1 July 2016
EMA/CVMP/779158/2015
Committee for Medicinal Products for Veterinary Use

European public MRL assessment report (EPMAR)

Eprinomectin (all ruminants) – after provisional maximum residue limits (MRLs)

On 3 June 2016 the European Commission adopted a Regulation[1] establishing maximum residue limits for eprinomectin in all ruminants, 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 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. Subsequently provisional MRLs were established for caprine and ovine species with an expiry date of 30 June 2016[2].

Merial submitted the responses to the list of questions further to the establishment of the provisional MRLs to the European Medicines Agency, on 28 August 2015. Based on the data in the dossier, the Committee for Medicinal Products for Veterinary Use recommended on 10 December 2015 the establishment of final maximum residue limits for eprinomectin in ovine and caprine species. Furthermore, the Committee agreed to extrapolate its recommendation to all ruminants.

Subsequently the Commission recommended on 20 April 2016 that maximum residue limits in all ruminants are established. This recommendation was confirmed on 11 May 2016 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 3 July 2016.

[1] Commission Implementing Regulation (EU) No 2016/885, O.J. L 148, of 04 June 2016
[2] Commission Implementing Regulation (EU) No 2014/1390, O.J. L369/65 of 19.12.2014

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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:	EU/10/173/MER
Applicant:	Merial
Applicant's target species:	Ovine species
Intended therapeutic indication:	Treatment and control of internal parasites sensitive to eprinomectin and ectoparasites
Route(s) of administration:	Cutaneous use (pour-on)

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 is used in cattle and sheep for the treatment and control of internal and external parasites. The recommended dosage in cattle is a single dose of 0.5 mg/kg bw (0.1 ml/10 kg bw) applied cutaneously along the midline of the animal's back. In sheep the recommended dose is 1 mg/kg bw applied cutaneously as a pour-on.

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.

Eprinomectin is included in Commission Regulation (EU) No 37/2010[3] as indicated in the table below.

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Eprinomectin	Eprinomectin B1a	Bovine	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
		Ovine, caprine	50 µg/kg 250 µg/kg 1500 µg/kg 300 µg/kg 20 µg/kg	Muscle Fat Liver Kidney Milk	Provisional maximum residue limits expire on 30 June 2016	

Provisional maximum residue limits were recommended for eprinomectin as issues relating to the analytical method proposed for monitoring of residues remained to be resolved. Further to the establishment of provisional MRLs for eprinomectin in ovine and caprine species, the applicant submitted additional data on the validation of the analytical method.

[3] O.J. L369/65 of 19.12.2014

The scientific assessment previously carried out by the Committee leading to the recommendation for the establishment of provisional MRLs in ovine and caprine species is reported in the paragraphs below. Section 2.2.4 on the analytical method for monitoring of residues has been updated to take account of the additional information provided by the applicant following the recommendation for the establishment of provisional MRLs, and the considerations, conclusions and recommendations presented in section 3 have been modified accordingly.

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

Two original Good Laboratory Practice (GLP) plasma kinetic studies of eprinomectin in sheep were provided following cutaneous application (as a pour-on) of a commercial eprinomectin-containing preparation. In addition, an *in vitro* comparative metabolism study using cattle, sheep and goat liver microsomes was provided. Finally, a number of published reports providing information on the pharmacokinetic parameters of eprinomectin in cattle, sheep and goat plasma and milk were submitted.

The two original GLP studies were performed in sheep (using 8 animals and 9 animals respectively) following cutaneous (pour-on) application of a commercial eprinomectin-containing preparation at 0.5 or 1 mg of eprinomectin/kg bw. Plasma concentrations were measured, but no kinetic analysis was performed.

Following 0.5 mg/kg bw of cutaneous application, the mean maximal eprinomectin B1a concentrations in plasma (Cmax) was 2.106 ng/ml (range 1.634 to 3.095 ng/ml), observed at a median Tmax of 48 hours (range 32 to 104 hours) following administration. Following 1 mg/kg bw of cutaneous application, the mean Cmax was 3.720 ng/ml (range 1.889 to 6.178 ng/ml), observed at a median Tmax of 48 hours (range 24 to 72 hours) after administration.

From the *in vitro* metabolism study it can be concluded 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.

The published studies provided information on pharmacokinetic parameters (such as AUC, Cmax, half-life) in cattle, sheep and goat plasma and milk, primarily following cutaneous (pour-on) application.

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

Two GLP non-radiolabelled residue depletion studies were performed in sheep (20 animals were dosed in each study) following a single cutaneous (pour-on) application of a commercial eprinomectin-containing product at a dose of 1 mg/kg bw. One study examined residues in tissues (4 animals were sacrificed at 5 time points) while the other examined residues in milk (over a 10-day period). The residue levels were assayed by a validated HPLC method with fluorescence detection.

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 residue depletion studies was eprinomectin B1a, the marker residue established for cattle. Eprinomectin B1a was detected in all tissues examined and in milk.

Selection of marker residue and ratio of marker to total residues

The Committee noted that the guidance provided in the CVMP Note for guidance on the risk analysis approach for residues of veterinary medicinal products in food of animal origin (EMEA/CVMP/187/00-FINAL) indicates that, for major species a full package of residue data (i.e. including a residue study using the radiolabelled substance) should be provided in order to allow the determination of maximum residue limits. However, while no studies with radiolabelled eprinomectin in sheep (which is a major species) have been performed, the available data clearly demonstrate similarities in pharmacokinetics in cattle, sheep, goats and rats, and indicate that the metabolism of eprinomectin in sheep (as in cattle) is very limited. Furthermore, the residue depletion studies successfully monitored the depletion of eprinomectin B1a in sheep tissues and milk. It is therefore accepted that eprinomectin B1a is an appropriate marker residue for use in monitoring residues of eprinomectin in ovine species and that the ratios of marker to total residues established for bovine species (0.75 for muscle, 1.0 for fat, 0.80 for liver, 0.78 for kidney and 0.80 for milk) can be safely applied also to ovine species.

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

Three analytical methods using HPLC with fluorescence detection were provided, one proposed for monitoring eprinomectin B1a in ovine tissues (muscle, kidney, liver and fat), another proposed for monitoring of eprinomectin B1a in ovine milk and a third proposed for monitoring of eprinomectin B1a residues in edible caprine tissues. The methods (which are different to those presented for monitoring of residues in bovine species) are fully described according to the internationally recognised standard layout ISO 78/2.

The method proposed for monitoring of residues in ovine tissues was validated across a range including 5 to 100 µg/kg, 10 to 500 µg/kg, 50 to 3000 µg/kg and 25 to 600 µg/kg for muscle, fat, liver and kidney, respectively.

The method proposed for monitoring of residues in edible caprine tissues was validated across a range including 10 to 100 µg/kg, 10 to 500 µg/kg, 10 to 600 µg/kg and 10 to 3000 µg/kg for muscle, fat, kidney and liver, respectively.

The method proposed for monitoring of residues in ovine milk was validated across a range including 1 µg/kg to 60 µg/kg, which is acceptable. The method has also been demonstrated to be applicable for caprine milk.

The relevant European Reference Laboratory has reviewed the proposed analytical methods and is in agreement with the above conclusions.

2.2.5. Findings of EU or international scientific bodies

No evaluations by other international committees were available with regard to ovine 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 established an ADI of 600 µg/person (10 µg/kg bw) and 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

Based on data indicating that the pharmacokinetic behaviour of eprinomectin is similar in sheep and cattle and that eprinomectin is poorly metabolised in both of these species, the CVMP concluded that the MRLs established for bovine species can be safely applied also for ovine species.

Therefore, the following MRLs were recommended for ovine species:

- Muscle: 50 µg/kg
- Fat: 250 µg/kg
- Liver: 1500 µg/kg
- Kidney: 300 µg/kg
- Milk: 20 µg/kg

Calculation of theoretical daily intake of residues

Detailed calculation of theoretical daily intake of residues from ovine tissues and milk based on the proposed MRLs for ovine tissues and milk:

Edible tissue or products	Daily consumption (kg)	MRL proposal (µg/kg)	Ratio of the marker/total residue	Amount per edible tissue or product (µg)
Muscle	0.30	50	0.75	20.0

Edible tissue or products	Daily consumption (kg)	MRL proposal (µg/kg)	Ratio of the marker/total residue	Amount per edible tissue or product (µg)
Fat	0.05	250	1	12.5
Liver	0.10	1500	0.8	187.5
Kidney	0.05	300	0.78	19.0
Milk	1.50	20	0.8	37.5
Total				276.5
ADI (µg/person)				300

Based on the recommended maximum residue limits the theoretical maximum daily intake of residues from ovine tissues and milk represents approximately 92% of the ADI.

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 recommended for eprinomectin to other food producing species and foodstuffs. Taking into account the current scientific knowledge the recommendations on extrapolation are justified as follows:

Animal species/ foodstuffs	Extrapolation possible (Yes/No)	Justification
All ruminants (including milk)	Yes	Existing data indicate that the pattern of metabolites seen in rats, cattle, sheep and goats is similar. The assumption can therefore be made that eprinomectin B1a will be the predominant residue in all ruminants and consequently it is accepted as the marker residue for all ruminants rather than for just cattle and sheep. The available data demonstrate similar and very limited metabolism cattle, sheep and goats (as well as rats). It can therefore be concluded that the ratios of marker to total residues retained for sheep, which are the same as those accepted for cattle, can also be accepted for other ruminants. Therefore the MRL values established for cattle and recommended for sheep can also be recommended for other ruminants without compromising the safety of the consumer. A validated analytical method is available for the monitoring of residues in caprine tissues. The analytical method proposed for the monitoring of residues in ovine milk has been demonstrated to be applicable also for caprine milk. No data are available to demonstrate that the available analytical methods are applicable for monitoring of residues in other ruminant species but there is no reason for believing that they would not be.
Pigs	No	No pharmacokinetic or residue depletion data were available for pigs. As pigs meat is consumed on a regular basis and in

		large quantities across the EU, species specific data are considered necessary in order to quantify the possible impact on consumer safety of exposure to residues. No analytical method for monitoring of residues in pig tissues was available for evaluation.
Poultry (including eggs)	No	No pharmacokinetic or residue depletion data were available for chicken. As chicken meat is consumed on a regular basis and in large quantities across the EU, species specific data are considered necessary in order to quantify the possible impact on consumer safety of exposure to residues. No analytical method for monitoring of residues in chicken tissues and eggs was available for evaluation.
Horses	No	Although existing data indicate that the pattern of metabolites seen in rats, cattle, sheep and goats is similar and it could be expected that the predominant metabolite in these species would also be the predominant metabolite in horses, no information was available to confirm the marker residue in horses. No data are available to demonstrate that the analytical method proposed for monitoring of residues is applicable for monitoring of residues in horse tissues.
Rabbits	No	Although existing data indicate that the pattern of metabolites seen in rats, cattle, sheep and goats is similar and it could be expected that the predominant metabolite in these species would also be the predominant metabolite in rabbits, no information was available to confirm the marker residue in rabbits. No data are available to demonstrate that the analytical method proposed for monitoring of residues is applicable for monitoring of residues in rabbits tissues.
Fin fish	No	Metabolism in fin fish is generally less complicated than in cattle and sheep, and given that the marker residue is a component of the parent compound it could be assumed that eprinomectin B1a would also be a suitable marker residue for meat of fin fish. However, no analytical method for monitoring of residues in fin fish was available for evaluation.
Honey	No	Residue depletion in honey does not occur through metabolism and therefore conclusion drawn from data in other food products cannot be extrapolated to honey. Honey specific data are required in order to allow adequate evaluation of the risk to consumer safety posed by residues in honey. No data are available to demonstrate that the analytical method for monitoring of residues is applicable for monitoring

		of residues in 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;
- as the available data indicate that the pharmacokinetic behaviour of eprinomectin in ovine species is similar to that seen in bovine species, with very limited metabolism of eprinomectin, the marker residue retained for bovine tissues and milk (eprinomectin B1a), and the ratios of marker to total residues retained for bovine tissues and milk (0.75 for muscle, 1.0 for fat, 0.80 for liver, 0.78 for kidney and 0.80 for milk) are considered to be applicable also for ovine tissues and milk;
- the maximum residue limits established for bovine species and recommended for ovine species can be extrapolated to caprine species based on data demonstrating similar pharmacokinetic behaviour of eprinomectin in these species, and further, this similar pharmacokinetic profile provides justification for extrapolating the maximum residue limits to all ruminants;
- a validated analytical method for the monitoring of residues of eprinomectin in edible ovine tissues (muscle, liver, kidney and fat) is available;
- a validated analytical method for the monitoring of residues of eprinomectin in edible caprine tissues is available;
- a validated analytical method for the monitoring of residues of eprinomectin in ovine milk is available and has been demonstrated to be applicable also for caprine milk;
- although it was not specifically demonstrated, the analytical methods proposed for monitoring of residues in bovine, ovine and caprine species are expected to be basically applicable for monitoring of residues in other ruminant species;

the Committee, having considered the application and having evaluated the response to the list of questions after the establishment of provisional maximum residue limits, recommends the establishment of maximum residue limits for eprinomectin in ovine and caprine species. Furthermore, and with reference to Article 5 of Regulation (EC) No 470/2009, the Committee agreed to extrapolate the conclusions to all ruminants, 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	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

Based on the recommended maximum residue limits the theoretical maximum daily intake of residues from ruminant tissues and milk represents approximately 92% of the ADI.

4. Background information on the procedure

Submission of the dossier	30 April 2010
Steps taken for assessment of the substance	
Application validated:	18 May 2010
Clock started:	19 May 2010
List of questions adopted:	15 September 2010
Consolidated response to list of questions submitted:	11 November 2011
Clock re-started:	12 November 2011
Oral explanation provided by the applicant	11 April 2012
CVMP opinion on provisional MRLs adopted	13 April 2012
Submission of responses to the List of questions	4 April 2014
CVMP opinion on extension of provisional MRLs adopted:	5 June 2014
Submission of responses to the List of questions	28 August 2015
CVMP opinion adopted (after provisional MRLs):	10 December 2015