27 July 2018
EMA/CVMP/607398/2017
Committee for Medicinal Products for Veterinary Use

European public MRL assessment report (EPMAR)

Eprinomectin (Fin fish; extrapolation to horses and rabbits)

On 16 May 2018 the European Commission adopted a Regulation[1] establishing maximum residue limits for eprinomectin in fin fish, *Equidae* and rabbits, valid throughout the European Union. These maximum residue limits were based on the favourable opinion and the assessment report adopted by the Committee for Medicinal Products for Veterinary Use.

Eprinomectin, applied cutaneously, is used in cattle and sheep for the treatment and control of internal and external parasites.

Maximum residue limits were originally established for eprinomectin in bovine species[2]. Subsequently, maximum residue limits were established for eprinomectin in all ruminants[3].

Farmacologia en Aquacultura Veterinaria FAV S.A. submitted to the European Medicines Agency an application for the extension of maximum residue limits on 16 May 2017.

Based on the data in the dossier, the Committee for Medicinal Products for Veterinary Use recommended, on 9 November 2017, the extension of maximum residue limits for eprinomectin to fin fish and the extrapolation of the MRLs established in ruminants to *Equidae* and rabbits.

Subsequently the Commission recommended on 29 March 2018 that maximum residue limits in fin fish, *Equidae* and rabbits are established. This recommendation was confirmed on 19 April 2018 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 16 May 2018.

[1] Commission Implementing Regulation (EU) No 2018/722, O.J. L 122, of 17 May 2018
[2] Commission Regulation (EC) No 17/97, O.J. L 5, of 08 January 1997
[3] Commission Implementing Regulation (EU) No 2016/885, O.J. L 148, of 04 June 2016

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Summary of the scientific discussion for the establishment of MRLs

Substance name:	Eprinomectin
Therapeutic class:	Antiparasitic agents / Agents (acting) against endo- and ectoparasites
Procedure number:	EMEA/V/MRL/003141/EXTN/0004
Applicant:	Farmacologia en Aquacultura Veterinaria FAV S.A.
Target species requested:	Salmonidae and other fin fish
Intended therapeutic indication:	Control of sea lice
Route(s) of administration:	Bath (immersion)

1. Introduction

Eprinomectin is a semi-synthetic compound of the avermectin family. Eprinomectin is a mixture of two homologues, eprinomectin B1a (90%) and eprinomectin B1b (10%), which differ by a methylene group in the C25-position.

Eprinomectin, applied cutaneously, is used in cattle and sheep for the treatment and control of internal and external parasites.

The intended use in salmon and other fin fish is for the control of sea lice following application by immersion.

Eprinomectin is not used in human medicine.

Eprinomectin was previously assessed by the CVMP and a toxicological ADI of 5 µg/kg bw, *i.e* 300 µg/person, established.

Currently, eprinomectin is included in Commission Regulation (EU) No 37/2010 of 22 December 2009 in accordance with the table below:

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Eprinomectin	Eprinomectin B1a	All ruminants	50 µg/kg 250 µg/kg 1500 µg/kg 300 µg/kg 20 µg/kg	Muscle Fat Liver Kidney Milk	NO ENTRY	Antiparasitic agents/Agents acting against endo- and ectoparasites

2. Scientific risk assessment

2.1. Safety assessment

The CVMP has previously assessed the consumer safety of eprinomectin and established an ADI of 5 µg/kg bw, i.e. 300 µg/person based on the NOEL of 1.0 mg/kg bw for mydriasis and focal neuronal degeneration observed in a 53-week toxicity study in dogs and applying a safety factor of 200 (a safety

factor of 200 was used for all avermectins when setting an ADI based on mydriasis in dogs; this was done to account for the uncertain sensitivity of the test system used to assess the neurotoxicity, in absence of data in the CF1 mouse strain). Therefore, no further assessment regarding the consumer safety of the substance is required for the purpose of this extension application.

2.2. Residues assessment

2.2.1. Pharmacokinetics in target species

No pharmacokinetic data in fish were provided for this extension application. Pharmacokinetic data in bovine and ovine species were previously assessed by the CVMP, with the bovine data reported in the 1996 Summary Report recommending establishment of MRLs in cattle (EMEA/MRL/114/96-FINAL) and the 1998 Summary Report recommending modification of the ADI and MRLs for cattle (EMEA/MRL/520/98-FINAL) and ovine data reported in the 2015 European Public MRL Assessment Report (EPMAR) recommending establishment of MRLs in all ruminants (EMA/CVMP/779112/2015). These are briefly summarised below.

Following a single cutaneous application of 0.5 mg/kg bw of eprinomectin plasma eprinomectin B1a levels were seen to peak on days 2 and 3 after application in adult bovines and between days 4 to 8 in young non-ruminating calves.

Following a single cutaneous application eprinomectin containing radiolabelled eprinomecting B1a to cows at a dose of 0.750 mg/kg bw, plasma radioactivity was seen to peak between days 1 and 5 after application. The major residue was eprinomectin B1a, representing approximately 90% of total residues.

Eprinomectin was highly bound (greater than 99%) to cattle plasma proteins. The fraction of eprinomectin B1a absorbed after the application of a pour-on formulation was found to be 29%. After a cutaneous application of 0.500 mg/kg bw of radiolabelled eprinomectin, 54% of the radiolabelled dose remained on the hide. Eighty nine percent of the total extractable radioactivity was non-metabolised eprinomectin B1a.

Plasma kinetics in sheep have been studied in two Good Laboratory Practice (GLP) studies in which eprinomectin was applied cutaneously (as a pour-on) at a dose of 0.5 or 1.0 mg/kg bw. Plasma concentrations of eprinomectin B1a peaked at a median Tmax of 48 hours in both studies.

In addition, an *in vitro* comparative metabolism study using cattle, sheep and goat liver microsomes was provided. This study indicates that metabolism of eprinomectin by cattle, sheep and goat liver microsome preparations was very limited. Approximately 80% of eprinomectin remained unchanged in the incubation solution. Multiple metabolites were observed, but none represented more than 6.6% of the total residues.

Finally, a number of published reports providing information on the pharmacokinetic parameters of eprinomectin in cattle, sheep and goat plasma and milk are available.

Overall, the available data indicate that the pharmacokinetic behaviour of eprinomectin is similar in the different species investigated and that metabolism of the substance is limited in these species.

2.2.2. Residue depletion studies

No residue data in fish were provided for this extension application. Residue data in bovine and ovine species were previously assessed by the CVMP, with the bovine data reported in the 1996 Summary Report recommending establishment of MRLs in cattle (EMEA/MRL/114/96-FINAL) and the 1998

Summary Report recommending modification of the ADI and MRLs for cattle (EMEA/MRL/520/98-FINAL) and ovine data reported in the 2015 EPMAR recommending establishment of MRLs in all ruminants (EMA/CVMP/779112/2015). These are briefly summarised below.

A number of radiometric studies of residues of eprinomectin in cattle tissues and milk have been evaluated. These used cutaneous application of eprinomectin applied at doses of 0.500 mg/kg bw and 0.750 mg/kg bw in lactating and non-lactating cattle as well as in pregnant dairy cows. The data show that eprinomectin B1a was the major residue in all tissues, accounting for 75, 100, 80 and 78% of total radioactivity in muscle, fat, liver and kidney respectively, at 21 days after treatment. The homologue eprinomectin B1b was shown to represent up to 9.3% of total radioactivity, with individual minor metabolites each contributing less than 4% of total residues in tissues. Similarly, eprinomectin B1a was the major residue in milk, accounting for 80-85.6% of the total extractable radioactivity, with a number of minor metabolites contributing up to 2.5% of total residues in milk.

The half-lives for depletion of radioactivity in liver, kidney, fat and muscle were 8.6, 8.1, 7.9 and 7.8 days respectively. At the application site the depletion half-life was longer (36.1 days).

Non-radiolabelled residue depletion studies in cattle using cutaneous application have also been previously evaluated and report residue depletion for up to 44 days. These have used doses of 0.50 mg/kg bw applied to lactating cows, non-lactating adult cattle and young non-ruminating calves. Eprinomectin B1a was detected in all tissues and milk. In tissues the highest residue levels were observed in liver followed by kidney followed by fat and finally muscle.

Two non-radiolabelled residue depletion studies have been performed in sheep following a single cutaneous (pour-on) application of eprinomectin at a dose of 1 mg/kg bw. One study examined residues in tissues while the other examined residues in milk (over a 10-day period). In tissues the highest residue levels were observed in liver, and residue depletion was slowest in kidney. The peak concentration in milk was observed at the 4th milking after treatment. The residue assayed in these studies was eprinomectin B1a, which was detected in all tissues examined and in milk.

Selection of marker residue and ratio of marker to total residues

The residue data in cattle demonstrate that eprinomectin B1a is the major metabolite in cattle tissues and milk and is therefore a suitable marker residue. The data allow establishment of the following ratios of marker to total residues: 0.75 for muscle, 1.0 for fat, 0.80 for liver, 0.78 for kidney and 0.80 for milk.

As indicated in the CVMP's 2016 EPMAR recommending establishment of MRLs for eprinomectin in all ruminants, available data clearly demonstrate similarities in pharmacokinetics in cattle, sheep, goats and rats. Metabolism of eprinomectin was very limited in all species examined, with eprinomectin B1a being the predominant residue in all tissues and milk. Eprinomectin B1a has therefore been accepted as an appropriate marker residue for use in monitoring residues of eprinomectin in all ruminants and the ratios of marker to total residues established for bovine species have been accepted for use in all ruminants.

As indicated in the CVMP note for guidance on the establishment of maximum residue limits for *Salmonidae* and other fin fish (EMEA/CVMP/153b/97-FINAL) metabolism in fin fish is generally less complex than in mammalian species. In line with the note for guidance, as eprinomectin is poorly metabolised in major mammalian species, eprinomectin B1a is considered an appropriate marker residue for use in monitoring residues of eprinomectin in fin fish.

2.2.3. Monitoring or exposure data

No monitoring or exposure data other than that described elsewhere in this report are available.

2.2.4. Analytical method for monitoring of residues

Analytical methods for measurement of residues of the marker residue, eprinomectin B1a, in bovine, ovine and caprine tissues and in bovine and ovine milk have been previously evaluated and accepted as validated, as reported in the 1996 CVMP Summary Report recommending establishment of MRLs in cattle (EMEA/MRL/114/96-FINAL) and the 2016 CVMP EPMAR recommending establishment of MRLs in all ruminants (EMA/CVMP/779112/2015).

A new HPLC-FD method for the determination of residues of eprinomectin in muscle and skin in *Salmonidae* and other fin fish has been developed. The method is based on eprinomectin B1a as the marker residue, as for the currently approved MRL for bovine muscle. The method was sufficiently described according to an internationally recognised format closely resembling ISO 78/2, and adequately validated in muscle and skin from salmon. The limit of quantification was established at 10 µg/kg.

It was concluded that a suitable analytical method for monitoring the levels of the residues of eprinomectin in muscle and skin in fin fish is available. The relevant European Reference Laboratory (EURL) has reviewed the analytical method and is in agreement with this conclusion.

2.2.5. Findings of EU or international scientific bodies

No evaluations by other international committees were available with regard to fish species. However, in 2003 Codex Alimentarius, following the JECFA (Joint FAO/WHO Expert Committee on Food Additives) recommendations, adopted the following MRLs for cattle: 100 µg/kg for muscle; 250 µg/kg for fat; 2000 µg/kg for liver; 300 µg/kg for kidney and 20 µg/L for milk. JECFA recommended eprinomectin B1a as marker residue.

3. Risk management considerations

3.1. Potential effects on the microorganisms used for industrial food processing

Microbiological effects are not expected for this type of substance and therefore no data were required.

3.2. Other relevant risk management considerations for the establishment of maximum residue limits

No relevant factors were identified for consideration of the risk management recommendations.

3.3. Elaboration of MRLs

For the evaluation of this application for the extension of MRLs for eprinomectin to *Salmonidae* and other fin fish the CVMP Note for guidance on the establishment of maximum residue limits for *Salmonidae* and other fin fish (EMEA/CVMP/153b/97-FINAL) was taken into account. As indicated in the note for guidance metabolism in fin fish is generally less complex than in mammalian species. The note for guidance indicates that where an MRL has been established for a substance in muscle in a major mammalian species it may be applied to *Salmonidae* and other fin fish.

In line with the above note for guidance, and considering that available data indicate that eprinomectin is poorly metabolised and that the established marker residue, eprinomectin B1a, is a component of the parent substance, the MRL established for ruminant muscle (50 µg/kg) can be safely applied to fin fish (where the relevant tissue is muscle and skin in natural proportions).

3.4. Considerations on possible extrapolation of MRLs

In line with Article 5 of Regulation (EC) No 470/2009, the CVMP considered the possibility of extrapolating the maximum residue limits established in ruminants to other food-producing species and food commodities. Taking into account the provisions laid down in Regulation (EU) 2017/880, the recommendations on extrapolation are justified as follows:

Animal species/ foodstuffs	Extrapolation possible (Yes/No)	Justification
Pigs	No	No data on pharmacokinetics or residues in pigs are available. As pigs are unrelated to cattle and sheep, the species for which data are available, and in line with Commission Regulation (EU) 2017/880, MRLs cannot be extrapolated to pigs without supporting data demonstrating similarity of metabolism.
Poultry (including eggs)	No	No data on pharmacokinetics or residues in poultry are available. As poultry are unrelated to cattle and sheep, the species for which data are available, and in line with Commission Regulation (EU) 2017/880, MRLs cannot be extrapolated to poultry without supporting data demonstrating similarity of metabolism.
Horses	Yes	No data on pharmacokinetics or residues in horses are available. However, horses are a minor species, and previously reviewed data relating to rats and cattle suggest that the metabolism is similar and equally limited in monogastric and polygastric mammals. Thus, in line with Commission Regulation (EU) 2017/880, extrapolation of cattle MRLs to horses can be accepted.
Rabbits	Yes	No data on pharmacokinetics or residues in rabbits are available. However, rabbits are a minor species, and previously reviewed data relating to rats and cattle suggest that metabolism is similar and equally limited in monogastric and polygastric mammals. Thus, in line with Commission Regulation (EU) 2017/880, extrapolation of cattle MRLs to rabbits can be accepted.
Honey	No	No data on residues in honey are available. In the absence of such data, and in line with Commission Regulation (EU) 2017/880, MRLs cannot be extrapolated to honey.

3.5. Conclusions and recommendation for the establishment of maximum residue limits

Having considered that:

- the toxicological ADI of 5 µg/kg bw (*i.e* 300 µg/person) was established as the overall ADI for eprinomectin;
- eprinomectin is poorly metabolised in species for which data are available;
- the marker residue established in ruminants, eprinomectin B1a, is a component of the parent substance and can be retained as the marker residue for fin fish;
- a validated analytical method for the monitoring of residues of eprinomectin in edible fin fish tissues is available;
- although it was not specifically demonstrated, the analytical methods available for monitoring of residues in bovine and ovine tissues are expected to be basically applicable for monitoring of residues in tissues of horses and rabbits,

the CVMP recommends the extension of the maximum residue limits established for eprinomectin in ruminant muscle to muscle (muscle and skin in natural proportions) of fin fish. Furthermore, and with reference to Article 5 of Regulation (EC) No 470/2009, the CVMP considers that the MRLs established in ruminant species can be extrapolated to horses and rabbits in accordance with the following table:

Pharmaco-logically active substance	**Marker residue**	**Animal species**	**MRLs**	**Target tissues**	**Other provisions**	**Therapeutic classification**
Eprinomectin	Eprinomectin B1a	All ruminants, *Equidae*	50 µg/kg 250 µg/kg 1500 µg/kg 300 µg/kg 20 µg/kg	Muscle Fat Liver Kidney Milk	No entry	Antiparasitic agents/Agents acting against endo- and ectoparasites
		Fin fish	50 µg/kg	Muscle and skin in natural proportions		
		Rabbits	50 µg/kg 250 µg/kg 1500 µg/kg 300 µg/kg	Muscle Fat Liver Kidney		

4. Background information on the procedure

Submission of the dossier

Steps taken for assessment of the substance

Application validated:	7 June 2017
Clock started:	8 June 2017
Opinion adopted:	9 November 2017