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	Pharmaceutical form	Strength	Animal species	Route of administration
Austria	Novartis Animal Health Inc. Schwarzwaldallee 215 CH-4058 Basel Switzerland	STRENZEN 500/125 mg/g Pulver zum Eingeben über das Trinkwasser für Schweine	Amoxicillin trihydrate and potassium clavulanate	Powder for use in drinking water	500/125 mg/g	Pigs	Oral: In drinking water
Czech Republic	Novartis Animal Health Inc. Schwarzwaldallee 215 CH-4058 Basel Switzerland	STRENZEN 500/125 mg/g prášek pro podání v pitné vodě pro prasata	Amoxicillin trihydrate and potassium clavulanate	Powder for use in drinking water	500/125 mg/g	Pigs	Oral: In drinking water
Denmark	Novartis Animal Health Inc. Schwarzwaldallee 215 CH-4058 Basel Switzerland	STRENZEN 500/125 mg pulver til anvendelse i drikkevand til svin	Amoxicillin trihydrate and potassium clavulanate	Powder for use in drinking water	500/125 mg/g	Pigs	Oral: In drinking water
France	Novartis Animal Health Inc. Schwarzwaldallee 215 CH-4058 Basel Switzerland	STRENZEN 500/125 mg/g poudre pour eau de boisson porcs	Amoxicillin trihydrate and potassium clavulanate	Powder for use in drinking water	500/125 mg/g	Pigs	Oral: In drinking water
Germany	Novartis Animal Health Inc. Schwarzwaldallee 215 CH-4058 Basel Switzerland	STRENZEN 500/125 mg/g Pulver zum Eingeben über das Trinkwasser für Schweine	Amoxicillin trihydrate and potassium clavulanate	Powder for use in drinking water	500/125 mg/g	Pigs	Oral: In drinking water
Ireland	Novartis Animal Health Inc. Schwarzwaldallee 215 CH-4058 Basel Switzerland	STRENZEN 500/125 mg/g powder for use in drinking water for pigs	Amoxicillin trihydrate and potassium clavulanate	Powder for use in drinking water	500/125 mg/g	Pigs	Oral: In drinking water
Italy	Novartis Animal Health Inc. Schwarzwaldallee 215 CH-4058 Basel Switzerland	STRENZEN 500/125 mg/g polvere per somministrazione in acqua da bere per suini	Amoxicillin trihydrate and potassium clavulanate	Powder for use in drinking water	500/125 mg/g	Pigs	Oral: In drinking water

Member State EU/EEA	Applicant	Name	INN	Pharmaceutical form	Strength	Animal species	Route of administration
The Netherlands	Novartis Animal Health Inc. Schwarzwaldallee 215 CH-4058 Basel Switzerland	STRENZEN 500/125 mg/g poeder voor gebruik in drinkwater voor varkens.	Amoxicillin trihydrate and potassium clavulanate	Powder for use in drinking water	500/125 mg/g	Pigs	Oral: In drinking water
Portugal	Novartis Animal Health Inc. Schwarzwaldallee 215 CH-4058 Basel Switzerland	STRENZEN 500/125 mg/g pó para utilização na água de bebida em suínos	Amoxicillin trihydrate and potassium clavulanate	Powder for use in drinking water	500/125 mg/g	Pigs	Oral: In drinking water
Spain	Novartis Animal Health Inc. Schwarzwaldallee 215 CH-4058 Basel Switzerland	STRENZEN 500/125 mg/g polvo para uso en agua de bebida para porcino	Amoxicillin trihydrate and potassium clavulanate	Powder for use in drinking water	500/125 mg/g	Pigs	Oral: In drinking water
United Kingdom	Novartis Animal Health Inc. Schwarzwaldallee 215 CH-4058 Basel Switzerland	STRENZEN 500/125 mg/g powder for use in drinking water for pigs	Amoxicillin trihydrate and potassium clavulanate	Powder for use in drinking water	500/125 mg/g	Pigs	Oral: In drinking water

Annex II

Scientific conclusions and grounds for the granting of the marketing authorisation for STRENZEN 500/125 mg/g powder for use in drinking water for pigs

Overall summary of the scientific evaluation of STRENZEN 500/125 mg/g powder for use in drinking water for pigs

1. Introduction

STRENZEN 500/125 mg/g powder for use in drinking water for pigs contains amoxicillin and clavulanic acid as active ingredients. Amoxicillin is a semi-synthetic aminopenicillin with broad-spectrum bactericidal activity. Clavulanic acid, a naturally-occurring substance is a beta-lactamase inhibitor and chemical synergist for amoxicillin. The combination of active substances is included in veterinary medicinal products currently authorised in the European Union for use in cattle, pigs, dogs and cats. The proposed indications for STRENZEN 500/125 mg/g powder for use in drinking water for pigs are treatment of respiratory tract infections caused by microorganisms susceptible to the combination amoxicillin/clavulanic acid i.e. *Actinobacillus pleuropneumoniae*, *Pasteurella* spp, *Streptococcus* spp. and gastrointestinal infections caused by *Clostridium* spp., *E. coli* and *Salmonella* spp.

The applicant submitted an application for a decentralised procedure for STRENZEN 500/125 mg/g powder for use in drinking water for pigs according to Article 13(1) Directive 2001/82/EC, as amended, referring to the reference product Amoksiklav 500/125 mg/g powder for use in drinking water authorised in the Czech Republic (MA No. 96/069/98-C). The reference Member State (RMS) is the Czech Republic and 10 concerned Member States (CMS) are involved: Austria, Denmark, France, Germany, Ireland, Italy, the Netherlands, Portugal, Spain and the United Kingdom.

Potential serious risks were identified during the decentralised procedure by the Netherlands and the United Kingdom regarding lack of data on the degradation in soil of amoxicillin and clavulanic acid and the adsorption/desorption of amoxicillin in soil, due to which the environmental risk assessment (ERA) could not be completed. These issues remained unsolved and therefore a referral under Article 33(1) of Directive 2001/82/EC to the CMD(v) was started. The Member States concerned failed to reach an agreement regarding the product and consequently the matter was referred to the CVMP on 11 July 2012.

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 STRENZEN 500/125 mg/g powder for use in drinking water 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 an adapted ERA for STRENZEN 500/125 mg/g powder for use in drinking water for pigs and further information on the degradation in soil and sorption to soil. The applicant did not propose any risk mitigation measures, because they did not identify any environmental risks. Considering the data submitted, the Committee concluded as follows on issues raised in the notification received from the Czech Republic.

2.1. Environmental risk assessment of the product

The Committee considered whether the environmental risk assessment can be completed based on the information available, or further data needs to be provided.

The product containing amoxicillin and clavulanic acid (in the form of the potassium salt) at a ratio 4:1 is indicated for treatment of infections caused by microorganisms in intensively reared pigs including respiratory diseases. The target species are treated by 20 mg/kg bw of amoxicillin and 5 mg/kg bw of clavulanic acid for 5 consecutive days. The exposure to the environment will be via slurry application onto land.

According to the guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005) the Environmental Risk Assessment targets at effects of the combination product.

Soil

Predicted environmental concentrations (PECs) of amoxicillin and clavulanic acid in soil were calculated in phase I. All PEC_{soil} values for amoxicillin exceeded the trigger value 100 µg/kg. Treatment of weaner pigs was considered to be the worst case scenario. The PEC_{soil} value 869 µg/kg was used in the subsequent assessment. PEC_{soil} values for clavulanic acid administered in weaner pigs and fattening pigs exceeded the trigger value 100 µg/kg. The worst case scenario was also considered the treatment of weaner pigs. The PEC_{soil} value 217 µg/kg was used in the subsequent assessment. PEC_{soil} (combination) was 1086 µg/kg. The assessment in phase II was required.

The provided study on soil degradation of amoxicillin is considered acceptable even though non-labelled material was used and the extraction efficiencies were slightly below those recommended in the OECD guideline 307. The metabolites of amoxicillin are not considered to pose a higher risk than the parent compound, therefore the presented ERA is considered the worst case scenario and is acceptable, despite the fact that it does not take into account the transformation products of the active substance.

Terrestrial effects studies

The risk quotients (RQs) calculated for terrestrial plants and earthworms were below the trigger value of 1 and the product can be considered as safe for terrestrial organisms.

Water

Based on the PEC_{soil} values the $PEC_{groundwater}$ and $PEC_{surfacewater}$ were calculated.

The $PEC_{groundwater}$ for both compounds was above the trigger value 0.1 µg/l ($PEC_{groundwater}$ for amoxicillin was 95.40 µg/l and for clavulanic acid 3.27 µg/l). $PEC_{groundwater}$ (combination) was 98.67 µg/l.

Hence the applicant used advanced models for PEC calculation in groundwater (FOCUS), as described in the CVMP guideline on environmental impact assessment for veterinary medicinal products (EMEA/CVMP/ERA/418282/2005-Rev.1).

Advanced models for PECs in groundwater with the lowest K_{OC} value (40.4 ml/g) as the worst case confirm that predicted environmental concentrations in all scenarios were below the trigger value of 0.1 µg/l and the product does not pose any risk to groundwater.

Aquatic environment

The $PEC_{surfacewater}$ was calculated to be 31.80 µg/l for amoxicillin and 1.09 µg/l for clavulanic acid. The $PEC_{surfacewater}$ (combination) was 32.89 µg/l. This value was subsequently used in calculations of RQs for aquatic organisms. The RQs for daphnids and fish were below the trigger value of 1 but for algae the RQ was above the trigger value. Further assessment was required for algae, hence the applicant submitted advanced models for PECs in surfacewater (FOCUS).

A $PEC_{surfacewater}$ refined by FOCUS modelling and corrected as a sum of predicted surface water concentration of amoxicillin and clavulanic acid (combination) was calculated as 0.036 µg/l. The refined $PEC_{surfacewater}$ value was used for recalculation of RQ for algae.

The refined RQ of 0.7 is below the trigger value of 1, hence the product does not pose a risk for the aquatic environment – surface water.

Based on the revised ERA and considering additional information from peer-reviewed scientific literature, no serious risk for the environment was identified and the risk can be properly managed by the proposed conditions for use of the product as per the currently proposed SPC.

The environmental risk assessment indicates that the product will not pose an unacceptable risk for the environment when used in accordance with the proposed SPC.

Having considered all the overall submitted data in writing and in the oral explanation the CVMP concluded the data package regarding environmental risk assessment submitted by the applicant is considered sufficient and the overall benefit-risk balance of the product is positive.

Therefore, the CVMP recommended the granting of the marketing authorisation for STRENZEN 500/125 mg/g powder for use in drinking water for pigs and associated names for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III of the CVMP Opinion.

3. Benefit-risk assessment

Introduction

STRENZEN 500/125 mg/g powder for use in drinking water for pigs and associated names contains amoxicillin and clavulanic acid (in the form of the potassium salt) at a ratio 4:1 as active ingredients. Amoxicillin is a semi-synthetic aminopenicillin with broad-spectrum bactericidal activity. Clavulanic acid, a naturally-occurring substance is a beta-lactamase inhibitor and chemical synergist for amoxicillin. The combination of active substances is included in veterinary medicinal products currently authorised in the European Union for use in cattle, pigs, dogs and cats.

The application in question, submitted via the decentralised procedure, is a generic application according to Art. 13(1) Directive 2001/82/EC, as amended, referring to the reference product Amoksiklav 500/125 mg/g powder for use in drinking water registered in the Czech Republic (No.96/069/98-C).

Direct therapeutic benefit

The benefit of STRENZEN 500/125 mg/g powder for use in drinking water for pigs is that treatment of infections caused by microorganisms in intensively reared pigs including respiratory diseases can be treated.

Indirect or additional benefits

None.

Risk assessment

Quality, Target animal safety, User safety, Residues, Resistance and Efficacy were not assessed in this referral procedure.

Environmental risk

Considering the total evidence presented in the dossier and the data available in the public domain, the absence of the data concerning metabolites does not affect the positive benefit-risk ratio of the product. The data collected from different public sources on metabolites indicate that there are no environmental risks (according to current ERA methodology).

It can be concluded that the product in not expected to pose a risk to the environment when used according to the recommendations in the SPC.

Risk management or mitigation measures

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

Evaluation of the benefit-risk balance

Overall, the data package submitted by the applicant regarding environmental risk assessment is considered sufficient taking into account the nature of this application for marketing authorisation (generic application). In conclusion, the benefit-risk ratio is considered positive for STRENZEN 500/125 mg/g powder for use in drinking water for pigs.

Grounds for the granting of marketing authorisation for STRENZEN 500/125 mg/g powder for use in drinking water for pigs

Having considered all data submitted the CVMP concluded that:

- The studies on the degradation in soil of amoxicillin and clavulanic acid and the adsorption/desorption of amoxicillin in soil provided by the applicant are acceptable;
- The publicly available scientific literature demonstrates that metabolites of amoxicillin wouldn't pose a higher risk than the parent compound, and using amoxicillin in the environmental impact assessment is justified;
- The ERA can be completed and the product poses no unacceptable risk to the environment.

Therefore, the CVMP recommended the granting of the marketing authorisation for the veterinary medicinal products referred to in annex I for which the valid Summary of Product Characteristics, labelling and package leaflet remain as per the final versions achieved during the Coordination group procedure as mentioned in annex III.

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.