Annex I

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

Member State EU / EEA	Applicant / marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Austria	Pfizer Corporation Austria Gesellschaft m.b.H. Floridsdorfer Hauptstraße 1, 1210 Wien AUSTRIA	Dectomax 1% - Injektionslösung für Rinder und Schafe	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep
Austria	Pfizer Corporation Austria Gesellschaft m.b.H. Floridsdorfer Hauptstraße 1, 1210 Wien AUSTRIA	Dectomax S 10 mg/ml Injektionslösung für Schweine	Doramectin	10 mg/ml	Solution for injection	intramuscular	Pigs
Austria	Pfizer Corporation Austria Gesellschaft m.b.H. Floridsdorfer Hauptstraße 1, 1210 Wien AUSTRIA	Dectomax Pour-On 5 mg/ml Lösung für Rinder	Doramectin	5 mg/ml	Pour-on solution	topical - on the back of the animal	Cattle
Belgium	Eli Lilly Benelux S.A. Division Elanco Animal Health Stoofstraat 52 1000 Brussel BELGIUM	DECTOMAX	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep
Belgium	Eli Lilly Benelux S.A. Division Elanco Animal Health Stoofstraat 52 1000 Brussel BELGIUM	DECTOMAX POUR-ON	Doramectin	5 mg/ml	Pour-on solution	topical - on the back of the animal	Cattle
Belgium	Eli Lilly Benelux S.A. Division Elanco Animal Health Stoofstraat 52 1000 Brussel BELGIUM	DECTOMAX SOLUTION INJECTABLE POUR PORCS	Doramectin	10 mg/ml	Solution for injection	intramuscular	Pigs
Bulgaria	Pfizer S.A., Z.I. De Poce-sur-Cisse, B.P. 109 37401 Amboise Cedex, FRANCE	Дектомакс 1% инжективен разтвор	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep, pigs

Member State EU / EEA	Applicant / marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Bulgaria	BIOVET AD 39 Petar Rakov str. Peshtera 4550 BULGARIA	Ендектовет 1% инжекционен разтвор за говеда, овце и свине	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep, pigs
Cyprus	PFIZER HELLAS AE 243 Av Mesogeion 15451, Athens GREECE	DECTOMAX 1% ενέσιμο διάλυμα για βοοειδή, χοίρους και πρόβατα	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep, pigs
Czech republic	Pfizer s.r.o. Stroupežnického 17 150 00 Praha CZECH REPUBLIC	DECTOMAX 10 mg/ml injekční roztok	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep, pigs
Czech republic	Pfizer Limited Veterinary Medical Research & Development Sandwich Kent CT13 9NJ UNITED KINGDOM	Prontax 10 mg/ml Solution for Injection for Cattle, Sheep and Pigs	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep, pigs
Denmark	Pfizer Oy, Animal Health, Tietokuja 4 00330 Helsinki FINLAND	Dectomax Pour-On Vet.	Doramectin	5 mg/ml	Pour-on solution	topical - on the back of the animal	Cattle
Denmark	Pfizer Oy, Animal Health, Tietokuja 4 00330 Helsinki FINLAND	Dectomax Vet.	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, pigs
Denmark	Pfizer Oy, Animal Health, Tietokuja 4 00330 Helsinki FINLAND	Prontax	Doramectin	5 mg/ml	Pour-on solution	topical - on the back of the animal	Cattle
Denmark	Pfizer Oy, Animal Health, Tietokuja 4 00330 Helsinki FINLAND	Prontax	Doramectin	10 mg/ml	Solution for injection	subcutaneous	Cattle

Member State EU / EEA	Applicant / marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Estonia	Pfizer Animal Health S.A., Rue Laid Burniat 1, 1348 Louvain-la-Neuve, BELGIUM	Dectomax	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep, pigs
Estonia	Pfizer Limited Veterinary Medical Research & Development Sandwich Kent CT13 9NJ UNITED KINGDOM	Prontax 10 mg/ml Solution for injection for Cattle, Sheep and Pigs	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep, pigs
Finland	Pfizer Oy, Animal Health, Tietokuja 4 00330 Helsinki FINLAND	DECTOMAX vet 10 mg/ml injektioneste, liuos	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, reindeer, pigs
Finland	Pfizer Oy, Animal Health, Tietokuja 4 00330 Helsinki FINLAND	Prontax 5 mg/ml kertavaleluliuos	Doramectin	5 mg/ml	Pour-on solution	topical - on the back of the animal	Cattle
Finland	Pfizer Oy, Animal Health, Tietokuja 4 00330 Helsinki FINLAND	Prontax 10 mg/ml injektioneste, liuos	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep, pigs
France	Lilly France 13 Rue Pages 92158 Suresnes Cedex FRANCE	ZEARL	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep
France	Lilly France 13 Rue Pages 92158 Suresnes Cedex FRANCE	ZEARL POUR ON	Doramectin	5 mg/ml	Pour-on solution	topical - on the back of the animal	Cattle
France	Lilly France 13 Rue Pages 92158 Suresnes Cedex FRANCE	ZEARL PORCS	Doramectin	10 mg/ml	Solution for injection	intramuscular	Pigs

Member State EU/EEA	Applicant/marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
France	Pfizer Limited Veterinary Medical Research & Development Sandwich Kent CT13 9NJ UNITED KINGDOM	PRONTAX 5 MG/ML SOLUTION POUR POUR ON POUR BOVINS	Doramectin	5 mg/ml	Pour-on solution	topical - on the back of the animal	Cattle
France	Pfizer Limited Veterinary Medical Research & Development Sandwich Kent CT13 9NJ UNITED KINGDOM	PRONTAX 10 MG/ML SOLUTION INJECTABLE POUR BOVINS OVINS ET PORCINS	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep, pigs
Germany	Lilly Deutschland GmbH Teichweg 3 35396 Gießen GERMANY	Dectomax	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep
Germany	Lilly Deutschland GmbH Teichweg 3 35396 Gießen GERMANY	Dectomax Pour-On	Doramectin	5 mg/ml	Pour-on solution	topical - on the back of the animal	Cattle
Germany	Lilly Deutschland GmbH Teichweg 3 35396 Gießen GERMANY	Dectomax-S Injektionslösung	Doramectin	10 mg/ml	Solution for injection	intramuscular	Pigs
Greece	PFIZER HELLAS AE 243 Av Mesogeion 15451, Athens GREECE	DECTOMAX ing sol	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep, pigs
Hungary	Pfizer Kft. Alkotás u. 53. 1123 Budapest HUNGARY	Dectomax injekció A.U.V.	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep, pigs
Iceland	Pfizer Oy, Animal Health, Tietokuja 4 00330 Helsinki FINLAND	Dectomax, vet.	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep, pigs

Member State EU/EEA	Applicant/marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Iceland	Pfizer Oy, Animal Health, Tietokuja 4 00330 Helsinki FINLAND	Prontax	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep, pigs
Iceland	Pfizer Oy, Animal Health, Tietokuja 4 00330 Helsinki FINLAND	Prontax	Doramectin	5 mg/ml	Pour-on solution	topical - on the back of the animal	Cattle
Ireland	Elanco Animal Health Eli Lilly & Company Limited Lilly House Priestly Road Basingstoke, Hampshire RG24 9NL UNITED KINGDOM	Zearl Pour-On Solution for Cattle 5 mg/ml	Doramectin	5 mg/ml	Pour-on solution	topical - on the back of the animal	Cattle
Ireland	Elanco Animal Health Eli Lilly & Company Limited Lilly House Priestly Road Basingstoke, Hampshire RG24 9NL UNITED KINGDOM	Zearl 10 mg/ml Solution for Injection for Cattle and Sheep	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep
Ireland	Elanco Animal Health Eli Lilly & Company Limited Lilly House Priestly Road Basingstoke, Hampshire RG24 9NL UNITED KINGDOM	Zearl 10 mg/ml Solution for Injection for Pigs	Doramectin	10 mg/ml	Solution for injection	intramuscular	Pigs
Ireland	Pfizer Limited Veterinary Medical Research & Development Sandwich Kent CT13 9NJ UNITED KINGDOM	Dectomax 5 mg/ml Pour-On Solution for Cattle	Doramectin	5 mg/ml	Pour-on solution	topical - on the back of the animal	Cattle

Member State EU/EEA	Applicant/marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Ireland	Pfizer Limited Veterinary Medical Research & Development Sandwich Kent CT13 9NJ UNITED KINGDOM	DECTOMAX 10 mg/ml Solution for Injection for Cattle, Sheep and Pigs	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep, pigs
Italy	Pfizer Italia S.r.l. Via Isonzo, 71 04100 Latina ITALY	DECTOMAX 10 mg/ml soluzione iniettabile per bovini, ovini e suini	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep, pigs
Italy	Pfizer Italia S.r.l. Via Isonzo, 71 04100 Latina ITALY	DECTOMAX POUR ON 5mg/ml	Doramectin	5 mg/ml	Pour-on solution	topical - on the back of the animal	Cattle
Latvia	Pfizer Animal Health S.A., Rue Laid Burniat, 1, 1348 Louvain-la-Neuve, BELGIUM	Dectomax	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep, pigs
Latvia	Pfizer Limited Veterinary Medical Research & Development Sandwich Kent CT13 9NJ UNITED KINGDOM	Dectomax	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep, pigs
Lithuania	Pfizer S.A., Z.I. De Poce-sur-Cisse, B.P. 109 37401 Amboise Cedex, FRANCE	DECTOMAX, injekcinis tirpalas galvijams, avims ir kiaulėms	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep, pigs
Lithuania	Pfizer Limited Veterinary Medical Research & Development Sandwich Kent CT13 9NJ UNITED KINGDOM	PRONTAX 10 mg/ml, injekcinis tirpalas galvijams, avims ir kiaulėms	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep, pigs

Member State EU/EEA	Applicant/marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
The Netherlands	Pfizer Animal Health B.V. Rivium Westlaan 142 2909 LD Capelle a/d IJssel THE NETHERLANDS	Dectomax Pour-On Oplossing voor Rundvee 5 mg/ml	Doramectin	5 mg/ml	Pour-on solution	topical - on the back of the animal	Cattle
The Netherlands	Pfizer Animal Health B.V. Rivium Westlaan 142 2909 LD Capelle a/d IJssel THE NETHERLANDS	DECTOMAX oplossing voor injectie 10 mg/ml voor rundvee, varkens en schapen	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep, pigs
Norway	Pfizer Oy, Animal Health, Tietokuja 4 00330 Helsinki FINLAND	Dectomax Pour-On vet	Doramectin	5 mg/ml	Pour-on solution	topical - on the back of the animal	Cattle
Norway	Pfizer Oy, Animal Health, Tietokuja 4 00330 Helsinki FINLAND	Dectomax vet	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep, pigs
Norway	Pfizer Oy, Animal Health, Tietokuja 4 00330 Helsinki FINLAND	Prontax	Doramectin	5 mg/ml	Pour-on solution	topical - on the back of the animal	Cattle
Norway	Pfizer Oy, Animal Health, Tietokuja 4 00330 Helsinki FINLAND	Prontax	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep, pigs
Poland	Pfizer Trading Polska s.p. z o.o. ul. Postępu 17 B 02-676 Warszawa POLAND	Dectomax 10 mg/ml, roztwór do wstrzykiwań dla bydła, świń i owiec	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep, pigs
Portugal	LABORATÓRIOS PFIZER, LDA. Lagoas Park - Edifício 10 2740-244 Porto Salvo PORTUGAL	Dectomax Pour-on	Doramectin	5 mg/ml	Pour-on solution	topical - on the back of the animal	Cattle
Portugal	LABORATÓRIOS PFIZER, LDA. Lagoas Park - Edifício 10 2740-244 Porto Salvo PORTUGAL	Dectomax solução injectável	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep, pigs

Member State EU / EEA	Applicant / marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Romania	Pfizer Limited Veterinary Medical Research & Development Sandwich Kent CT13 9NJ UNITED KINGDOM	DECTOMAX	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep, pigs
Romania	Pfizer Limited Veterinary Medical Research & Development Sandwich Kent CT13 9NJ UNITED KINGDOM	PRONTAX 10 mg/ml Injectable Solution for Cattle, Sheep and Pigs	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep, pigs
Romania	Pfizer Limited Veterinary Medical Research & Development Sandwich Kent CT13 9NJ UNITED KINGDOM	PRONTAX 5 mg/ml Pour On Solution for Cattle	Doramectin	5 mg/ml	Pour-on solution	topical - on the back of the animal	Cattle
Slovakia	Pfizer Luxemburg SARL, o.z. Pfizer AH Pribinova 25 811 09 Bratislava SLOVAK REPUBLIC	Dectomax 10 mg/ml injekčný roztok	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep, pigs
Slovenia	Pfizer Luxembourg SARL 51, Avenue J.F. Kennedy L-1855 Luxembourg LUXEMBOURG	DECTOMAX 10 mg/ml raztopina za injiciranje	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep, pigs
Spain	PFIZER S.A. Avda. de Europa 20 B. Parque Empresarial La Moraleja 28108 - Alcobendas Madrid SPAIN	DECTOMAX 10 MG/ML SOLUCIÓN INYECTABLE PARA PORCINO	Doramectin	10 mg/ml	Solution for injection	intramuscular	Pigs

Member State EU / EEA	Applicant / marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Spain	PFIZER S.A. Avda. de Europa 20 B. Parque Empresarial La Moraleja 28108 - Alcobendas Madrid SPAIN	DECTOMAX POUR-ON SOLUCION 5MG/ML PARA BOVINO	Doramectin	5 mg/ml	Pour-on solution	topical - on the back of the animal	Cattle
Spain	PFIZER S.A. Avda. de Europa 20 B. Parque Empresarial La Moraleja 28108 - Alcobendas Madrid SPAIN	DECTOMAX SOLUCION INYECTABLE	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep
Sweden	Pfizer Oy, Animal Health, Tietokuja 4 00330 Helsinki FINLAND	Dectomax vet.	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep, reindeer
Sweden	Pfizer Oy, Animal Health, Tietokuja 4 00330 Helsinki FINLAND	Dectomax Suis vet.	Doramectin	10 mg/ml	Solution for injection	intramuscular	Pigs
Sweden	Pfizer Oy, Animal Health, Tietokuja 4 00330 Helsinki FINLAND	Prontax	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep, pigs
Sweden	Pfizer Oy, Animal Health, Tietokuja 4 00330 Helsinki FINLAND	Dectomax pour-on vet.	Doramectin	5 mg/ml	Pour-on solution	topical - on the back of the animal	Cattle
Sweden	Pfizer Oy, Animal Health, Tietokuja 4 00330 Helsinki FINLAND	Prontax	Doramectin	5 mg/ml	Pour-on solution	topical - on the back of the animal	Cattle

Member State EU/EEA	Applicant/marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
United Kingdom	Elanco Animal Health Eli Lilly & Company Limited Lilly House Priestly Road Basingstoke, Hampshire RG24 9NL UNITED KINGDOM	Dectomax 10 mg/ml Solution for Injection for Cattle and Sheep	Doramectin	10 mg/ml	Solution for injection	subcutaneous, intramuscular	Cattle, sheep
United Kingdom	Elanco Animal Health Eli Lilly & Company Limited Lilly House Priestly Road Basingstoke, Hampshire RG24 9NL UNITED KINGDOM	Dectomax 10 mg/ml Solution for Injection for Pigs	Doramectin	10 mg/ml	Solution for injection	intramuscular	Pigs
United Kingdom	Elanco Animal Health Eli Lilly & Company Limited Lilly House Priestly Road Basingstoke, Hampshire RG24 9NL UNITED KINGDOM	Dectomax Pour-on Solution for Cattle 5 mg/ml	Doramectin	5 mg/ml	Pour-on solution	topical - on the back of the animal	Cattle

Annex II

Scientific conclusions and grounds for amendment of the summaries of product characteristics, labelling and package leaflets

Overall summary of the scientific evaluation of all injectable and pour-on veterinary medicinal products containing doramectin that are intended for use in mammalian food producing species *(see Annex I)*

1. Introduction

Doramectin is an antiparasitic agent. It is a macrocyclic lactone closely related to ivermectin. Both compounds share a wide spectrum of antiparasitic activity and produce a similar paralysis in nematodes and parasitic arthropods. Doramectin is administered by subcutaneous injection to cattle at a dose of 200 µg/kg body weight (bw) for the treatment and control of gastrointestinal nematodes, lungworms, eyeworms, warbles, lice, mange mites and ticks. In sheep it is administered as a single intramuscular injection at a dose of 200 or 300 µg/kg bw for treatment and control of gastrointestinal roundworms, mange mites and nasal bots. In pigs it is administered as a single intramuscular injection at a dose of 300 µg/kg bw for treatment of mange mites, gastrointestinal roundworms, lungworms, kidney worms and sucking lice. In reindeer doramectin is administered as a single subcutaneous injection at a dose of 200 µg/kg bw for treatment of nematodes and throat bot.

In addition, in cattle doramectin is administered topically on the back of the animal at a dose of 500 µg/kg bw for treatment of infestations of gastrointestinal roundworms, lungworms, eyeworms, warbles, sucking and biting lice, mange mites and hornfly.

The Netherlands noted that identical or similar injectable veterinary medicinal products containing doramectin intended for food producing species have different withdrawal periods established by the Member States (EU/EEA). In addition, the Netherlands noted that injectable and pour-on veterinary medicinal products containing doramectin intended for food producing species contain different risk mitigation measures in the product information in relation to the risks for the environment. The information in some of these products is considered insufficient to mitigate the risk to the environment.

The Netherlands considered that it is in the interest of EU consumers and the environment to harmonise the withdrawal periods and the environmental risk mitigation measures and therefore, on 22 March 2012, the Netherlands presented to the European Medicines Agency a referral notification under Article 35 of Directive 2001/82/EC for all injectable and pour-on veterinary medicinal products containing doramectin that are intended for use in mammalian food producing species.

It should be noted that due to the absence of a maximum residue limit (MRL) in milk the veterinary medicinal products containing doramectin are not authorised for use in lactating animals. However, these products have been used during the dry period with different precautionary measures in place to limit residues in milk, in particular instructions are given on the time that must be allowed to elapse between treatment and calving or lambing. As part of the CVMP evaluation the Committee considered whether further recommendations are necessary in order to ensure that use during the non-lactating period would not lead to residues in milk that, combined with residues from other foodstuffs, would result in consumer exposure exceeding the acceptable daily intake (ADI) (60 µg/person per day).

2. Discussion

Residue data

It is noted that the majority of residue depletion studies made available for evaluation by the CVMP were performed before the introduction of current guidance relating to injection site sampling: VICH GL48 on marker residue depletion studies to establish product withdrawal periods

(EMA/CVMP/VICH/463199/2009)[1] which indicates that quality control measures should be introduced to ensure that the injection site is appropriately sampled, for example by collection of separate core and surrounding samples, which is the methodology recommended in the CVMP guideline on injection site residues (EMEA/CVMP/542/03)[2]. As a result these studies did not include quality control measures and the accuracy of the injection site sampling is therefore questionable. This is a likely source of the variation in the observed residue levels.

Pour-on veterinary medicinal product containing doramectin (cattle)

Meat and offal:

With regard to pour-on products the information received from Member States indicates that the withdrawal period for cattle meat and offal is 35 days in all Member States (EU/EEA), where the products are authorised or pending authorisations. Therefore an evaluation of the withdrawal periods in meat and offal for pour-on products was not necessary.

Milk - time span between treatment of non-lactating animals and calving:

The MRLs currently established for doramectin in tissues use 90% (60 µg/person per day) of the ADI, leaving 10% (6 µg) available to cover exposure to residues resulting from other sources, such as via milk. While no data were available that would allow the establishment of the ratio of marker to total residues for milk, it was considered that the ratio established by CVMP for fat (0.86) could be applied to milk. By applying this ratio to milk and using 6 µg as the total amount of doramectin residues that can be considered safe in 1.5 litres of milk (i.e. the amount of milk considered to be consumed on a daily basis), one can calculate the concentration of doramectin in milk that can be considered safe to be 3.44 µg/l (6 µg x 0.86/1.5 l). The value of 3.44 µg/l was rounded down to 3 µg/l, which was considered to represent a safe doramectin level in milk.

No milk residue data following treatment of dairy animals in the dry period were available to the CVMP. However, two non-GLP residue depletion studies performed in lactating cattle were available and provided data on residues in milk. However, the existing warning sentence in the product information *(Do not use in dry dairy cows including pregnant dairy heifers within 60 days prior to calving)* is considered to be conservative.

Injectable veterinary medicinal product containing doramectin

Cattle

Meat and offal:

Several studies in cattle were provided. However, study results were highly variable (the studies predate the current CVMP and VICH guidelines recommending injection site sampling procedures and consequently did not incorporate quality control measures to ensure that the injection site was appropriately sampled). The injection site was consistently the tissue in which the marker residue persisted for longest and was consequently the key tissue for the withdrawal period derivation. Using the data from the most appropriate study a calculated withdrawal period of 54 days could be derived. However, in view of the variability seen across the studies, in view of the fact that none of the studies were performed in line with standards in place today and considering that in a number of studies residue levels remained above the MRL at the last timepoint, it was considered appropriate to add a safety margin of 30% to compensate for the uncertainties associated with the overall data package. A

[1] VICH GL48: Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: marker residue depletion studies to establish product withdrawal periods (EMA/CVMP/VICH/463199/2009) - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/04/WC500105052.pdf
[2] CVMP guideline on injection site residues (EMEA/CVMP/542/03) - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004429.pdf

withdrawal period of 70 days for cattle meat and offal is therefore recommended for injectable veterinary medicinal products containing doramectin.

Milk - time span between treatment of non-lactating animals and calving:

One non-GLP residue depletion study in lactating dairy cattle and two GLP residue depletion studies in non-lactating cattle were available for evaluation by the CVMP. Based on these data it was considered that a time span of 2 months between treatment and calving in non-lactating cattle would ensure safe residue levels in milk following administration of injectable products containing doramectin at the recommended dose.

Sheep

Meat and offal:

Two studies in sheep were provided. The injection site was the tissue in which the marker residue persisted for longest and was consequently the tissue for the withdrawal period derivation. Using the data from a pivotal study with Dectomax Incjectable a withdrawal period of 65 days could be derived. However, in view of the fact that the study was not performed in line with standards in place today, it was considered that the withdrawal period of 70 days recommended in the 2005 referral procedure under Article 34 of Directive 2001/82/EC for Dectomax 1% injectable solution for cattle and sheep (EMEA/V/A/009) should be maintained. This withdrawal period (70 days) is recommended for both doses in sheep (i.e. 200 µg/kg bw and 300 µg/kg bw) approved for intramuscular administration.

Milk - Time span between treatment of non-lactating animals and lambing:

As indicated above 3 µg/l is considered to represent a safe level of doramectin in milk.

One GLP residue depletion study in non-lactating sheep was available for evaluation by the CVMP, as well as two published studies in lactating sheep.

Based on the data available it was considered that the existing warning sentence in the product information (*Do not use in dry dairy ewes including pregnant dairy ewes within 70 days prior to lambing*) is conservative and gives sufficient assurance in terms of consumer safety following administration at the highest recommended dose of 300 µg/kg bw.

Pigs

Meat and offal:

Three residue depletion studies were evaluated by the CVMP. The injection site was the tissue with the slowest rate of residue depletion in all studies and therefore data from the injection site provide the basis from which the withdrawal period is derived. From the pivotal study representative of the worst case a withdrawal period of 60 days could be calculated. However, in view of the fact that sampling of the injection site was not in line with standards in place today and in view of the relatively large extrapolation from the last time point of slaughter (35 days) to the calculated withdrawal period, it was considered appropriate to apply a 30% safety span to the calculated withdrawal period of 60 days.
A withdrawal period of 77 days is therefore recommended for pig meat and offal.

Reindeer

Meat and offal:

One GLP residue study (1998) in reindeer was available for evaluation by the CVMP but could not be used to determine the withdrawal period as there were only two slaughter time points, the number of animals/group was relatively small and at the last time point one of the injection site samples contained residues above the MRL for muscle (40 µg/kg).

However, as reindeer is considered to be a minor species (with cattle being the corresponding major species) the possibility of extrapolating a withdrawal period from cattle was considered appropriate. The CVMP guideline on safety and residue data requirements for veterinary medicinal products intended for minor uses or minor species (EMEA/CVMP/SWP/66781/2005)[3] suggests that, in the absence of any data in the minor species a withdrawal period of 1.5 times that approved for the major species can be considered. This would yield a withdrawal period of 105 days for reindeer. As some data in reindeer were available it was considered appropriate to refine this estimate.

Based on data in cattle a terminal half-life of 7 days was conservatively estimated for doramectin residues at the injection site in reindeer. The available study in reindeer provided residue data at the injection site at 10 days after product administration. Considering the highest residue levels seen at 10 days and taking account of the estimated half it was calculated that by 66 days after product administration doramectin levels at the injection site would be present at levels below half the MRL. The figure of 66 days was rounded up to 70 days, to bring it into line with the figure recommended for cattle. A withdrawal period of 70 days is therefore recommended for reindeer meat and offal.

Milk - Time span between treatment of non-lactating animals and parturition:

No studies in lactating or non-lactating doe were provided. For cattle it was considered that the standard 2 month period between treatment and calving could be accepted. This period was also considered sufficiently conservative for use in reindeer.

Environmental risk assessment

The marketing authorisation holders provided a 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 aquatic invertebrates (following direct excretion scenario) and dung fauna. This conclusion applies to both the pour-on and to the injectable products. According to the VICH Guideline 38 Phase II, a Tier B assessment is required. In the first case, the risk to aquatic invertebrates 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.

In respect to the environmental impact for the use of the solution for injection in sheep the CVMP considered that according to the CVMP guidance, only cattle are concerned with the scenario “direct excretion into surface water”. Therefore, this scenario was not considered for sheep. For the run-off scenario, as the highest PECcattle (0.84 µg/kg) is higher than the highest PECsheep (0.48 µg/kg), the conclusion from the cattle can be extrapolated to sheep. Aquatic organisms were considered not at risk from doramectin entering surface water bodies via run-off from use in sheep.

For the dung fauna, the results of the Tier A assessment showed a very high RQ indicating an unacceptable acute risk. This conclusion applies to both the pour-on and to the injectable products. 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), but nevertheless indicates doramectin being potentially bioaccumulative. The current data package does not allow the assessment of bioaccumulation and therefore, bioaccumulation of doramectin cannot be ruled out.

[3] CVMP guideline on safety and residue data requirements for veterinary medicinal products intended for minor uses or minor species (EMEA/CVMP/SWP/66781/2005) - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004581.pdf

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 for the pour-on veterinary medicinal products containing doramectin:

The following text should be included in SPC section 4.5 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 SPC section 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.

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 for the injectable veterinary medicinal products containing doramectin:

The following text should be included in SPC section 4.5 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 and sheep.

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 SPC section 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.

3. Benefit-Risk Assessment

Consumer safety

Having considered the residue depletion data submitted by the applicants/marketing authorisation holders for the injectable veterinary medicinal products containing doramectin, withdrawal periods of 70 days for cattle meat and offal, 70 days for sheep meat and offal, 77 days for pig meat and offal and 70 days for reindeer meat and offal were considered safe. Furthermore the evaluation concludes that use of injectable and pour-on veterinary medicinal products containing doramectin during the non-lactating period could lead to residue levels in milk resulting in consumer exposure over the acceptable daily intake. The Committee therefore calculated a minimum time spans of 2 months for cattle and

reindeer and 70 days for sheep that should elapse between administration of these doramectin containing products and calving or lambing.

Environmental safety

In addition to the fact that the available data do not allow to rule out bioaccumulation of doramectin, a risk to aquatic organisms 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 when the products are used in accordance with the recommended posology. Therefore, risk mitigation measures are considered necessary to be included in the product information as specified above.

Conclusion on the benefit-risk balance

The benefit-risk evaluation for the products concerned is deemed to be positive provided that (i) for the injectable products the withdrawal periods for meat and offal are set for cattle at 70 days, for sheep at 70 days, for pigs at 77 days and for reindeer at 70 days, (ii) for the injectable and pour-on products the following periods with regard to milk are set as the minimum time spans that must elapse between treatment and calving/lambing: 2 months for cattle and reindeer and 70 days for sheep and (iii) for the injectable and pour-on products risk mitigation measures are added to the product information regarding risk to aquatic organisms and dung fauna.

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

Whereas:

- On the basis of the residue depletion data in cattle, sheep, pigs and reindeer submitted by the applicants/marketing authorisation holders for the injectable veterinary medicinal products containing doramectin, the CVMP considered that withdrawal periods of 70 days for cattle meat and offal, 70 days for sheep meat and offal, 77 days for pig meat and offal and 70 days for reindeer meat and offal were safe;
- On the basis of the residue depletion data in cattle and sheep submitted by the applicants/marketing authorisation holders for the injectable veterinary medicinal products containing doramectin, and in the absence of maximum residue limits for doramectin in milk, the CVMP considered the minimum time spans of 2 months for cattle and reindeer and 70 days for sheep must elapse between administration of these doramectin containing products and calving or lambing;
- On the basis of the environmental risk assessment data submitted by the applicants/marketing authorisation holders for the injectable and pour-on veterinary medicinal products containing doramectin, the CVMP 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 measure should be applied;
- the CVMP considered that the overall benefit-risk balance is positive for the injectable and pour-on veterinary medicinal products containing doramectin, subject to amendments in the product information;

the CVMP has recommended variations of the marketing authorisations for all injectable and pour-on veterinary medicinal products containing doramectin that are intended for use in mammalian food producing species (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 leaflets

Amendments in the relevant sections of the product information for injectable veterinary medicinal products containing doramectin:

Summary of Product Characteristics

Add, to all products:

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 and sheep.

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

Amend where applicable:

4.11 Withdrawal period(s)

Cattle:

Meat and offal: 70 days

Not permitted for use in lactating animals producing milk for human consumption.

Do not use in pregnant cows or heifers, which are intended to produce milk for human consumption, within 2 months of expected parturition.

Sheep:

Meat and offal: 70 days

Not permitted for use in lactating animals producing milk for human consumption.

Do not use in pregnant ewes, which are intended to produce milk for human consumption, within 70 days of expected parturition.

Pigs:

Meat and offal: 77 days

Reindeer:

Meat and offal: 70 days

Not permitted for use in lactating animals producing milk for human consumption.

Do not use in pregnant does, which are intended to produce milk for human consumption, within 2 months of expected parturition.

Add, to all products:

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:

Amend where applicable:

8. WITHDRAWAL PERIOD

Cattle:

Meat and offal: 70 days

Not permitted for use in lactating animals producing milk for human consumption.

Do not use in pregnant cows or heifers, which are intended to produce milk for human consumption, within 2 months of expected parturition.

Sheep:

Meat and offal: 70 days

Not permitted for use in lactating animals producing milk for human consumption.

Do not use in pregnant ewes, which are intended to produce milk for human consumption, within 70 days of expected parturition.

Pigs:

Meat and offal: 77 days

Reindeer:

Meat and offal: 70 days

Not permitted for use in lactating animals producing milk for human consumption.

Do not use in pregnant does, which are intended to produce milk for human consumption, within 2 months of expected parturition.

Add, to all products:

9. SPECIAL WARNING(S), 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 and sheep.

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:

Amend where applicable:

10. WITHDRAWAL PERIOD

Cattle:

Meat and offal: 70 days

Not permitted for use in lactating animals producing milk for human consumption.

Do not use in pregnant cows or heifers, which are intended to produce milk for human consumption, within 2 months of expected parturition.

Sheep:

Meat and offal: 70 days

Not permitted for use in lactating animals producing milk for human consumption.

Do not use in pregnant ewes, which are intended to produce milk for human consumption, within 70 days of expected parturition.

Pigs:

Meat and offal: 77 days

Reindeer:

Meat and offal: 70 days

Not permitted for use in lactating animals producing milk for human consumption.

Do not use in pregnant does, which are intended to produce milk for human consumption, within 2 months of expected parturition.

Add, to all products:

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 and sheep.

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

……..

Amendments in the relevant sections of the product information for pour-on veterinary medicinal products containing doramectin:

Summary of Product Characteristics

Add, to all products:

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 reduced by keeping treated cattle away from water bodies for two to five weeks after treatment.

Add, to all products:

4.11 Withdrawal period(s)

Cattle:

……..

Not permitted for use in lactating animals producing milk for human consumption.

Do not use in pregnant cows or heifers, which are intended to produce milk for human consumption, within 2 months of expected parturition.

Add, to all products:

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:

Add, to all products:

8. WITHDRAWAL PERIOD

Cattle:

……..

Not permitted for use in lactating animals producing milk for human consumption.

Do not use in pregnant cows or heifers, which are intended to produce milk for human consumption, within 2 months of expected parturition.

Add, to all products:

9. SPECIAL WARNING(S), 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:

Add, to all products:

10. WITHDRAWAL PERIOD

Cattle:

……

Not permitted for use in lactating animals producing milk for human consumption.

Do not use in pregnant cows or heifers, which are intended to produce milk for human consumption, within 2 months of expected parturition.

Add, to all products:

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.

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