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EMA/CVMP/752339/2013
Committee for Medicinal Products for Veterinary Use

European public MRL assessment report (EPMAR)

Clorsulon (bovine milk) – after the provisional maximum residue limit (MRL)

On 20 June 2014 the European Commission adopted a Regulation[1] establishing a MRL for clorsulon in bovine 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).

Clorsulon is used in bovine species for the treatment and control of adult liver flukes and is administered subcutaneously or by the oral route.

Clorsulon had MRLs already established[2] in muscle, kidney and liver of bovine species. A provisional MRL in bovine 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 6 September 2013.

Based on the data available, the CVMP recommended on 12 December 2013 the establishment of a MRL for clorsulon in bovine 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 outstanding issues identified at the time of the establishment of the provisional MRL in bovine milk.

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

Subsequently the Commission recommended on 7 April 2014 that a MRL for clorsulon in bovine milk is established. This recommendation was confirmed on 28 April 2014 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 20 June 2014.

[1] Commission Implementing Regulation (EU) No 683/2014, O.J. L 182, of 21.06.2014
[2] Commission Regulation (EC) No 1942/1999, O.J. L 241, of 11.04.1999
[3] Commission Implementing Regulation (EU) No 466/2012, O.J. L 143, of 01.06.2012

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 extrapolation of MRLs

Substance name:	Clorsulon
Therapeutic class:	Antiparasitic agents/Agents against endoparasites
Procedure number:	EU/ART27/11/190/IMB
Requesting Member State:	Ireland
Target species:	Bovine milk
Intended therapeutic indication:	Treatment and control of adult liver flukes
Route(s) of administration:	Subcutaneous route

1. Introduction

Clorsulon is a substance belonging to the benzenensulphonamide family which is used for the treatment and control of adult flukes. Veterinary medicinal products containing clorsulon are currently marketed in the EU for the treatment of cattle. They are available as injectable formulations to be administered subcutaneously (recommended dose 2 mg/kg) or by the oral route (recommended dose 7 mg/kg). Clorsulon is frequently used in association with ivermectin.

Clorsulon was previously assessed by the CVMP resulting in the establishment of MRLs in bovine tissues.

On 19 August 2011, the Irish Medicines Board submitted a request for an opinion for the extrapolation of maximum residue limits for clorsulon to bovine milk. On 8 December 2011, the CVMP recommended a provisional MRL for clorsulon in milk.

The Commission subsequently amended the entry for closulon 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
Clorsulon	Clorsulon	Bovine	35 µg/kg 100 µg/kg 200 µg/kg	Muscle Liver Kidney		Antiparasitic agents/Agents against endoparasites
			16 µg/kg	Milk	Provisional MRL expires on 1 January 2014	

Further to the establishment of a provisional maximum residue limit for clorsulon in milk, Ireland submitted to the European Medicines Agency on 6 September 2013, 30 October, 27 November and 2 December 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 clorsulon 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

Clorsulon was previously assessed by the CVMP and a toxicological ADI of 0.002 mg/kg bw, i.e. 0.120 mg/person was established based on the toxicological NOEL of 2 mg/kg bw/day in dogs and applying a safety factor of 1000. Therefore, no further assessment regarding the consumer safety of the substance is required for the purpose of this request.

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

In cattle, after intraruminal administration of radiolabelled clorsulon at a dose of 10 mg/kg bw, maximum plasma levels (close to 3000 µg/l) were observed about 24 hours after administration. The elimination of total radioactivity from plasma was biphasic. The mean concentration in plasma was 14 µg/l at 21 days after treatment.

After subcutaneous administration of 2 or 3 mg/kg bw, maximum plasma concentrations (1290 and 2500 µg/l) were attained 6 hours after the injection. At seven days, the plasma concentrations were close to the limit of detection (10 µg/l).

After a single intraruminal administration of 6.6 mg radiolabelled clorsulon/kg bw or of 15 mg radiolabelled clorsulon/kg bw, about 90% of the administered dose was excreted within 7 days, the major fraction being excreted in the faeces (approximately 70%) and a minor fraction (about 30%) in urine.

No radiolabelled pharmacokinetic data in milk are available and there is no information on the metabolic profile in milk.

2.2.2. Residue depletion studies

Three studies are available to illustrate the depletion of clorsulon residues in cow's milk (one GLP and 2 non-GLP). The findings of the three studies are broadly similar.

In the GLP study, 8 lactating dairy cows were injected subcutaneously 300 µg ivermectin + 3 mg clorsulon/kg bw (1.5 the recommended dose rate). Milk residues were quantified using a HPLC UV method. The maximum daily mean clorsulon concentration in milk (853 ng/ml) was reached approximately 7 hours after administration. Mean concentrations in milk depleted rapidly to 152 µg/l within 3 days after treatment and to approximately 11 µg/l at 7 days after treatment. The depletion half life in milk was calculated to be 31.2 hours.

Selection of marker residue and ratio of marker to total residues

No radiolabelled study is available to confirm the identity of the marker residue in milk and on which to base a ratio of marker to total residues for milk. However, based on the fact that the parent compound clorsulon is the marker residue for tissues and that it has been identified in bovine milk in a number of studies, clorsulon can be accepted as the marker residue in bovine milk.

Since the metabolism of clorsulon in milk has not been characterised and the ratio has not been determined, any approach to setting a ratio of marker to total residues should be suitably conservative. Marker to total ratios established for cattle tissues were 0.41 in muscle, 0.55 in liver, 0.75 in kidney. It is proposed to use the worst case value of 0.4, established for muscle, as the ratio of marker to total residues in bovine milk.

2.2.3. Monitoring or exposure data

Results of the national residue monitoring programme for the years 2008 to October 2010 were provided. Clorsulon residues were not detected in any samples analysed.

2.2.4. Analytical method for monitoring of residues

A UPLC-MS/MS (ultra-performance liquid chromatography coupled to tandem mass spectrometry) method was developed by a national reference laboratory for the purpose of residue surveillance in cow's milk. The method is well described and considered in general suitable for monitoring of residues. A validation package was submitted based on the requirements of Volume 8 of The rules governing medicinal products in the European Union and was considered acceptable. The limit of quantification of the method is 8 µg/kg.

Although the analytical method proposed was considered generally suitable for monitoring of residues of clorsulon in milk further validation data were considered necessary concerning accuracy, precision and taking into account the Volume 8 requirements in relation to the concentration range. 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 clorsulon and that the accuracy and precision were acceptable at the level of the proposed MRL. Repeatability and reproducibility were satisfactorily demonstrated. Linearity of the method was also demonstrated.

The proposed method has been reviewed by the relevant Union Reference Laboratory, which confirmed the overall suitability of the method.

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

2.2.5. Findings of EU or international scientific bodies

No information was available on evaluation from other scientific bodies.

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 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 clorsulon 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 no data on total residues in milk are available.

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, authorised for the treatment of immature fluke in animals producing milk for human consumption;
- Liver fluke is a highly debilitating disease. The availability of an adequate range of products for the treatment of 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 would 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

Based on existing MRLs values, the daily intake from bovine tissues will represent 57 µg (equivalent to 48% of the ADI), leaving 63 µg (equivalent to 52% of the ADI) for establishment of a MRL for milk.

Given the available information relating to ratio of marker to total residue in other tissues, it is proposed to use the worst case value of 0.4, established for muscle, as the ratio of marker to total residues in milk.

As the standard food basket indicates a consumption value for milk of 1.5 kg per consumer per day, the maximum allowable total residue in milk would be 0.063 mg, or 0.042 mg/litre (to stay within the ADI). Considering that the percentage of marker residue to total residues in milk is assumed to be 40% an MRL of 16 µg/kg is proposed.

Based on the milk residue data, when clorsulon is administered by subcutaneous injection to lactating animals, there is a steady depletion in clorsulon residues with average clorsulon concentrations in milk less than the proposed MRL of 16 µg/l by seven days after product 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 products	Daily consumption (kg)	MRL (µg/kg)	Ratio of the marker/total residue	Amount per edible tissue or product
Muscle	0.30	35	0.41	25.6 µg
Fat	0.05	---	---	---
Liver	0.10	100	0.55	18 µg
Kidney	0.05	200	0.75	13.3 µg
Milk	**1.5**	**16**	**0.40**	**60 µg**
Total				116.9 µg (**97.4 % of the ADI**)

The MRL for milk (16 µg/kg) accounts for approximately 48 % of the ADI.

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

Having considered that:

- a toxicological ADI of 2 µg/kg bw (i.e. 120 µg/person) was previously established as the overall ADI for clorsulon;
- clorsulon was accepted as the marker residue in milk;
- the marker to total residues ratio of 0.4 established for muscle was considered a suitable conservative value to be considered in relation to milk as it reflects the worst case scenario;
- there is a lack of products for the treatment of fluke in animals producing milk for human consumption;
- there is a need for a reference level for control purposes to enable the use of the substance in milk producing animals;

and that:

- following the responses to the outstanding issues identified in the EPMAR recommending a provisional MRL for clorsulon in bovine milk, the analytical method can be considered validated for the purpose of monitoring residues in bovine milk.

the CVMP confirms the maximum residue limit extrapolated to bovine milk and recommends by consensus the removal of the provisional status of the maximum residue limit in milk for clorsulon 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:

Pharmacologi-cally active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Clorsulon	Clorsulon	Bovine	35 µg/kg 100 µg/kg 200 µg/kg 16 µg/kg	Muscle Liver Kidney Milk	NO ENTRY	Antiparasitic agents/Agents against endoparasites

Based on these values, the theoretical maximum daily intake from bovine tissues and milk is 116.9 µg, which corresponds to 97.4% of the ADI.

4. Background information on the procedure

Submission of the dossier

Steps taken for assessment of the substance

Application validated:	19 August 2011
Clock started:	20 August 2011
CVMP opinion adopted (provisional MRLs):	10 November 2011
Submission of response to list of questions:	6 September 2013
Adoption of opinion:	12 December 2013
Request for the review by the Commission	8 January 2014
Revised opinion adopted	15 January 2014