



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Veterinary Use (CVMP)

European public MRL assessment report (EPMAR)

Eprinomectin (ovine and caprine species) – provisional MRLs

On 19 December 2014 the European Commission adopted a Regulation¹ establishing provisional maximum residue limits for eprinomectin in caprine and ovine species, valid throughout the European Union. These maximum residue limits were based on the favourable opinion and the assessment report adopted by the CVMP.

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

Maximum residue limits had previously been established for eprinomectin in bovine species. Provisional MRLs for caprine and ovine species had been previously established with an expiry date of 1 July 2014.

Merial submitted the responses to the list of questions further to the establishment of the provisional MRLs to the European Medicines Agency, on 4 April 2014. Following the assessment of the responses to the list of questions the CVMP considered that additional data was needed to complete the validation of the analytical method and recommend, on 5 June 2014, a 2-year extension of the provisional maximum residue limits for eprinomectin in caprine and ovine species.

Subsequently the Commission recommended on 15 October 2014 that provisional maximum residue limits in caprine and ovine species are extended. This recommendation was confirmed on 5 November 2014 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 19 December 2014.

¹ Commission Implementing Regulation (EU) No 116/2013, O.J. L 38, of 09.02.2013



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 |
| 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 37/2010² as indicated in the following table:

² O.J. L38/14 of 09.02.2013

| Pharmacologically 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 1 July 2014 | |

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, the applicant submitted additional data on the validation of the analytical method. 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 maximal eprinomectin B1a concentrations ranged from 1.634 to 3.095 ng/ml (mean was 2.106 ng/ml), observed 48 hours (i.e. median value) following administration (32 to 104 hours). Following 1 mg/kg bw of cutaneous application, the maximal concentrations ranged from 1.889 to 6.178 ng/ml (mean was 3.720 ng/ml), observed 48 hours following administration (24 to 72 hours).

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 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, C_{max}, 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 (EMA/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

Two analytical methods using HPLC with fluorescence detection were provided, one proposed for monitoring eprinomectin B1a residues in ovine tissues (muscle, kidney, liver and fat) and one proposed for monitoring of eprinomectin B1a residues in ovine milk. 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 50 µg/kg, 10 to 250 µg/kg, 50 to 1500 µg/kg and 25 to 300 µg/kg for muscle, fat, liver and kidney, respectively. The upper limits of the validation range are the same as the proposed maximum residue limits in these tissues while Volume 8 of The rules governing medicinal products in the European Union specifies that the range across which the method should be validated must include at least twice the value of the maximum residue limit. Consequently, the method proposed for ovine tissues could not be considered to be fully validated, with the result that provisional MRLs were recommended in ovine tissues pending provision of the additional data needed to demonstrate validation up to the required residue concentrations.

The applicant subsequently provided additional validation data at residue concentrations up to twice the established provisional MRLs. However, these data were generated using a slightly modified method (a different derivatisation procedure and different HPLC conditions were used). As the impact of these modifications has not been demonstrated the additional data cannot be considered to adequately complete the validation package.

The method proposed for monitoring of residues in edible ovine tissues has been demonstrated to be applicable for caprine tissues.

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 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 therefore no data were required.

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

No such considerations were identified.

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, it was 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

In the CVMP's previous evaluation, in view of outstanding concerns over the validation of the analytical method for monitoring of residues in ovine tissues, only provisional MRLs could be recommended.

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 |
| 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 intake of residues from ovine tissues and milk represents approximately 92% of the ADI. In line with this, there are no grounds for supposing that residues at the proposed MRLs would constitute a hazard to human health.

However, as further data are needed on the analytical method for monitoring of residues, final MRLs cannot be recommended at present. In view of this, and having received confirmation that data are being generated to complete the required validation of the analytical method, an extension of the provisional status of the MRLs is recommended.

3.4. Considerations on possible extrapolation of MRLs

In line with Article 5 of Regulation (EU) No 470/2009 the CVMP considered the possibility of extrapolating the maximum residue limits recommended for eprinomectin to other food producing species and food commodities. Taking into account the current scientific knowledge the recommendations on extrapolation are justified as follows:

| Animal species/ food commodities | Extrapolation possible (Yes/No) | Justification |
|--|---------------------------------------|--|
| Goats (including milk) | Yes | <p>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 the goat and consequently it is accepted as the marker residue for goats as well as for cattle and sheep.</p> <p>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 goats. Therefore the MRL values recommended for sheep can also be recommended for goats without compromising the safety of the consumer.</p> <p>The analytical methods proposed for the monitoring of residues in ovine tissues and milk have been demonstrated to be applicable also for caprine tissues and milk.</p> |
| Pigs | No | <p>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.</p> <p>No analytical method for monitoring of residues in pig tissues was available for evaluation.</p> |
| Poultry (including eggs) | No | <p>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.</p> <p>No analytical method for monitoring of residues in chicken tissues and eggs was available for evaluation.</p> |
| Horses | No | <p>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</p> |

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| | | <p>horses, no information was available to confirm the marker residue in horses</p> <p>No data are available to demonstrate that the analytical method proposed for monitoring of residues is applicable for monitoring of residues in horse tissues.</p> |
| Rabbits | No | <p>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.</p> <p>No data are available to demonstrate that the analytical method proposed for monitoring of residues is applicable for monitoring of residues in rabbits tissues.</p> |
| Fin fish | No | <p>Metabolism in fin fish is generally less complicated than in cattle and sheep, and given that the marker residue is 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.</p> |
| Honey | No | <p>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.</p> <p>No data are available to demonstrate that the analytical method for monitoring of residues is applicable for monitoring of residues in honey.</p> |

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

Whereas:

- 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;

- an analytical method for the monitoring of residues of eprinomectin in edible ovine tissues (muscle, liver, kidney and fat) is available, although further method validation is required;
- the analytical method proposed for monitoring of residues of eprinomectin in edible ovine tissues has been demonstrated to be applicable for caprine tissues;
- 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;

and having considered that:

- the additional data generated to validate the analytical method proposed for monitoring of residues in ovine tissues at concentrations of up to twice the MRLs was not considered adequate;
- additional data needed to complete the validation package for the analytical method are being generated;

the Committee, having considered the response to the list of questions after the establishment of the provisional maximum residue limits, and in accordance with Article 14(4) of Regulation (EC) 470/2009, recommends by consensus the extension of the time period applying to the provisional maximum residue limits, in accordance with the following table:

| Pharmacologically 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 | |

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

List of questions

1. Provisional maximum residue limits were initially recommended because the analytical method for monitoring of residues had not been validated over a concentration range including twice the recommended MRLs. The applicant subsequently provided additional validation data at residue concentrations up to twice the established provisional MRLs. However, these data were generated using a slightly modified method. As the impact of these modifications was not demonstrated the additional data cannot be considered to adequately complete the validation package. Consequently, in accordance with Volume 8 of The rules governing medicinal products in the European Union, the applicant is requested to demonstrate that the analytical method proposed for the monitoring of residues in ovine tissues is validated over a concentration range including half and twice the recommended MRL values. This could be achieved by the provision of new validation data relevant to the original or modified methods.

4. Background information on the procedure

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| 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 |