Annex I

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

Member State EU/EEA	Applicant	Name	Pharmaceutical form	INN/Strength	Animal species	Route of administration	Recommended dose	Withdrawal periods
Austria	Pfizer Limited Veterinary Medical Research & Development Sandwich Kent CT13 9NJ United Kingdom	Prontax 5 mg/ml Pour-On Solution for Cattle	Pour-on solution	Doramectin 5 mg/ml	Cattle	topical - on the back of the animal	1 ml per 10 kg bodyweight	**CATTLE:** Meat and offal: 35 days. Do not use in lactating cows used to produce milk for human consumption, or in dry cows or pregnant dairy heifers within 60 days prior to calving
Bulgaria	Pfizer Limited Veterinary Medical Research & Development Sandwich Kent CT13 9NJ United Kingdom	Prontax 5 mg/ml Pour-On Solution for Cattle	Pour-on solution	Doramectin 5 mg/ml	Cattle	topical - on the back of the animal	1 ml per 10 kg bodyweight	**CATTLE:** Meat and offal: 35 days. Do not use in lactating cows used to produce milk for human consumption, or in dry cows or pregnant dairy heifers within 60 days prior to calving
Denmark	Pfizer Limited Veterinary Medical Research & Development Sandwich Kent CT13 9NJ United Kingdom	Prontax 5 mg/ml Pour-On Solution for Cattle	Pour-on solution	Doramectin 5 mg/ml	Cattle	topical - on the back of the animal	1 ml per 10 kg bodyweight	**CATTLE:** Meat and offal: 35 days. Do not use in lactating cows used to produce milk for human consumption, or in dry cows or pregnant dairy heifers within 60 days prior to calving

Member State EU/EEA	Applicant	Name	Pharmaceutical form	INN/Strength	Animal species	Route of administration	Recommended dose	Withdrawal periods
Spain	Pfizer Limited Veterinary Medical Research & Development Sandwich Kent CT13 9NJ United Kingdom	Dectomax 5 mg/ml Pour-On Solution for Cattle	Pour-on solution	Doramectin 5 mg/ml	Cattle	topical - on the back of the animal	1 ml per 10 kg bodyweight	**CATTLE:** Meat and offal: 35 days. Do not use in lactating cows used to produce milk for human consumption, or in dry cows or pregnant dairy heifers within 60 days prior to calving
Finland	Pfizer Limited Veterinary Medical Research & Development Sandwich Kent CT13 9NJ United Kingdom	Prontax 5 mg/ml Pour-On Solution for Cattle	Pour-on solution	Doramectin 5 mg/ml	Cattle	topical - on the back of the animal	1 ml per 10 kg bodyweight	**CATTLE:** Meat and offal: 35 days. Do not use in lactating cows used to produce milk for human consumption, or in dry cows or pregnant dairy heifers within 60 days prior to calving
France	Pfizer Limited Veterinary Medical Research & Development Sandwich Kent CT13 9NJ United Kingdom	Prontax 5 mg/ml solution pour pour on pour bovins	Pour-on solution	Doramectin 5 mg/ml	Cattle	topical - on the back of the animal	1 ml per 10 kg bodyweight	**CATTLE:** Meat and offal: 35 days. Do not use in lactating cows used to produce milk for human consumption, or in dry cows or pregnant dairy heifers within 60 days prior to calving

Member State EU/EEA	Applicant	Name	Pharmaceutical form	INN/Strength	Animal species	Route of administration	Recommended dose	Withdrawal periods
Hungary	Pfizer Limited Veterinary Medical Research & Development Sandwich Kent CT13 9NJ United Kingdom	Prontax 5 mg/ml Pour-On Solution for Cattle	Pour-on solution	Doramectin 5 mg/ml	Cattle	topical - on the back of the animal	1 ml per 10 kg bodyweight	**CATTLE:** Meat and offal: 35 days. Do not use in lactating cows used to produce milk for human consumption, or in dry cows or pregnant dairy heifers within 60 days prior to calving
Ireland	Pfizer Limited Veterinary Medical Research & Development Sandwich Kent CT13 9NJ United Kingdom	Dectomax 5 mg/ml Pour-On Solution for Cattle	Pour-on solution	Doramectin 5 mg/ml	Cattle	topical - on the back of the animal	1 ml per 10 kg bodyweight	**CATTLE:** Meat and offal: 35 days. Do not use in lactating cows used to produce milk for human consumption, or in dry cows or pregnant dairy heifers within 60 days prior to calving
Iceland	Pfizer Limited Veterinary Medical Research & Development Sandwich Kent CT13 9NJ United Kingdom	Prontax 5 mg/ml Pour-On Solution for Cattle	Pour-on solution	Doramectin 5 mg/ml	Cattle	topical - on the back of the animal	1 ml per 10 kg bodyweight	**CATTLE:** Meat and offal: 35 days. Do not use in lactating cows used to produce milk for human consumption, or in dry cows or pregnant dairy heifers within 60 days prior to calving

Member State EU/EEA	Applicant	Name	Pharmaceutical form	INN/Strength	Animal species	Route of administration	Recommended dose	Withdrawal periods
The Netherlands	Pfizer Limited Veterinary Medical Research & Development Sandwich Kent CT13 9NJ United Kingdom	Prontax 5 mg/ml Pour-On Solution for Cattle	Pour-on solution	Doramectin 5 mg/ml	Cattle	topical - on the back of the animal	1 ml per 10 kg bodyweight	**CATTLE:** Meat and offal: 35 days. Do not use in lactating cows used to produce milk for human consumption, or in dry cows or pregnant dairy heifers within 60 days prior to calving
Norway	Pfizer Limited Veterinary Medical Research & Development Sandwich Kent CT13 9NJ United Kingdom	Prontax 5 mg/ml Pour-On Solution for Cattle	Pour-on solution	Doramectin 5 mg/ml	Cattle	topical - on the back of the animal	1 ml per 10 kg bodyweight	**CATTLE:** Meat and offal: 35 days. Do not use in lactating cows used to produce milk for human consumption, or in dry cows or pregnant dairy heifers within 60 days prior to calving
Poland	Pfizer Limited Veterinary Medical Research & Development Sandwich Kent CT13 9NJ United Kingdom	Prontax 5 mg/ml Pour-On Solution for Cattle	Pour-on solution	Doramectin 5 mg/ml	Cattle	topical - on the back of the animal	1 ml per 10 kg bodyweight	**CATTLE:** Meat and offal: 35 days. Do not use in lactating cows used to produce milk for human consumption, or in dry cows or pregnant dairy heifers within 60 days prior to calving

Member State EU/EEA	Applicant	Name	Pharmaceutical form	INN/Strength	Animal species	Route of administration	Recommended dose	Withdrawal periods
Portugal	Pfizer Limited Veterinary Medical Research & Development Sandwich Kent CT13 9NJ United Kingdom	Prontax 5 mg/ml Pour-On Solution for Cattle	Pour-on solution	Doramectin 5 mg/ml	Cattle	topical - on the back of the animal	1 ml per 10 kg bodyweight	**CATTLE:** Meat and offal: 35 days. Do not use in lactating cows used to produce milk for human consumption, or in dry cows or pregnant dairy heifers within 60 days prior to calving
Romania	Pfizer Limited Veterinary Medical Research & Development Sandwich Kent CT13 9NJ United Kingdom	Prontax 5 mg/ml Pour-On Solution for Cattle	Pour-on solution	Doramectin 5 mg/ml	Cattle	topical - on the back of the animal	1 ml per 10 kg bodyweight	**CATTLE:** Meat and offal: 35 days. Do not use in lactating cows used to produce milk for human consumption, or in dry cows or pregnant dairy heifers within 60 days prior to calving
Sweden	(Applicant) Pfizer Limited Veterinary Medical Research & Development Sandwich Kent CT13 9NJ United Kingdom	Prontax 5 mg/ml Pour-On Solution for Cattle	Pour-on solution	Doramectin 5 mg/ml	Cattle	topical - on the back of the animal	1 ml per 10 kg bodyweight	**CATTLE:** Meat and offal: 35 days. Do not use in lactating cows used to produce milk for human consumption, or in dry cows or pregnant dairy heifers within 60 days prior to calving

Member State EU/EEA	Applicant	Name	Pharmaceutical form	INN/Strength	Animal species	Route of administration	Recommended dose	Withdrawal periods
Slovenia	Pfizer Limited Veterinary Medical Research & Development Sandwich Kent CT13 9NJ United Kingdom	Dectomax 5 mg/ml Pour-On Solution for Cattle	Pour-on solution	Doramectin 5 mg/ml	Cattle	topical - on the back of the animal	1 ml per 10 kg bodyweight	**CATTLE:** Meat and offal: 35 days. Do not use in lactating cows used to produce milk for human consumption, or in dry cows or pregnant dairy heifers within 60 days prior to calving

Annex II

Scientific conclusions and grounds for amendment of the summary of product characteristics, labelling and package leaflet

Overall summary of the scientific evaluation of Prontax 5 mg/ml pour-on solution for cattle and associated names

1. Introduction

Prontax 5 mg/ml pour-on solution for cattle and associated names is a clear, colourless pour-on solution containing doramectin. Doramectin is an antipatasitic agent, isolated from the fermentation of selected strains derived from the soil organism Streptomyces avermitilis. It is a macrocyclic lactone and is closely related to ivermectin. Both compounds share a wide spectrum of antiparasitic activity and produce a similar paralysis in nematodes and parasitic arthropods.

The product is indicated for treatment of gastrointestinal roundworms, lungworms, eyeworms, warbles, sucking and biting lice, mange mites and hornfly in cattle.

The applicant Pfizer Limited has submitted an application for a decentralised procedure for Dectomax 5 mg/ml pour-on solution for cattle. The Reference Member State was Ireland and the Concerned Member States were Austria, Bulgaria, Denmark, Spain, Finland, France, Hungary, Iceland, the Netherlands, Norway, Poland, Portugal, Romania, Slovenia and Sweden. The application was submitted in accordance with the Article 13(1) of the Directive 2001/82/EC (i.e. an application for a generic product). The reference product for this generic application was Dectomax 5 mg/ml pour-on solution for cattle.

The following two changes to the initial application that were made during the decentralised procedure and the CVMP referral procedure should be noted:

- During the decentralised procedure the proposed product name was changed from Dectomax 5 mg/ml pour-on solution for cattle to Prontax 5 mg/ml pour-on solution for cattle[1].
- During this referral procedure in Ireland the marketing authorisation of the reference product Dectomax 5 mg/ml pour-on solution for cattle was transferred from Pfizer Healthcare Ireland to Elanco Animal Health, Eli Lilly and Company Limited and the name of the reference product in Ireland was changed to Zearl 5 mg/ml pour-on solution for cattle.

During the procedure, there was disagreement between the Reference Member State and Concerned Member States on the data presented to support the environmental risk assessment. Two Concerned Member States (the Netherlands and France) considered that the authorisation of Dectomax 5 mg/ml pour-on solution for cattle may present a potential serious risk to the environment. Consequently the matter was referred to the CVMP.

The CVMP was asked to give its opinion on the concerns raised by the Concerned Member States and to conclude on the benefit/risk balance for Prontax 5 mg/ml pour-on solution for cattle.

2. Assessment of the data submitted

The referral for Prontax 5 mg/ml pour on solution for cattle relates to the potential serious risks raised by France and the Netherlands regarding the environmental risk assessment (ERA).

[1] During the decentralised procedure it was agreed that the authorisation of the generic product under the name "Dectomax" will not be issued until the reference product under the name "Dectomax" has either been withdrawn or re-named.

The potential serious risks regarding the environment identified by France and the Netherlands are risks to dung fauna and Daphnia in accordance with the proposed instructions for use and a risk identified by the Netherlands due to the bioaccumulation potential linked to the determination of the log K_{OW} by using a test method, which was not considered appropriate for the active ingredient.

Environmental risk assessment

An ERA was performed by the applicant in accordance with the VICH guidelines for Phase I and Phase II assessment adopted by the CVMP (CVMP/VICH/592/98-FINAL, CVMP/VICH/790/03-final) as well as the CVMP guideline on Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH Guidelines GL6 and GL38 (CVMP/ERA/418282/2005-corr). A Phase II, Tier A assessment was required.

The n-octanol/water coefficient (log Pow) was determined as 4.4 using the shake flask method. This method is however not considered suitable for substances with a log Pow above 4. The CVMP considered that the test method for the determination of the n-octanol/water partition coefficient was not appropriate. The log Pow of 4.4 can therefore only be considered as an indicator of the actual value.
As a result of a log Pow ≥ 4 the assessment of bioaccumulation is required. However, no bioaccumulation study was provided; also no assessment of secondary poisoning was performed. The CVMP considered that the available data package does not allow the assessment of bioaccumulation and therefore, bioaccumulation of doramectin cannot be ruled out.

Several studies and published literature on the toxicity to dung fauna were available. The risk characterisation for dung fauna was performed using Predicted Environmental Concentrations (PECs) for dung, which were derived using the metabolism study provided. The concentration of total doramectin residues excreted in cattle faeces peaked at 21 days after administration (270 µg/kg) and declined thereafter, accounting for 52 µg/kg at 35 days and 3.9 µg/kg at 56 days. The parent drug accounted for 79% of the total radioactive faecal residue. No data on the nature and rates of metabolites are available. Therefore no PEC refinement based on metabolism is possible, the risk assessment is based on total residues.

Based on the Predicted No Effect Concentrations (PNECs) derived from the LC50 of 1.34 µg/kg soil for horn flies (*Haematobia irritans*) and the NOEC of 4.0 µg/kg soil for dung beetles (*Ontophagus gazelle*) the resulting risk quotients for both species were high (20149 and 675, respectively, based on the amount of total residues in dung at day 21 after administration), indicating a high acute risk to dung insects in Tier A. Consequently a Tier B assessment should be performed. However, it is recognised that no harmonised guidance on how to conduct Tier B assessment studies for dung insects is currently available.

The risk characterisation for the aquatic environment was conducted based on an EC50 of 0.1 µg/l and a NOEC of 0.025 derived from an acute toxicity study of doramectin in Daphnia (*D. magna*). Based on Predicted Environmental Concentrations (PEC) for surface water PECsw of 0.0026 µg doramectin/l surface water (run-off scenario) and PECsw of 0.5225 µg doramectin/l surface water (direct excretion) an acute risk for Daphnia was identified in Tier A for both exposure scenarios with PEC/PNEC risk quotients (RQ) of 26 and 5225, respectively. After refinement of PECsw using the FOCUS model as recommended by CVMP guideline CVMP/ERA/418282/2005, the RQ remains above 1 for Daphnia.

Further PEC refinement considering that peak excretion of total residues occurred on day 21 after administration and accounted for 2.3% of the administered dose, as well as based on sediment partitioning lead to a PECsw-refined-direct of 0.00037 µg/l, resulting in a RQ for Daphnia (3.7) still higher than 1.

As the risk for Daphnia could not be ruled out by PEC refinements Tier B assessment should be performed according VICH Guideline 38 be performed for which a *Daphnia magna* reproduction study is required. However, this study is not available and cannot be requested in this referral.

Conclusions regarding the environmental impact

The applicant provided a targeted Phase II environmental risk assessment. The outcome of the ERA indicates that RQ are higher than 1 in the Tier A assessment in two cases, namely daphnids (following direct excretion scenario) and dung fauna. According to the VICH Guideline 38 Phase II, a Tier B assessment is required. In the first case, the risk to daphnids could not be ruled out by performing several PEC refinements for the direct excretion scenario. A *Daphnia magna* reproduction study for conducting a Tier B assessment was not submitted in the ERA.

For the dung fauna, the results of the Tier A assessment showed a very high RQ indicating an unacceptable acute risk. The supplementary data provided did not allow ruling out a medium to long-term risk to dung insects. As no harmonised guidance on how to conduct Tier B assessment studies for dung insects is currently available, risk mitigation measures to reduce exposure are considered to overcome the identified risk.

In terms of bioaccumulation the log Pow value is not considered to be robust given the method employed (shake flask). The current data package does not allow the assessment of bioaccumulation and therefore, bioaccumulation of doramectin cannot be ruled out.

In order to address the identified risks for aquatic organisms and dung fauna as well as any remaining uncertainty regarding bioaccumulation the following risk mitigation measures are recommended:

The following text is proposed in section 4.5 of the SPC(special precautions for use):

Doramectin is very toxic to dung fauna and aquatic organisms and may accumulate in sediments.

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

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

The following text should be included in section 5.3 of the SPC (environmental properties):

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

Doramectin is very toxic to aquatic organisms and may accumulate in sediments.

Benefit-risk assessment

Introduction

Prontax 5 mg/ml pour-on solution for cattle contains doramectin as active ingredient. The application has been presented in accordance with Article 13(1) of Directive 2001/82/EC as amended, i.e. it is a generic application.

Benefit assessment

Benefits have not been subject of this referral; they were considered in the preceding decentralised procedure.

Direct benefits

The product has the same indications as the reference product. The product is intended for the treatment of gastrointestinal roundworms, lungworms, eyeworms, warbles, sucking and biting lice, mange mites and hornfly in cattle.

The internal and external parasites indicated for this product are recognised as causing significant loss of production and negatively impact on animal welfare.

The product is applied topically along the mid-line of the back in a narrow strip between the withers and tailhead.

Indirect benefits

Additional benefits of this product are the same as the reference product.

The product has claims for persistent efficacy ranging from 21 to 49 days. The product has dual action against endo- and ecto-parasites and may reduce the number of treatments with different pharmaceutical products.

Risk assessment

As for the benefits, quality of the product was not discussed by CVMP as part of this referral.

In general terms, as for the benefits, that except for the risks identified in particular by the referral (ERA) all other risks are expected to be the same as for the reference product and have not been discussed in any detail by CVMP.

In terms of environmental safety, in addition to the fact that the current data package does not allow to rule out bioaccumulation of doramectin, a risk to the aquatic compartment has been identified based on available toxicity data (acute toxicity for *Daphnia magna*) as well as a risk to dung fauna exposed to residue-containing dung out when the product is used in accordance with the recommended posology. Therefore, risk mitigation measures are considered necessary, as specified in the product information.

Conclusions on the benefit-risk balance

The benefit-risk evaluation is deemed to be positive provided that the recommended risk mitigation measures are added to the product literature regarding risk to aquatic organisms and dung fauna.

Grounds for amendments of the product information

Whereas:

- On the basis of environmental risk assessment data submitted with the application it was considered that in order to address the identified risks for aquatic organisms and dung fauna as well as any remaining uncertainty regarding bioaccumulation risk mitigation measures should be applied;

the CVMP concluded that the objections raised by the Netherlands and France should not prevent the granting of a marketing authorisation for Prontax 5 mg/ml pour-on solution for cattle and associated names (see annex I) as the overall benefit-risk balance for the product is positive subject to the recommended changes in the product information set out in annex III.

Annex III

Amendments in the relevant sections of the 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 with the following amendments:

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

Summary of Product Characteristics

4.5 Special precaution for use

…….

Other precautions

Doramectin is very toxic to dung fauna and aquatic organisms and may accumulate in sediments.

The risk to aquatic ecosystems and dung fauna can be reduced by avoiding too frequent and repeated use of doramectin (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, doramectin has the potential to adversely affect non-target organisms. Following treatment, excretion of potentially toxic levels of doramectin may take place over a period of several weeks. Faeces containing doramectin excreted onto pasture by treated animals may reduce the abundance of dung feeding organisms which may impact on the dung degradation.

Doramectin is very toxic to aquatic organisms and may accumulate in sediments

Labelling:

9. Special warnings, if necessary

Doramectin is very toxic to dung fauna and aquatic organisms and may accumulate in sediments.

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

The risk to aquatic ecosystems and dung fauna can be reduced by avoiding too frequent and repeated use of doramectin (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.

…….

Package leaflet:

12. Special warnings

Doramectin is very toxic to dung fauna and aquatic organisms and may accumulate in sediments.

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

The risk to aquatic ecosystems and dung fauna can be reduced by avoiding too frequent and repeated use of doramectin (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.

…….