Annex I

List of the names, pharmaceutical forms, strengths of the veterinary medicinal products, 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
Germany	Norbrook Laboratories Limited Station Works Camlough Road Newry Co. Down BT35 6JP Northern Ireland	Norbonex 5 mg/ml Pour-On Solution for Beef and Dairy Cattle	Eprinomectin	5 mg/ml	Pour-on solution	Cattle	Topical use
The Netherlands	Norbrook Laboratories Limited Station Works Camlough Road Newry Co. Down BT35 6JP Northern Ireland	Norbonex 5 mg/ml Pour-On Solution for Beef and Dairy Cattle	Eprinomectin	5 mg/ml	Pour-on solution	Cattle	Topical use
United Kingdom	Norbrook Laboratories Limited Station Works Camlough Road Newry Co. Down BT35 6JP Northern Ireland	Norbonex 5 mg/ml Pour-On Solution for Beef and Dairy Cattle	Eprinomectin	5 mg/ml	Pour-on solution	Cattle	Topical use

Annex II

Scientific conclusions and grounds for the granting of the marketing authorisation for Norbonex 5 mg/ml Pour-On Solution for Beef and Dairy Cattle

Overall summary of the scientific evaluation of Norbonex 5 mg/ml Pour-On Solution for Beef and Dairy Cattle

1. Introduction

Norbonex 5 mg/ml Pour-On Solution for Beef and Dairy Cattle contains eprinomectin, a synthetic avermectin. The active substance is well known and is included in veterinary medicinal products currently authorised in the EU for use in cattle.

The application in question, submitted via the decentralised procedure, is a 'hybrid' application according to Art. 13(3) of Directive 2001/82/EC, as amended, referring to the reference product Eprinex Pour-On Solution for Beef and Dairy Cattle authorised in the United Kingdom. The reference Member State is the United Kingdom. The concerned Member States involved are Germany and the Netherlands.

Potential serious risks were identified during the decentralised procedure by Germany who considered that eprinomectin might potentially be a PBT (persistent, bioaccumulative and toxic) substance. Based on available data, the P and T criteria are met and so the remaining B component should be fully assessed. However, Germany considered no acceptable data in the environmental risk assessment has been provided on bioaccumulation in order to assess the B criterion. Therefore, a referral to CVMP under Article 33(4) of Directive 2001/82/EC was made.

2. Assessment of the data submitted

In order to address the concerns raised by the referral, the applicant provided an environmental risk assessment (ERA) in accordance with VICH guidelines GL6[1] and GL38[2] and in accordance with the CVMP guideline in support of VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005)[3]. Additionally, risk mitigation measures (RMM) have been considered and proposed for the risk identified for dung insects. On the basis of the ERA no other RMMs were proposed by the applicant. Considering the data submitted, the Committee concluded as follows on issues raised in the notification received from Germany.

An ERA was provided for Norbonex 5 mg/ml Pour-On Solution for Beef and Dairy Cattle which was in accordance with VICH and CVMP guidelines. It provided all the information required to be able to make a conclusion on the environmental risk presented by the use of this product. The ERA was full and complete in terms of data requirements.

Eprinomectin residues will be introduced into the environment following direct excretion onto pasture. Because eprinomectin is a parasiticide a Phase II assessment according to VICH GL38 was presented

[1] VICH GL6: Guideline on Environmental Impact Assessment (EIAS) for Veterinary Medicinal Products – Phase I (CVMP/VICH/592/98) – http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004394.pdf

[2] VICH GL38: Guideline on Environmental Impact Assessment for Veterinary Medicinal Products Phase II (CVMP/VICH/790/03) – http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004393.pdf

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

for the active ingredient in order to assess the fate of the substance and the effects on organisms that might occur in the environment by the use of the product.

Eprinomectin has a n-octanol/water partition coefficient (K_{OW}, expressed as log K_{OW}) of 6.5 which was tested in a valid K_{OW} study according to guideline 117 of the Organisation for Economic Co-operation and Development (OECD)[4]. The deriving bioaccumulation potential and the potential for being considered a PBT compound and secondary poisoning were addressed as required by VICH and CVMP guidelines. Results from a bioaccumulation study according to OECD guideline 305[5] demonstrate that eprinomectin is not likely to concentrate to levels that would pose a risk to aquatic organisms. A screening for PBT properties as required by the CVMP guidelines indicated that eprinomectin fulfils the criteria for 'P' and 'T' but it was considered not to be 'B'. In conclusion eprinomectin was not considered to be a PBT compound. Evaluation of secondary poisoning showed the risk quotient values for terrestrial and aquatic predators were <1 and further assessment was not required.

Valid data on the acute and developmental toxicity of eprinomectin to dung beetle larvae were provided which indicated that risk quotient values for dung insects were >1. No additional studies were carried out in order to further refine the risk as guidance in this area is not currently available. Consequently in order to mitigate the risk for dung insects RMM were included in the product information. Based on the fate data of eprinomectin and the outcome of the PBT assessment it was additionally considered to address the persistency in soil.

3. Benefit-risk assessment

Introduction

Norbonex 5 mg/ml Pour-On Solution for Beef and Dairy Cattle contains eprinomectin, a synthetic avermectin. The active substance is well known and is included in veterinary medicinal products currently authorised in the EU for use in cattle.

Direct therapeutic benefit

The benefit of the products is treatment and control of infections from gastrointestinal roundworms (adults and fourth stage larvae), lungworms (adults and fourth stage larvae), warbles (parasitic stages, mange mites, lice and horn flies by using this product.

Risk assessment

Quality, target animal safety, user safety, residues and resistance were not assessed in this referral procedure, but all risks were addressed during the decentralised procedure.

An ERA in accordance with VICH and CVMP guidelines was provided which contained a mixture of published and bespoke studies from the applicant and addressed all aspects of environmental risk. The use of the product poses a risk for aquatic organisms in groundwater and surface water as well as for dung fauna. Based on the identified risks in the ERA RMM were proposed to address the risk.

Risk management or mitigation measures

The RMM and warnings in the summary of product characteristics (SPC) and package leaflet address the risk to dung fauna and aquatic organisms by advising on the frequency of re-treatments, the

[4] OECD guidelines for the testing of chemicals, Test No. 117: Partition Coefficient (n-octanol/water), HPLC Method: http://www.oecd-ilibrary.org/environment/test-no-117-partition-coefficient-n-octanol-water-hplc-method_9789264069824-en

[5] OECD guidelines for the testing of chemicals, Test No.305: Bioaccumulation in Fish: Aqueous and Dietary Exposure: http://www.oecd-ilibrary.org/content/book/9789264185296-en

duration of eprinomectin excretion and the keep off from water bodies two to five weeks after treatment. Eprinomectin fulfils the 'P' criterion as a conclusion from the PBT assessment and has a high adsorption coefficient (K_{OC}). These characteristics are also addressed in the SPC and the package leaflet with the information "... is persistent in soils and may accumulate in sediments ". These warnings are appropriate.

Evaluation of the benefit-risk balance

The benefit-risk balance is considered positive for Norbonex 5 mg/ml Pour-On Solution for Beef and Dairy Cattle.

Grounds for the granting of the marketing authorisation for Norbonex 5 mg/ml Pour-On Solution for Beef and Dairy Cattle

Having considered all the overall submitted data in writing the CVMP concluded that the ERA for Norbonex 5 mg/ml Pour-On Solution for Beef and Dairy Cattle shows that the product is not expected to pose a risk for the environment when used as recommended in the SPC which includes following the recommended RMM. The benefit-risk for the product can be considered to be positive.

Therefore, the CVMP recommended the granting of the marketing authorisation for Norbonex 5 mg/ml Pour-On Solution for Beef and Dairy Cattle with amendment to the summary of product characteristics and package leaflet of the reference Member State. The amended summary of product characteristics and package leaflet of the reference Member State are set out in Annex III.

Annex III

Amendments in the relevant sections of the Summary of product characteristics and package leaflet

The valid Summary of product characteristics, labelling and package leaflet are the final versions achieved during the Coordination Group procedure with the following amendments:

Add the following text in the relevant sections of the product information:

Summary of product characteristics

4.5 Special precautions for use

……

iii. Other precautions

Eprinomectin is very toxic to aquatic organisms, is persistent in soils and may accumulate in sediments.

The risk to aquatic ecosystems and dung fauna can be reduced by avoiding too frequent and repeated use of eprinomectin (and products of the same anthelmintic class) in cattle.

The risk to aquatic ecosystems will be further reduced by keeping treated cattle away from water bodies for two to five weeks after treatment.

5.3 Environmental properties

Like other macrocyclic lactones, eprinomectin has the potential to adversely affect non-target organisms. Following treatment, excretion of potentially toxic levels of eprinomectin may take place over a period of several weeks. Faeces containing eprinomectin excreted onto pasture by treated animals may reduce the abundance of dung feeding organisms which may impact on the dung degradation.

Eprinomectin is very toxic to aquatic organisms, is persistent in soils and may accumulate in sediments.

Package leaflet:

12. SPECIAL WARNINGS

……

Eprinomectin is very toxic to aquatic organisms, is persistent in soils and may accumulate in sediments.

The risk to aquatic ecosystems and dung fauna can be reduced by avoiding too frequent and repeated use of eprinomectin (and products of the same anthelmintic class) in cattle.

The risk to aquatic ecosystems will be further reduced by keeping treated cattle away from water bodies for two to five weeks after treatment.

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