Annex I

List of the name, pharmaceutical form, strength of the veterinary medicinal product, animal species, route of administration, applicant in the Member States

Member State EU/EEA	Applicant	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Austria	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Suifertil 4 mg/ml Lösung zum Eingeben für Schweine	Altrenogest	4 mg/ml	Oral solution	Pigs (sexually mature gilts)	For oral use as a top-dressing
France	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Synchroplan 4 mg/ml solution buvable porcins	Altrenogest	4 mg/ml	Oral solution	Pigs (sexually mature gilts)	For oral use as a top-dressing
Germany	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Suifertil 4 mg/ml Oral Solution for Pigs	Altrenogest	4 mg/ml	Oral solution	Pigs (sexually mature gilts)	For oral use as a top-dressing
Hungary	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Suifertil 4 mg/ml belsőleges oldat sertések részére A.U.V.	Altrenogest	4 mg/ml	Oral solution	Pigs (sexually mature gilts)	For oral use as a top-dressing
The Netherlands	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Suifertil 4 mg/ml orale oplossing voor varkens	Altrenogest	4 mg/ml	Oral solution	Pigs (sexually mature gilts)	For oral use as a top-dressing
Poland	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Suifertil 4 mg/ml Oral Solution for Pigs	Altrenogest	4 mg/ml	Oral solution	Pigs (sexually mature gilts)	For oral use as a top-dressing
Romania	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Suifertil 4 mg/ml Oral Solution for Pigs	Altrenogest	4 mg/ml	Oral solution	Pigs (sexually mature gilts)	For oral use as a top-dressing

Member State EU/EEA	Applicant	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Spain	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Suifertil 4 mg/ml solución oral para porcino	Altrenogest	4 mg/ml	Oral solution	Pigs (sexually mature gilts)	For oral use as a top-dressing
United Kingdom	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany	Suifertil 4 mg/ml Oral Solution for Pigs	Altrenogest	4 mg/ml	Oral solution	Pigs (sexually mature gilts)	For oral use as a top-dressing

Annex II

Scientific conclusions and grounds for the granting of the marketing authorisation for Suifertil 4 mg/ml Oral Solution for Pigs and associated names

Overall summary of the scientific evaluation of Suifertil 4 mg/ml Oral Solution for Pigs

1. Introduction

Suifertil 4 mg/ml Oral Solution for Pigs contains altrenogest as active ingredient. 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). The proposed indication for Suifertil 4 mg/ml Oral Solution for Pigs is to synchronise oestrus in sexually mature gilts.

The applicant submitted an application for a decentralised procedure for Suifertil 4 mg/ml Oral Solution for Pigs. This is a generic application according to Art. 13(1) of Directive 2001/82/EC, as amended, referring to the reference product Regumate oily solution 4 mg/ml. The reference member state (RMS) is France and 8 concerned member states (CMS) are involved: Austria, Germany, Hungary, the Netherlands, Poland, Romania, Spain and the United Kingdom.

The Phase I environmental risk assessment (ERA) conducted by the applicant for Suifertil indicated a predicted environmental concentration (PEC) in soil below the value of 100 µg active substance per kg soil which triggers a Phase II ERA, therefore no further assessment was carried out. Germany expressed concerns regarding a potential serious risk for the environment as the active ingredient 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 at environmental concentrations far below the trigger value in nanogram range. Germany considered that the data provided are inadequate to conclude that altrenogest will not pose a risk to the environment and that a tailored Phase II ERA based on the so called 'however clause' of VICH GL6: Guideline on environmental impact assessment (EIAs) for veterinary medicinal products - Phase I[1] is necessary. Furthermore, Germany considered that appropriate risk mitigation measures (RMM) are missing in the SPC as a consequence of the identified unacceptable risk to aquatic organisms.

This referral under Article 33(4) of Directive 2001/82/EC was made due to concerns that the applicant had not satisfactorily demonstrated the environmental safety of Suifertil 4 mg/ml Oral Solution for Pigs due to lack of pivotal data without which it is not possible to conclude on the environmental safety of the product.

2. Assessment of the data submitted

In order to address the concerns raised by the referral, the applicant provided a Phase I ERA, references from public literature and a scientific justification why the ERA can stop at Phase I and the 'however clause' should not be invoked. No further risk mitigation measures were considered than the ones proposed in the decentralised procedure. Lastly, an expert report was provided which discusses the need for altrenogest-containing products in pig farming. Considering the data submitted, the Committee concluded as follows on issues raised in the notification received from France.

2.1. Application of the 'however clause' or can the ERA stop at Phase I

In this procedure, the Committee was asked to consider whether in the case of Suifertil 4 mg/ml Oral Solution for Pigs, containing as the active substance a synthetic hormone (altrenogest), the 'however clause' should be applied and a tailored Phase II environmental risk assessment should be provided in

[1] 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

order to assess the potential risk of Suifertil 4 mg/ml Oral Solution for Pigs to the environment. The referenced 'however clause' is a provision in the introduction section of VICH GL6 which states "Phase I also identifies VMPs that require a more extensive EIA under Phase II. Some VMPs that might otherwise stop in Phase I may require additional environmental information to address particular concerns associated with their activity and use."

The applicant provided a Phase I ERA, in which $PEC_{soil\ initial}$ for the active ingredient was calculated to be 0.93 µg/kg for open systems and 0.36 µg/kg for closed systems, which is considered plausible and acceptable. Both values are less than the trigger value of 100 µg/kg. Consequently, the applicant concluded that the ERA can stop at Phase I. Additionally, the applicant provided a scientific justification why the 'however clause' of VICH GL6 should not be invoked.

The applicant used Quantitative structure–activity relationship models (QSAR models) to calculate excretion levels of altrenogest and compared them with the measured total gestagen excretion by pigs reported in public literature. The use of QSAR is very limited and only refers to metabolism, which is considered acceptable. In parallel of the QSAR calculation, the applicant has considered the worst case where altrenogest is not metabolised at all. The calculated values for altrenogest were 13.5 (in the case of 80% metabolism) and 2.7 (in the case of 0% metabolism) times lower than the total gestagen excretion by pigs.

Surface water for altrenogest was modelled using FOCUS simulation models, using the two scenarios (open and closed models) with 0% and 80% metabolism each. For $DT_{50\ soil}$ a conservative approach of 10 days was used, based on reported half-lives of different hormones. For the $DT_{50\ water}$ the conservative approach of 1000 days was used. These scenarios led to a $PEC_{surfacewater}$ ranging from 0.641 ng/l (for a closed system with 80% metabolism) up to 8.98 ng/l (for an open system with 0% metabolism). The modelling of the surface water concentrations is principally accepted.

The applicant argued that the environmental load of altrenogest is comparable to other hormones measured and provided public available literature regarding effect concentrations of different hormones in the low ng/l range, but none with altrenogest. Effect data with altrenogest are not available in the public domain. The submitted published literature on effect studies for three other hormones, the gestagens levonorgestrel, drosperinone and progestrerone, is indicating adverse effects at concentrations far below the trigger value of 100 µg/kg soil. The two studies with the most sensitive results display effects in amphibians and fish already at the lowest test concentration of 1.3 and 0.8 ng/l, respectively. Therefore, a NOEC could not be derived in these studies. This indicates potential adverse effects of steroid hormones in the environment.

The concerns expressed by the objecting CMS in respect to the risk to aquatic organisms do not relate specifically to the product Suifertil 4 mg/ml Oral Solution for Pigs, but equally to all relevant veterinary medicinal products containing the active substance altrenogest. A class referral under Article 35 of Directive 2001/82/EC has been initiated in April 2013 for all veterinary medicinal products containing altrenogest to be administered orally to pigs and horses, the scope of which also includes Suifertil. Within this referral the submission of further ecotoxicity and environmental fate data are expected. This procedure will allow an assessment of all available data and harmonised outcome in relation to all products concerned.

Benefit-risk assessment

Introduction

Suifertil 4 mg/ml Oral Solution for Pigs contains altrenogest as an active ingredient. Altrenogest is a synthetic steroidal hormone, an orally active (pro)gestagen. The active substance is included in veterinary medicinal products currently licensed in several countries in the European Union for use in gilts and mares for synchronisation of oestrus.

The application in question, submitted via the decentralised procedure, is a generic application according to Article 13(1) Directive 2001/82/EC, as amended, referring to the reference product Regumate oily solution 4 mg/ml.

Direct therapeutic benefit

Suifertil 4 mg/ml Oral Solution for Pigs is intended for synchronisation of oestrus in sexually mature pigs. The efficacy of Suifertil has been demonstrated according to current rules during the decentralised procedure. Efficacy was not assessed in this referral procedure.

Risk Assessment

Quality, target animal safety, user safety and residues were not assessed in this referral procedure, as no concern was notified by the reference Member State.

Environmental risk

A Phase I environmental risk assessment in compliance with the relevant guidelines was provided, which showed that the PEC_{soil} value for pigs does not exceed the VICH threshold of 100 µg/kg. Using the total residue approach for intensively reared animals the PEC_{soil} for pigs was determined to be 3.01 µg/kg and refining by means of FOCUS models led to values of 0.93 µg/kg for open systems and 0.36 µg/kg for closed systems.

Studies in the published literature on effects of several hormones other than altrenogest on aquatic organisms indicate adverse effects at concentrations far below the trigger value of 100 µg/kg soil. It is not possible to conclude at present whether these findings could be extrapolated to altrenogest.

Within the ongoing Article 35 referral for all veterinary medicinal products containing altrenogest to be administered orally to pigs and horses, further ecotoxicity and environmental fate data are expected to be submitted. The environmental risk assessment will be reviewed within the Article 35 referral.

As there is no product specific concern identified for Suifertil 4 mg/ml Oral Solution for Pigs that is different from the other, already authorised altrenogest containing veterinary medicinal products, it is considered appropriate to await the outcome of the ongoing Article 35 referral before any different conclusions regarding the environmental risk assessment or specific measures would be envisaged for Suifertil 4 mg/ml Oral Solution for Pigs.

Risk management or mitigation measures

The warnings in the product literature remain appropriate at present in absence of new findings. No further risk management or mitigation measures are required as a consequence of this referral procedure.

Evaluation of the benefit-risk balance

Based on the currently available data, and in anticipation of a more in-depth assessment of the environmental risk assessment under an ongoing Article 35 referral, the benefit-risk ratio is considered positive for Suifertil 4 mg/ml Oral Solution for Pigs at present.

Grounds for the granting of the marketing authorisation for Suifertil 4 mg/ml Oral Solution for Pigs

Having considered all the overall submitted data in writing the CVMP concluded that there is no product specific concern identified for the Suifertil 4 mg/ml Oral Solution for Pigs that is different from the other, already authorised, altrenogest containing veterinary medicinal products. It is considered appropriate to await the outcome of the ongoing Article 35 referral before any specific measures would be envisaged for Suifertil 4 mg/ml Oral Solution for Pigs.

Therefore, the CVMP recommended the granting of the marketing authorisation for Suifertil 4 mg/ml Oral Solution for Pigs for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III of the CVMP opinion.

Annex III

Summary of product characteristics, labelling and package leaflet

The valid Summary of Product Characteristics, labelling and package leaflet are the final versions achieved during the Coordination group procedure.