Finland	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	REGUMATE EQUINE 2.2 mg/ml oraaliliuos	Altrenogest	2.2 mg/ml	Oral solution	Horses	Oral
France	Intervet Rue Olivier de Serres Angers Technopole 49071 Beaucouze Cedex France	REGUMATE SOLUTION HUILEUSE A 4 POUR MILLE	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
France	Intervet Rue Olivier de Serres Angers Technopole 49071 Beaucouze Cedex France	REGUMATE EQUIN 2,2 MG/ML SOLUT ION BUVABLE POUR CHEVAUX	Altrenogest	2.2 mg/ml	Oral solution	Horses	Oral

Member State EU/EEA	Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
France	Ceva Sante Animale 10 Avenue de la Ballastiere 33500 Libourne France	ALTRESYN	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
France	Virbac 1ère Avenue 2065 m - LID 06516 Carros Cedex France	VIRBAGEST 4 MG/ML SOLUTION BUV ABLE POUR PORCS	Altrenogest	4 mg/ml	Oral solution.	Pigs	Oral
France	Intervet Rue Olivier de Serres Angers Technopole 49071 Beaucouze Cedex France	FOLLIPLAN	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
France	aniMedica GmbH Im Südfeld 9 D-48308 Senden-Bösensell Germany	SYNCHROPLAN 4 MG/ML SOLUTION B UVABLE POUR PORCINS	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Germany	aniMedica GmbH Im Südfeld 9 D-48308 Senden-Bösensell Germany	Suifertil 4 mg/ml Oral Solution for Pigs	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral

Member State EU/EEA	Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Germany	Intervet Deutschland GmbH Feldstr. 1a D-85716 Unterschleißheim Germany	Regumate 4 mg/ml Lösung zum Eingeben	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Germany	Intervet Deutschland GmbH Feldstr. 1a D-85716 Unterschleißheim Germany	Regumate Equine 2,2 mg/ml	Altrenogest	2.2 mg/ml	Oral solution	Horses	Oral
Germany	CEVA Tiergesundheit GmbH Kanzlerstr. 4 D-40472 Düsseldorf Germany	Altresyn 4 mg/ml Lösung zum Eingeben für Schweine	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Germany	Virbac 1ère Avenue 2065 m - LID 06516 Carros Cedex France	Virbagest 4 mg/ml	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Greece	Intervet Hellas AE Ag.Dimitriou 63 17456 Alimos Attikis Greece	REGUMATE EQUINE	Altrenogest	2.2 mg/ml	Oral solution	Horses	Oral

Member State EU/EEA	Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Greece	Ceva Hellas EPE Ag.Nikolaou 15 17455 Alimos Attikis Greece	ALTRESYN	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Greece	Virbac SA France 1ère Avenue 2065 m - LID 06516 Carros Cedex France	VIRBAGEST	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Hungary	Ceva-Phylaxia Zrt. 1107 Budapest Szállás u. 5. Hungary	Altresyn 4 mg/ml belsőleges oldat	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Hungary	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	FolliPlan	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Hungary	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Regumate Equine 2,2 mg/ml belsőleges oldat lovaknak	Altrenogest	2.2 mg/ml	Oral solution	Horses	Oral
Hungary	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Regumate Porcine	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral

Member State EU/EEA	Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Hungary	Virbac 1ère avenue 2065 m - LID 06516 Carros Cedex France	VIRBAGEST 4 mg/ml belsőleges oldat sertések részére	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Hungary	aniMedica GmgH, Im Südfeld 9 D-48308 Senden-Bösensell Germany	Suifertil 4 mg/ml belsőleges oldat sertéseknek	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Ireland	Ceva Sante Animale 10, avenue de La Ballastiere 33500 Libourne France	Altresyn 4 mg/ml oral solution	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Ireland	Intervet Ireland Limited Magna Drive Magna Business Park Dublin 24 Ireland	Regumate Equine 2.2 mg/ml oral solution for horses	Altrenogest	2.2 mg/ml	Oral solution	Horses	Oral
Ireland	Virbac S.A. 1ère avenue 2065 m - LID 06516 Carros Cedex France	VIRBAGEST 4 mg/ml oral solution for pigs	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral

Member State EU / EEA	Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Italy	Ceva Salute Animale Viale Colleoni, 15 20864 Agrate Brianza Italy	Altresyn 4mg/ml	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Italy	Intervet International Wim de Korverstraat 35 P.O. Box 31 Boxmeer The Netherlands	Folliplan 4mg/ml soluzione orale per suini	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Italy	Intervet International Wim de Korverstraat 35 P.O. Box 31 Boxmeer The Netherlands	Regumate equini	Altrenogest	2.2 mg/ml	Oral solution	Horses	Oral
Italy	Intervet International Wim de Korverstraat 35 P.O. Box 31 Boxmeer The Netherlands	Regumate suini soluzione orale per suini	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Italy	Virbac S.A. 1ère avenue 2065 m – LID 06516 Carros Cedex France	Virbagest	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral

Member State EU/EEA	Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Latvia	Ceva Sante Animale ZI La Ballastiere 33500 Libourne France	Altresyn	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Lithuania	Ceva Sante Animale ZI La Ballastiere 33500 Libourne France	ALTRESYN 4 mg/ml geriamasis tirpalas	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Lithuania	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Regumate Porcine, 0,4 % geriamasis tirpalas	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Malta	Intervet UK Ltd Walton Manor Walton Milton Keynes Buckinghamshire MK7 7AJ United Kingdom	REGUMATE PORCINE	Altrenogest	0.4% w/w	Oral solution	Pigs	Oral
The Netherlands	Intervet Nederland BV Wim de Korverstraat 35 5831 AN Boxmeer The Netherlands	Regumate pig	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
The Netherlands	Intervet Nederland BV Wim de Korverstraat 35 5831 AN Boxmeer The Netherlands	Regumate equine	Altrenogest	2.2 mg/ml	Oral solution	Horses	Oral

Member State EU / EEA	Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
The Netherlands	Ceva Santé Animale B.V. Tiendweg 8c - 2671 SB Naaldwijk The Netherlands	Altresyn	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
The Netherlands	Virbac S.A. 1ère avenue 2065 m – LID 06516 Carros Cedex France	Virbagest	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
The Netherlands	Intervet Nederland BV Wim de Korverstraat 35 5831 AN Boxmeer The Netherlands	Folliplan	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
The Netherlands	aniMedica GmbH Im Südfeld 9 D-48308 Senden-Bösensell Germany	Suifertil	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Norway	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands	Regumate Equine	Altrenogest	2.2 mg/ml	Oral solution	Horses	Oral
Poland	Ceva Animal Health Polska Sp. z o.o. Okrzei 1A Str. 03-715 Warsaw Poland	ALTRESYN	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral

Member State EU/EEA	Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Poland	Intervet International B.V. Wim de Körverstraat B.V. 5831 AN Boxmeer The Netherlands	REGUMATE PORCINE 4 mg/ml roztwór doustny dla świń	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Poland	Virbac S.A. 1ère avenue 2065 m - LID 06516 Carros Cedex France	VIRBAGEST 4 mg/ml roztwór doustny dla świń	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Poland	AniMedica GmbH Im Südfeld 9 D-48308 Senden - Bösensell Germany	Suifertil 4 mg/ml Oral Solution for Pigs	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Portugal	Ceva Saúde Animal Produtos Farmacêuticos e Imunológicos, Lda. Rua Doutor António Loureiro Borges, nº 9/9A, 9ºA Miraflores - 1495-131 Algés Portugal	ALTRESYN 4 mg/ml solução oral	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Portugal	MSD Animal Health Lda Quinta da Fonte Edificio Vasco da Gama, 19 2770-192 Paço de Arcos Portugal	Regumate Equinos, 2,2 mg/ml solução oral para cavalos	Altrenogest	2.2 mg/ml	Oral solution	Horses	Oral

Member State EU/EEA	Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Portugal	Virbac S.A. 1ère avenue - 2065 m - L.I.D. 06516 Carros Cedex France	Virbagest 4 mg/ml solução oral para suínos	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Romania	Ceva Sante Animale Z.I. La Ballastiere 33500 Libourne France	Altresyn	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Romania	Intervet International B.V Wim de Korverstr.35 5831 AN Boxmeer The Netherlands	Regumate porcine 0,4% solution	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Romania	Virbac SA 1ère Avenue 2065 m - LID 06516 Carros Cedex France	Virbagest 4 mg/ml	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Romania	aniMedica GmbH Im Südfeld 9 D-48308 Senden - Bösensell Germany	Suifertil 4mg/ml Oral Solution for Pigs	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Slovakia	Ceva AH Slovakia Račianska 77, 831 02 Bratislava Slovak Republic	Altresyn 4 mg/ml MRP perorálny roztok	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral

Member State EU / EEA	Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Slovakia	Intervet Ltd Cookstown Tallaght Dublin 24 Ireland	Regumate Equine 2.2 mg/ml perorálny roztok pre kone	Altrenogest	2.2 mg/ml	Oral solution	Horses	Oral
Slovenia	Ceva Santé Animale 10 avenue de La Ballastière 33500 Libourne France	ALTRESYN 4 mg/ml peroralna raztopina	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Spain	Laboratorios Intervet S.A. Polig. Industrial El Montalvo Parcela 39 Carbajosa de la Sagrada (Salamanca) 37188 Spain	REGUMATE EQUINO 2,2 mg/ml SOLUCION ORAL PARA CABALLOS	Altrenogest	2.2 mg/ml	Oral solution	Horses	Oral
Spain	Merck Sharp & Dohme Animal Health S.L. Pol. Ind. El Montalvo I C/ Zeppelin, 6 Parcela 38 Carbajosa de la Sagrada (Salamanca) 37008 Spain	REGUMATE PORCINO SOLUCION ORAL	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral

Member State EU/EEA	Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Spain	Merck Sharp & Dohme Animal Health S.L. Pol. Ind. El Montalvo I C/ Zeppelin, 6 Parcela 38 Carbajosa de la Sagrada (Salamanca) 37008 Spain	REGUMATE PORCINO EMULSION ORAL	Altrenogest	4 mg/ml	Oral emulsion	Pigs	Oral
Spain	Virbac S.A. 1ère Avenue 2065 m – LID Carros Cedex 06516 France	VIRBAGEST 4 mg/ml SOLUCION ORAL PARA CERDOS	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Spain	Ceva Salud Animal, S.A. Carabela La Niña nº 12, 5ª planta 08017 Barcelona Spain	ALTRESYN	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
Spain	Merck Sharp & Dohme Animal Health S.L. Pol. Ind. El Montalvo I C/ Zeppelin, 6 Parcela 38 Carbajosa de la Sagrada (Salamanca) 37008 Spain	FOLIPLAN	Altrenogest	4 mg/ml	Oral emulsion	Pigs	Oral

Member State EU/EEA	Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Spain	aniMedica GmbH Im Sudfeld 48308 Senden-Bosensell Germany	SUIFERTIL 4 MG/ML SOLUCION ORAL PARA CERDOS	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
United Kingdom	Ceva Animal Health Ltd Unit 3 Anglo Office Park White Lion Road Amersham Buckinghamshire HP7 9FB United Kingdom	Altresyn 4 mg/ml Oral Solution	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
United Kingdom	Intervet UK Ltd Walton Manor Walton Milton Keynes Buckinghamshire MK7 7AJ United Kingdom	Folliplan, 0.4% w/v Oral Solution	Altrenogest	0.4% w/v	Oral solution	Pigs	Oral
United Kingdom	Intervet UK Ltd Walton Manor Walton Milton Keynes Buckinghamshire MK7 7AJ United Kingdom	Regumate Equine 2.2 mg/ml Oral Solution for Horses	Altrenogest	2.2 mg/ml	Oral solution	Horses	Oral

Member State EU/EEA	Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
United Kingdom	Intervet UK Ltd Walton Manor Walton Milton Keynes Buckinghamshire MK7 7AJ United Kingdom	Regumate Porcine, 0.4% w/v Oral Solution	Altrenogest	0.4% w/v	Oral suspension	Pigs	Oral
United Kingdom	aniMedica GmbH Im Sudfeld 48308 Senden-Bosensell Germany	Suifertil 4 mg/ml Oral Solution for Pigs	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral
United Kingdom	Virbac S.A. 1ère avenue 2065 m - LID 06516 Carros Cedex France	Virbagest 4 mg/ml Oral Solution for Pigs	Altrenogest	4 mg/ml	Oral solution	Pigs	Oral

Annex II

Scientific conclusions

Overall summary of the scientific evaluation of veterinary medicinal products containing altrenogest to be administered orally to pigs and horses (see Annex I)

1. Introduction

Altrenogest is a synthetic steroidal hormone, an orally active progestogen. It is included in veterinary medicinal products currently authorised in the European Union for gilts and mares for zootechnical purposes (oestrus synchronisation).

According to the CVMP guideline on environmental impact assessment for veterinary medicinal products in support of VICH GL6 and GL38[1] when "*adverse environmental effects are anticipated from the use of products, further assessment of possible exposure of the environment can be performed, even if straightforward application of the Phase I guidance would indicate exemption from further testing*." This provision implies that some products, which do not meet the trigger value for entering a Phase II environmental risk assessment (ERA), may however require further assessment to address specifically the concerns related to their activity and use.

Germany expressed concerns that veterinary medicinal products containing altrenogest may present a potential serious risk for the environment as the active substance is a steroid hormone and data from publicly available literature show a high risk to aquatic organisms arising from other steroids with a similar molecular structure. Germany considered that, although according to the VICH GL6: Guideline on environmental impact assessment (EIAs) for veterinary medicinal products - Phase I[2], the estimated Predicted Environmental Concentrations in soil (PEC_{soil}) for altrenogest (<100 µg/kg) would not trigger a Phase II ERA, hazard concerns related to endocrine disruption and identified in structurally very similar molecules, require a deeper understanding of the potential environmental impacts of altrenogest when used following the recommended use, and a tailored Phase II ERA is consequently considered necessary.

Therefore on 21 March 2013 Germany initiated a procedure under Article 35 of Directive 2001/82/EC for veterinary medicinal products containing altrenogest to be administered orally to pigs and horses.

2. Discussion of data available

The environmental risk assessment is focused on the risk to the environment as a result of the zootechnical use of veterinary medicinal products containing altrenogest in gilts. The CVMP notes that veterinary medicinal products containing altrenogest are also authorised for use in mares. However, it is for the treatment of individual mares, i.e. not for the treatment of the entire herd for the synchronisation of ovulation. Consequently the use of altrenogest in mares is not considered to pose a risk to the environment when used as specified in the SPCs given the minimal environmental exposure associated with this use, and the environmental risk assessment presented below is based on the use of altrenogest in gilts.

Environmental fate studies

The anaerobic and aerobic degradation of altrenogest were investigated for altrenogest in manure and soil, respectively.

[1] CVMP guideline on environmental impact assessment for veterinary medicinal products in support of VICH GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1) - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004386.pdf

[2] VICH GL6: Guideline on environmental impact assessment (EIAs) for veterinary medicinal products - Phase I http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004394.pdf

The anaerobic transformation of altrenogest was investigated in pig manure incubated anaerobically according to the CVMP guideline on determining the fate of veterinary medicinal products in manure (EMA/CVMP/ERA/430327/2009)[3]. Results show that the dissipation time (DT_{50}) of altrenogest in manure was 6.0 days (20±2 °C). After 45 days, altrenogest and its transformation products (the latter at or above 10%) were not detected in the manure using high performance liquid chromatography- radiochromatography (HPLC-RAM) and liquid chromatography tandem mass spectrometry (LC/MS-MS) (mean of two replicates). Mineralisation was negligible over the period of 100 days and non-extractable residues were formed during the incubation period and accounted for 26.5% of the applied radioactivity on day 45. The amount of non-extractable residues (NER) formed after 45 days is used for the predicted environmental concentration in soil (PEC_{soil}) refinement as this value is the closest to the half-maximal manure storage time for sows of 91 days, as explained in the CVMP guideline on the environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1).

The aerobic transformation of altrenogest was investigated in four different soils (OECD Test Guideline 307[4] (21.1 ± 0.1 °C for 21 days)). The DT_{50} values for soils 1, 2, 3 and 4 are 23.7, 5.3, 2.0, and
4.6 days, respectively, resulting in a geometric mean DT_{50} value of 5.8 days. Following normalisation from the 21.1 °C study temperature to standard 20°C laboratory conditions using the Arrhenius equation (equivalent to a correction factor of 1.11), the DT_{50} proposed for use in modelling is 6.5 days. This value is used for the calculation of the initial $PEC_{surfacewater}$ value.

Metabolism data

Based on the available data, the marketing authorisation holders (MAHs) considered a worst-case scenario of renal elimination of altrenogest as the major route of excretion with 60% of the total dose of altrenogest being excreted in urine as altrenogest or altrenogest conjugates, and a total amount of 31% altrenogest-equivalents being excreted (considering complete deconjugation). The MAHs used this latter value (69% metabolism) for the PEC_{soil} refinement. However, the CVMP considered that the assumption of 60% of the total dose being excreted via urine as an overly conservative value.

The CVMP considered that after administration of altrenogest at a daily oral dose of 20 mg/pig for 18 days, only 25% of the total dose of altrenogest was excreted in urine as altrenogest or altrenogest conjugates, and the remainder in bile. Of the total radioactivity in urine, 2% was identified as altrenogest and 24% as altrenogest conjugates, corresponding to 0.5% to 6% of the total dose. Of the total radioactivity in bile, 6% was altrenogest (after multiple dose) and 14% altrenogest conjugates, corresponding to 4.5% to 10.5% of the total dose. These results are considered to be in line with existing literature data for progestagens and also with residue concentrations found in liver and kidney of pigs. Consequently, based on metabolism studies the Committee concluded that the PEC_{soil} can be more realistically refined considering the total excretion altrenogest-equivalents being 5% to 16.5% of the dose. Thus, the PEC_{soil}, and hence $PEC_{surfacewater}$, could be conservatively reduced by 85% and not only by 69%.

Ecotoxicity data

A fish life cycle test with zebrafish (*Danio rerio*), covering a complete fish generation (parental) and also part of the filial generation, was conducted to investigate the effects of a continuous exposure of altrenogest on different life stages, (including early life, juvenile growth, and reproduction stages of the parental generation, and early life stages of the filial generation). Fertilisation rate of the parental fish and post hatch survival of the filial generation were the most sensitive parameters, suggesting that the early life stages of the F1 generation and reproduction are the most sensitive

[3] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/03/WC500104495.pdf
[4] OECD guideline for the testing of chemicals 307

life stages to altrenogest exposure. The shift in sex ratio towards males clearly underlines the androgenic potential of the substance. No NOEC (No-Observed Effect Concentration) could be derived (NOEC <0.4 ng/l) for altrenogest from the study, especially as analytical limitations proved difficult any further decrease in test concentrations. Extrapolation of EC_{10} values was not possible, in line with the recommendations of the OECD 54 guideline on Current Approaches in the Statistical Analysis of Ecotoxicity Data: A Guidance to Application (2006)[5]. A PNEC (Predicted No Effect Concentration) of <0.4 ng altrenogest/l was used for the risk assessment.

Exposure studies

A Phase I and a Phase II environmental risk assessment were conducted.

For the Phase I the PEC_{soil} initial for gilts, sows and mares was established using the daily doses and the default values from the CVMP guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL 38 (EMEA/CVMP/418282/2005-Rev.1). The PEC_{soil} initial was further refined using the results from the anaerobic transformation study of altrengest in pig manure which determined that 26.5% accounted for non-extractable residues at day 45, and could be considered potentially bioavailable altrenogest or conjugates of altrenogest. The PEC_{soil} initial was further refined with metabolism data (release rate 0.31%), and the rate of gilts that are integrated into the herd that is equivalent to the annual replacement rate (mean value 0.49). A PEC_{soil} refined of 0.013 µg/kg was determined accordingly, resulting on an application rate of 0.000094 kg/ha.

The $PEC_{groundwater}$ (Phase IIA STEP 1) was calculated using the recommended stepwise approach described in the CVMP guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL 38 (EMEA/CVMP/418282/2005-Rev.1), STEP 1 to STEP 3. STEP 1 resulted in a $PEC_{groundwater}$ being below the threshold value (0.1 µg/l), anticipating that a risk for groundwater could in principle be excluded. Yet, the results from the fish study indicate a potential environmental risk due to the endocrine disrupting properties of the substance below 0.4 µg/l. As a result, $PEC_{groundwater}$ was further refined with the Metamodel (STEP 2) and FOCUS PEARL model, both confirming that $PEC_{groundwater}$ being < 0.000001 µg/l.

For surface water the FOCUS STEP 2 and 3 (Phase IIA), were conducted as the STEP 1 resulted in a $PEC_{surfacewater}$ larger than the lowest predicted no effect concentration (PNEC) (0.4 ng/l). STEP 2 lead to a $PEC_{surfacewater}$ of 245 pg/l, and STEP 3 $PEC_{surfacewater}$ ranged between 16 to 219 pg/l depending on the scenarios considered, with scenario R3 having the highest $PEC_{surfacewater}$ value.

Using the scenario R4 (southern European Mediterranean) of the FOCUS STEP 4 modelling the maximum $PEC_{surfacewater}$ for a 1 m, 3 m, 5 m, and 10 m buffer zone were calculated, respectively, in relation to Directive 91/676/EEC[6] concerning the protection of waters against pollution caused by nitrates from agricultural sources which is implemented in national law in the EU Member States. These buffer zones are minimum distances to surface water which must be maintained when manure (or organic fertilizer) is spread onto cropland. A survey of the national legislation in relation to Directive 91/676/EEC revealed that countries with a minimum distance of 1 and 2 m from the water body represent almost two-thirds of the total pig production in Europe.

The CVMP acknowledges that buffer zones may be useful measures to reduce the release of altrenogest into surface water via run-off. However, for buffer zone calculations, which represent the highest tier exposure scenario, the entire representative R-scenario set is recommended. R1 (middle European land) and R3 (middle European Mediterranean) (but not R2) are also considered

[5] OECD 54 guideline on Current Approaches in the Statistical Analysis of Ecotoxicity Data: A Guidance to Application (2006) - http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono%282006%2918&doclanguage=en

[6] http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31991L0676&from=en

relevant for winter cereals, as proposed by the FOCUS-SW report and need to be calculated as well. R4 is often used to cover a conservative run-off scenario in FOCUS-SW and consequently has been used for the exposure assessment for the FOCUS-SW STEP 3 calculations.

Environmental risk assessment of altrenogest

To assess the risk to aquatic organisms from the use of veterinary medicinal products in gilts containing the synthetic steroidal hormone altrenogest, the MAHs conducted a Fish Full Life Cycle test to investigate and characterise the endocrine effects of this hormone, and also determined the $PEC_{surfacewater}$ from the use of the product as indicated in the summary of product characteristics (SPC), to establish if the concentrations expected in surface water would exceed the concentration known to cause a detrimental effect to aquatic populations of organisms in different representative EU scenarios (R1: Middle European land, R3: Middle European Mediterranean, and R4: Southern European Mediterranean).

From the Fish Full Life Cycle no NOEC can be derived since significant population relevant effects have been shown already in the lowest concentration tested, i.e. 400 pg/l altrenogest (effects on fertilisation and F1 survival being the most sensitive developmental stages). Consequently, a PNEC of below
40 pg/l was established.

The $PEC_{surfacewater}$ was calculated according to FOCUS STEP 4, considering a DT_{50} value for soil of 6.5 days (geometric mean derived from four soils), an application rate of 0.000094 kg/ha, the result of the manure degradation study (factor: 0.265), the fraction of herd treatment (factor: 0.49) as well as the metabolism (factor: 0.31). To determine $PEC_{surfacewater}$, the FOCUS STEP 4 approach is the highest tier exposure scenario, in which all relevant and representative R scenarios (R1, R3 and R4) were considered by the CVMP. The results from STEP 4 ranged from 16 pg/l (R1) to 219 pg/l (R3).

Based on a PNEC <40 pg/l as well as the $PEC_{surfacewater}$ values from the scenarios above (release factor: 0.31, application rate of 0.094 g/ha) a risk was identified in STEP 4 for the R3 scenario (buffer zone 1-10 m), with risk quotients (RQs) of 3.29 (1 m), 2.84 (3 m), 2.59 (5 m), and 2.18 (10 m).

The CVMP acknowledged these results, but concluded that data on the metabolism of altrenogest in gilts, indicating a total amount of excreted altrenogest equivalents corresponding to 5% to 16.5% (release factor 0.05-0.15) of the total dose, should have been considered instead of the release factor of 0.31, given the reliability and quality of the study and its results being in line with existing literature data for progestogens and also with residue concentrations found in liver and kidney of pigs. Based on this more realistic approach, and considering metabolism of up to 85% (release factor 0.15), no risk could be identified for R1 and R4 scenarios (in line with the MAHs calculation considering 69% metabolism, release factor 0.31). However, the RQs calculated for the R3 scenario were above the threshold, i.e. 1.67 (1 m), >1.36 (3 m), >1.24 (5 m), and >1.04 (10 m), thus, indicating a risk for the aquatic environment for this scenario.

Risk mitigation measures

The MAHs make reference to the Council Directive 91/676/EEC concerning the protection of waters against pollution caused by nitrates from agricultural sources, which requires minimum distances to surface water which must be maintained when manure (or organic fertilizer) is spread onto cropland. The MAHs proposes the following risk mitigation measure: *"When spreading manure from treated animals, the minimum distance to surface water as defined in the national or local regulations has to be strictly respected, because the manure may contain altrenogest which could cause adverse effects in the aquatic environment".*

The CVMP noted that measures are already in place to reduce runoff based on European and national legislation. However it was agreed that risk mitigation measures need to be included in the product information for veterinary medicinal products containing altrenogest to be administered orally to pigs to lower the risk to the environment and to make the user aware that altrenogest may be hazardous for fish and other aquatic organisms.

3. Benefit-risk assessment

Benefit assessment

Although efficacy has not been assessed specifically in this referral procedure, altrenogest is a well-established hormone widely used as standard treatment for the synchronisation of oestrus in sexually mature gilts. Veterinary medicinal products containing altrenogest are essential in modern pig production, as the synchronisation of gilts is a tool facilitating strict batch farrowing, with obvious benefits for the management and hygiene in these farms, and consequently the health of the animals. There is no alternative available for this purpose in the EU at present.

Risk assessment

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

Risks to the environment

The active substance altrenogest is a potent synthetic hormone which was demonstrated to affect reproduction in fish at very low concentrations. Maximum $PEC_{surfacewater}$ concentrations were calculated using FOCUS STEP 4 modelling for all representative scenarios for different buffer zone (1 m, 3 m, 5 m, 10 m (Directive 91/676/EEC) These buffer zones are minimum distances to surface water which must be maintained when manure (or organic fertilizer) is spread onto cropland for the protection of waters against pollution caused by nitrates from agricultural sources which is implemented in national law in the EU Member States. It was concluded that for R1 and R4 scenarios there is no risk for contamination of surface water with altrenogest after spreading manure from treated animals onto cropland, while a risk cannot be excluded for R3-scenario.

Risk management or mitigation measures

In order to lower the risk to the aquatic environment associated with the use of veterinary medicinal products containing altrenogest to be administered orally to pigs the following risk mitigation measures are recommended to be included in the product information:

SPC section 4.5 Special precautions for use.

Other precautions regarding impact on the environment

When spreading manure from treated animals, the minimum distance to surface water as defined in the national or local regulations has to be strictly respected, because the manure may contain altrenogest which could cause adverse effects in the aquatic environment.

SPC section 6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products.

{Invented name} should not enter water courses as this may be dangerous for fish and other aquatic organisms.

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

Evaluation and conclusions on the benefit-risk balance

Based on the available data and conservative calculations, a risk for fish and other aquatic organisms associated with the zootechnical use of veterinary medicinal products containing altrenogest in gilts cannot be excluded for certain geographical areas (i.e. Middle European Mediterranean). However, veterinary medicinal products containing altrenogest are essential in modern pig production since the synchronisation of gilts is a tool facilitating strict batch farrowing, with obvious benefits for the management and hygiene in these farms, and consequently the health of the animals. There is no alternative available for this purpose in the EU at present. Consequently, the benefit-risk balance is considered positive. Risk mitigation measures are recommended in the product information for veterinary medicinal products containing altrenogest to be administered orally to pigs to lower the risk to the environment and to make the user aware that altrenogest may be hazardous for fish and other aquatic organisms.

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

Whereas

- Based on the available data and conservative calculations, the CVMP considered that a risk for fish and other aquatic organisms associated with the zootechnical use of veterinary medicinal products containing altrenogest in gilts cannot be excluded for certain geographical areas;
- the CVMP considered that veterinary medicinal products containing altrenogest are essential in modern pig production since the oestrus synchronisation of gilts is a tool facilitating strict batch farrowing with obvious benefits for the management and hygiene in these farms, and consequently the health of the animals;
- the CVMP considered that at present in the EU there is no alternative available for oestrus synchronisation of gilts;
- the CVMP considered that in order to address the risk for fish and other aquatic organisms, risk mitigation measures should be included in the product information;
- the CVMP considered that the overall benefit-risk balance is positive for veterinary medicinal products containing altrenogest to be administered orally to pigs and horses;

the CVMP recommended variations of the marketing authorisations for veterinary medicinal products containing altrenogest to be administered orally to pigs (see Annex I) in order to amend the summaries of product characteristics, labelling and package leaflets in line with recommended changes in the product information as set out in Annex III.

Annex III

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

Summary of product characteristics

4.5 Special precautions for use

Other precautions regarding impact on the environment

When spreading manure from treated animals, the minimum distance to surface water as defined in the national or local regulations has to be strictly respected, because the manure may contain altrenogest which could cause adverse effects in the aquatic environment.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

{Invented name} should not enter water courses as this may be dangerous for fish and other aquatic organisms.

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

Labelling:

9. SPECIAL WARNING(S), IF NECESSARY

When spreading manure from treated animals, the minimum distance to surface water as defined in the national or local regulations has to be strictly respected, because the manure may contain altrenogest which could cause adverse effects in the aquatic environment.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

{Invented name} should not enter water courses as this may be dangerous for fish and other aquatic organisms.

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

Package leaflet

12. SPECIAL WARNING(S)

Other precautions regarding impact on the environment

When spreading manure from treated animals, the minimum distance to surface water as defined in the national or local regulations has to be strictly respected, because the manure may contain altrenogest which could cause adverse effects in the aquatic environment.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

{Invented name} should not enter water courses as this may be dangerous for fish and other aquatic organisms.

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.