22 August 2014
EMA/CVMP/649781/2013
Committee for Medicinal Products for Veterinary Use

European public MRL assessment report (EPMAR)

Triclabendazole (all ruminants milk) – after the provisional maximum residue limit (MRL)

On 19 June 2014 the European Commission adopted a Regulation[1] establishing a MRL for triclabendazole in milk, valid throughout the European Union. This MRL was based on the favourable opinion and the assessment report adopted by the Committee for Medicinal Products for Veterinary Use (CVMP).

Triclabendazole is used in cattle and sheep for the control of liver fluke (fasciolosis) and is administered orally.

Triclabendazole had MRLs already established[2] in muscle, fat, liver and kidney of all ruminants. A provisional MRL in milk had also been previously established[3] with an expiry date of 1 January 2014, further to a request from the Irish Medicines Board for the extrapolation of the MRLs to milk.

The Irish Medicines Board submitted the responses to the list of questions further to the establishment of the provisional MRL to the European Medicines Agency, on 5 August 2013.

Based on the data available, the CVMP recommended, on 7 November 2013, the establishment of a MRL for triclabendazole in milk further to the extrapolation previously recommended and the establishment of the provisional MRL.

On 8 January 2014 the European Commission requested the review of the opinion in order to have further clarification with regard to the assessment of the responses to the outstanding issues identified at the time of the establishment of the provisional MRL in milk.

On 15 January 2014 the CVMP adopted revised opinion confirming the MRL extrapolated to all ruminants milk and recommending the removal of the provisional status of this MRL.

Subsequently the Commission recommended on 7 April 2014 the removal of the provisional status of the MRL for triclabendazole in milk. This recommendation was confirmed on 28 April 2014 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 19 June 2014.

[1] Commission Implementing Regulation (EU) No 676/2014, O.J. L 180, of 20.06.2014
[2] Commission Regulation (EC) No 1729/2006, O.J. L 325, of 24.11.2006
[3] Commission Regulation (EU) No 222/2012, O.J. L 75, of 15.03.2012

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Summary of the scientific discussion for the extrapolation of MRLs

Substance name:	Triclabendazole
Therapeutic class:	Antiparasitic agents/Agents against endoparasites
Procedure number:	EU/ART27/11/193/IMB
Applicant:	Ireland
Target species:	All ruminants milk
Intended therapeutic indication:	Treatment of the liver fluke, *Fasciola hepatica*
Route (s) of administration:	Oral

1. Introduction

Triclabendazole is a benzimidazole anthelmintic mainly employed in the control of the liver fluke, *Fasciola hepatica,* in sheep and cattle. Typically, an oral dose of 10 or 12 mg/kg bw is administered to sheep and cattle, respectively, at 8 to 10-week intervals during the fluke season, or at 5 to 6-week intervals in acute or sub-acute cases.

Triclabendazole was previously assessed by the CVMP resulting in the establishment of MRLs in ruminant tissues.

On 19 August 2011, the Irish Medicines Board submitted a request for an opinion on the extrapolation of maximum residue limits for triclabendazole to bovine and ovine milk. On 10 November 2011, the CVMP recommended a provisional MRL for triclabendazole in milk of all ruminants.

The Commission subsequently amended the entry for triclabendazole in table 1 of the Annex to Commission Regulation (EU) No 37/2010 of 22 December 2009 as follows:

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Triclabendazole	Sum of the extractable residues that may be oxidised to ketotricla-bendazole	All ruminants	225 µg/kg 100 µg/kg 250 µg/kg 150 µg/kg	Muscle Fat Liver Kidney		Antiparasitic agents/Agents against endoparasites
			10 µg/kg	Milk	Provisional MRL shall expire on 1 January 2014	

Further to the establishment of a provisional maximum residue limit for triclabendazole in milk, Ireland submitted to the European Medicines Agency on 5 August 2013 additional data concerning the validation of the analytical method in milk in order to allow for the establishment of a final MRL in milk.

This EPMAR provides an overall assessment of the request for the extrapolation of the MRLs for triclabendazole to milk and so covers the review performed for the establishment of the provisional MRL in milk as well as the review of the additional data provided in response to the outstanding issues identified at the time of the establishment of the provisional MRL.

2. Scientific risk assessment

2.1. Safety assessment

The CVMP has previously performed a consumer safety evaluation for triclabendazole and established a toxicological ADI of 0.0015 mg/kg bw, i.e. 0.09 mg/person, based on a NOEL of 0.15 mg/kg bw/day for increased postpartum mortality of the F_2 generation in a two-generation rat reproduction study and applying an uncertainty factor of 100. Therefore, no further assessment regarding the establishment of the ADI of the substance is required for the purpose of this application.

2.2. Residues assessment

For the assessment of the request for extrapolation the Committee considered relevant residue data from the previous assessment and any new information made available as detailed below.

2.2.1. Pharmacokinetics in target species

A GLP compliant and well-designed study has been performed with the aim of measuring the concentration of radioactivity in milk and plasma during a 28-day period after a single oral dose of 11.57 mg triclabendazole/kg to a single lactating cow. The concentration of radioactivity in milk reached a maximum of 2102 µg equivalents/kg on day 2 before falling to 9 µg equivalents/kg on day 28. The terminal half-life was 3.22 days. Overall, 2% of the dosed radioactivity was excreted in milk over the 28-day study period. The metabolites identified were triclabendazole sulphoxide, triclabendazole sulphone and the parent compound. Extractable residues that could be oxidised to ketotriclabendazole accounted for 61 to 82% of the total radioactive residues. Ketotriclabendazole concentrations after 1, 10, 21 and 28 days were respectively 1156, 219, 14 µg/kg and below the limit of quantification (5 µg/kg).

No pharmacokinetic data concerning milk of other ruminant species were available.

2.2.2. Residue depletion studies

In an old non-GLP study (1987), a product containing triclabendazole was administered orally at the recommended treatment dose to 13 cows on a single occasion. The times between treatment and calving varied. Milk samples were collected from treated animals following calving and were analysed for triclabendazole and its primary metabolites. The parent compound was not detected in milk and triclabendazole sulfoxide was only detected at low concentrations in a small number of animals. Triclabendazole sulfone was detected in milk of all cows and appears to be the main residue with concentrations decreasing to close to or below the limit of detection (20 µg/kg) by 9 to 18 days after treatment.

No residue data concerning milk of other ruminant species were available.

Selection of marker residue and ratio of marker to total residues

Triclabendazole sulphone is the main metabolite identified in the radiolabelled study. The sum of the extractable residues that may be oxidised to ketotriclabendazole, which is the established marker residue for tissues, has also been proposed as marker residue for milk. The study results show that over the period of 1 to 21 days after administration, the proposed marker residue accounted for 61 to 82% of the total radioactive residues. Based on these data the ratio of marker to total residues in bovine milk can be considered to be 60%, which is the ratio observed closest to the time point at which the calculated intake of residues will be below the ADI.

No residue data were provided for other ruminants to demonstrate the presence of the marker residue in milk from other species and to derivate the ratio of marker to total residues. However, as triclabendazole metabolism is similar in bovine, ovine and caprine species it can be accepted that the marker residue established for bovine milk is equally applicable for ovine and caprine milk. Similarly the ratio of marker to total residues agreed to bovine milk (0.6) can be accepted to milk from other ruminant species.

2.2.3. Monitoring or exposure data

Results of the national residue monitoring programme for 2008 to 2010 were provided. Triclabendazole sulphone was detected in three out of 148 samples of tested bulk milk in 2008 and in one out of 179 samples of tested bulk milk in 2010. Levels of triclabendazole sulphone detected ranged from 2.2 µg/kg to greater than 50 µg/kg. No non-compliant results were reported for 2009.

2.2.4. Analytical method for monitoring of residues

A reverse phase HPLC/UV method, that measures the marker residue as 'the sum of all metabolites that can be oxidized to ketotriclabendazole' in milk was provided. This method is essentially the same as the established method for monitoring residues in tissues, which has been previously accepted by the CVMP as validated for monitoring of residues. The method converts triclabendazole, its sulfoxide and its sulfone to ketotriclabendazole, levels of which are determined using reverse phase HPLC/UV. The limit of quantification for bovine milk is 5 µg/kg.

Although the analytical method proposed was considered generally suitable for monitoring of residues of triclabendazole in milk further validation data were considered necessary concerning the specificity, accuracy, precision, reproducibility and linearity. As a result of these deficiencies only a provisional MRL could be recommended.

The additional data provided in response to the outstanding issues identified in the EPMAR for the recommendation for a provisional MRL demonstrated that the method was specific for triclabendazole and its metabolites and that the accuracy was acceptable at the level of the proposed MRL and twice the proposed MRL. Repeatability and reproducibility were satisfactorily demonstrated. Linearity of the method was also demonstrated.

The method can be considered validated for the purpose of monitoring residues in bovine milk.

While no specific data in sheep milk were provided, considering that the method to analyse milk is essentially the same as the established method for monitoring residues in tissues which is validated for tissues in bovine, ovine and caprine species, it is reasonable to assume that the method will perform equally well in milk of other ruminants.

The proposed method has been reviewed by the relevant European Union Reference Laboratory which confirmed the overall suitability of the method for monitoring purposes.

2.2.5. Findings of EU or international scientific bodies

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) recommended the following MRLs for which were adopted by the Codex Alimentarius:

- cattle: fat 100 µg/kg, kidney 400 µg/kg, liver 850 µg/kg, muscle 250 µg/kg
- sheep: fat 100 µg/kg, kidney 200 µg/kg, liver 300 µg/kg and muscle 200 µg/kg.

No MRL was established for milk.

3. Risk management considerations

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

Microbiological effects are not expected for this substance therefore such data are not considered necessary.

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

The data provided for the scientific evaluation of triclabendazole for the establishment of a maximum residue limit in milk were limited and do not comply with the requirements of Volume 8 of *The rules governing medicinal products in the European Union*. In particular the radiolabelled pharmacokinetic study was carried out with one animal only and the residue data provided were very limited.

Recognising the deficiencies in the data presented, the Committee took also into account the following:

- Although other flukicidal substances exist for which MRLs in ruminant milk have been established, these substances are not approved for the treatment of immature fluke, and consequently it is recognised that at present there is a lack of available products for the treatment of immature fluke in animals producing milk for human consumption;
- Liver fluke is a highly debilitating disease leading to loss of condition and ultimately cachexia and potentially death and therefore the availability of an adequate range of products for the treatment of immature fluke is essential in order to avoid unnecessary suffering of the animals;
- The establishment of a maximum residue limit is essential to provide the reference level for control purposes and to enable the use of the substance;
- The lack of available products coupled with welfare issues, may lead to increased use of the products under non-authorised conditions.

3.3. Extrapolation of MRLs

On the basis of the MRLs established in ruminant tissues, the bioavailability of the residues in tissues, and of the standard food package, the amount of total residues that may be daily ingested by the

consumer is approximately 63 µg per day (equivalent to 70% of the ADI). This leaves 27 µg (approximately 30% of the ADI) for the establishment of a MRL for milk.

Considering the ratio of marker to total residues of 0.6 agreed in bovine milk, a MRL of 10 µg/kg can be proposed.

In view of the information available and the risk management considerations the CVMP recommends the extrapolation of the existing MRLs for triclabendazole to bovine milk.

Information on depletion of residues in milk is available from studies in cattle only, however in view of the fact that the metabolism of triclabendazole is similar in bovine, ovine and caprine species it can be accepted that the marker residue established for bovine milk is equally applicable for ovine and caprine milk and that the ratio of marker to total residues (0.6) is also applicable. Therefore the MRL recommended for bovine milk can be extrapolated to all ruminants.

The limited data available suggest that following oral administration at the recommended dose to shortly before calving residues in milk are at or around the proposed MRL value (i.e. around 10 µg/l) approximately 21 to 28 days after administration.

Calculation of theoretical daily intake of residues

Details used in the calculation of theoretical daily intake of residues from bovine tissues and milk:

Edible tissue or product	Daily consumption (kg)	MRL (µg/kg)	Ratio of the marker/total residue	Bioavailability factor	Amount per edible tissue or product
Muscle	0.30	225	0.32	0.20	42.2 µg
Fat	0.05	100	0.30	0.10	1.7 µg
Liver	0.10	250	0.24	0.17	17.7 µg
Kidney	0.05	150	0.27	0.04	1.1 µg
Milk	**1.5**	**10**	**0.60**	**1.00**	**25 µg**
Total					87.7 µg (**97.4% of the ADI**)

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

Having considered that:

- a toxicological ADI of 0.0015 mg/kg bw (i.e. 0.09 mg/person) was previously established as the overall ADI for triclabendazole,
- the metabolic profile of triclabendazole in laboratory animals and the target species (rats, sheep, goats and cattle) is similar,
- the marker residue established for tissues (the sum of the extractable residues that may be oxidised to ketotriclabendazole) can also be accepted as the marker residue for milk,
- the ratio of marker to total residues for milk was estimated to be of 0.6,

- there is a lack of available products for the treatment of immature fluke in animals producing milk for human consumption,
- there is a need for a reference level for control purposes and to enable the use of the substance,

and that:

- following the responses to the outstanding issues identified in the EPMAR recommending a provisional MRLfor triclabendazole in milk of all ruminants, the analytical method can be considered validated for the purpose of monitoring residues in cattle milk and is assumed to be applicable to other ruminants milk;

the CVMP confirms the maximum residue limit extrapolated to milk and recommends by consensus the removal of the provisional status of the maximum residue limit in milk for triclabendazole and the amendment of the entry in Table 1 (Allowed substances) of the Annex to Commission Regulation (EU) No 37/2010 in accordance with the following table:

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Triclabendazole	Sum of the extractable residues that may be oxidised to ketotricla-bendazole	All ruminants	225 µg/kg 100 µg/kg 250 µg/kg 150 µg/kg 10 µg/kg	Muscle Fat Liver Kidney Milk	NO ENTRY	Antiparasitic agents/Agents against endoparasites

Based on this MRL, milk would account for approximately 28% of the ADI. Taking into account the residues in all tissues, the theoretical maximum daily intake from bovine tissues and milk is 87.7 µg, which corresponds to 97.4% of the ADI.

4. Background information on the procedure

Submission of the dossier	19 August 2011
Steps taken for assessment of the substance	
Clock started:	20 August 2011
CVMP opinion adopted (provisional MRLs):	10 November 2011
Submission of response to list of questions:	5 August 2013
Cock re-started	6 August 2013
CVMP opinion adopted:	7 November 2013
Request for the review by the Commission	8 January 2014
Revised opinion adopted	15 January 2014