11 November 2013
EMA/CVMP/685072/2013
Committee for Medicinal Products for Veterinary Use

European public MRL assessment report (EPMAR)

Manganese carbonate (All food producing species)

On 29 October 2013 the European Commission adopted a Regulation[1] modifying the maximum residue limits for manganese carbonate in all food producing species, valid throughout the European Union. This modification was based on the favourable opinion and the assessment report adopted by the Committee for Medicinal Products for Veterinary Use.

Manganese carbonate is intended for use in all food producing species as mineral supplementation.

Manganese carbonate had maximum residue limits already established[2] for all food producing species, restricted to oral use.

Warburton Technology submitted the application for the extension of maximum residue limits to the European Medicines Agency, on 3 February 2012.

Based on the original data in the dossier, the Committee for Medicinal Products for Veterinary Use recommended on 12 July 2012 the modification of maximum residue limits for manganese carbonate to all food producing species to cover the parenteral use.

On 29 November 2012 the European Commission requested the Committee to review the wording of its opinion with a view to providing clarification on a number of points. The Committee for Medicinal Products for Veterinary Use adopted its final opinion on 10 January 2013.

Subsequently the Commission recommended on 8 June 2013 that the modified maximum residue limits in all food producing species are established. This recommendation was confirmed on 29 June 2013 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 29 October 2013.

[1] Commission Implementing Regulation (EU) No 1057, O.J. 288, of 30.10.2013
[2] Commission Regulation (EC) No 2692, O.J. L 338 15.12.1998

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European public MRL assessment report (EPMAR)

Manganese carbonate (parenteral use)

Summary of the scientific discussion for the establishment of MRLs

Substance name:	Manganese carbonate
Therapeutic class:	Mineral supplement
Procedure number:	EU/12/200/WAR
Applicant:	Warburton Technology
Target species:	Bovine species
Intended therapeutic indication:	Mineral supplementation
Route(s) of administration:	subcutaneous

1. Introduction

Manganese is a trace mineral naturally present in small amounts in the body, mainly in bones, liver, kidneys and pancreas. In veterinary medicine manganese carbonate is used in mono-preparations and combination products to treat manganese deficiency and to prevent skeletal abnormalities in calves and perosis in poultry.

Manganese carbonate is authorised in the EU as a feed additive with a maximum dose of 250 mg manganese per kg feed.

Manganese salts are also used in human medicine and nutritional supplements for prevention and treatment of manganese deficiency.

Manganese carbonate was previously assessed by the CVMP and is currently included in table 1 of the annex to Commission Regulation (EU) No 37/2010 of 22 December 2009 in accordance with the following table:

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Manganese carbonate	NOT APPLICABLE	All food producing species	No MRL required	NOT APPLICABLE	For oral use only	NO ENTRY

Warburton Technology submitted an application for the extension of maximum residue limits for manganese carbonate in bovine species to include parenteral use, to the European Medicines Agency, on 3 February 2012. The proposed indication for cattle is for manganese supplementation and the proposed recommended dose for parenteral use is 0.2 mg/kg bw as a single subcutaneous injection.

2. Scientific risk assessment

2.1. Safety assessment

The CVMP has previously assessed the consumer safety of manganese carbonate together with other manganese salts and concluded that the available data did not allow the establishment of an ADI for manganese. However, in light of the fact that manganese is an essential element, that it is a normal component of the human diet, and that its use in veterinary medicinal products will add negligible amounts to the manganese intake from its use as feed additive, the Committee considered that the establishment of an ADI for the substance was not necessary.

In 2009, the EFSA published an opinion on some manganese salts (used in food supplements), in which the Panel on Food Additives and Nutrient Sources added to Food (ANS) summarised the EU safety assessments on manganese as follows (EFSA, 2009[3]):

> *"The SCF (1993) estimated that 1-10 mg/day was an acceptable range of manganese intake based on intake from food (SCF, 1993). In 1999, the SCF estimated that the use of manganese carbonate, chloride, citrate, gluconate, glycerophosphate and sulphate were acceptable sources of manganese for use in the manufacture of foods for particular nutritional purposes (PARNUTS) (SCF, 1999).*
>
> *The SCF considered that an upper level of 0.5 mg manganese/L in natural mineral waters appeared to be acceptable for human consumption (SCF, 1996). This amount would be equivalent to 1 mg manganese/day assuming an intake of 2 L of water/day.*
>
> *In its latest evaluation of manganese, the SCF could not set an Upper Tolerable Intake Level (UL) (SCF, 2000). The SCF considered that limitations in the human and animal data did not allow the identification of a No-Observed-Adverse-Effect-Level (NOAEL) for critical endpoints for manganese, and stressed that the margin, between oral effect levels in humans as well as in animals and the estimated intake from food, was very low (SCF, 2000). It was thus concluded that given the neurotoxicity findings and the potential higher susceptibility of some subgroups in the general population, oral exposure to manganese beyond the levels normally present in food and beverages could represent a risk of adverse health effects without evidence of any health benefit."*

Considering the SCF and EFSA conclusions from 2000 and 2009, respectively, the Committee concludes that the parenteral (veterinary) use of manganese carbonate must not significantly contribute to the human intake of manganese in the normal diet, and therefore the manganese concentrations in edible tissues from treated animals must not exceed the natural background levels.

No further assessment regarding the consumer safety of the substance was considered necessary for the purpose of this extension application.

2.2. Residues assessment

2.2.1. Pharmacokinetics in target species

No studies on the pharmacokinetics in target species are available.

[3] Scientific Opinion of the Panel on Food Additives and Nutrient Sources added to Food on manganese ascorbate, manganese aspartate, manganese bisglycinate and manganese pidolate as sources of manganese added for nutritional purposes to food supplements following a request from the European Commission. *The EFSA Journal* (2009) 1114, 1-23

2.2.2. Residue depletion studies

In a GLP residue depletion study, twenty-four cattle received a single subcutaneous injection with manganese carbonate (10 mg/ml) at a dose of 1 ml per 50 kg bw (0.2 mg/kg bw) at the left side of the neck. The injection site was marked by clipping. Groups of 6 animals were euthanised at 8, 24, 48 and 72 hours after injection, and samples of liver, kidney, fat, and injection site (core and surround) were taken and analysed for manganese concentrations using an ICP-MS (inductively coupled plasma mass spectrometry) method. Highest manganese residues were found in core injection sites at 8 hours after injection, with values ranging from less than 3 to 8.76 mg/kg (on average less than 4.2 mg/kg), however these concentrations dropped to below the limit of detection at 24 hours after injection. Residues in liver and kidney were slightly elevated at 8 hours, ranging from 3.58 to 4.68 mg/kg and less than 2 to 2.78 mg/kg respectively, and rapidly depleted to background levels thereafter.

No data on residues in milk were provided. However, considering the fact that tissue residues were only slightly elevated at 8 hours and depleted very rapidly to undetectable or background levels, it is concluded that any elevation of manganese residues in milk will be slight and temporary. This view is supported by publicly available literature, which indicates that manganese levels reported in cow's milk are generally well below levels reported in tissues.

2.2.3. Monitoring or exposure data

In 2009, the EFSA published the following information on dietary exposure to manganese salts[1]:

> *"Manganese dietary intake from food in Europe has been reported to be between 1.4 and 4.9 mg manganese/day on average and between 4.8 and 8.2 mg manganese/day at the high percentile intake for adults. For children, the average dietary intake from food was reported to be between 1.8 and 2.2 mg manganese/day and between 3.3 and 4.2 for the high percentile intake. The total anticipated exposure to manganese from the diet, and from the highest manganese supplementation level considered in this (EFSA) opinion, was estimated by the Panel to be on average between 6.4-9.9 and 6.8-7.2 mg manganese/day for adults and children, respectively, assuming a supplementation of 5 mg manganese/day. The highest percentile intakes estimated for adults and children would be between 9.8-13.2 and 8.9-9.2 mg manganese/day, respectively."*

2.2.4. Analytical method for monitoring of residues

Because a "No MRL required" status is established for manganese carbonate, an analytical method for the monitoring of residues was not provided and is not deemed necessary.

2.2.5. Findings of EU or international scientific bodies

Manganese carbonate is approved for use in feed additives (Commission Regulation (EC) No 1334/2003). MRL values are not set in relation to this use.

3. Risk management considerations

3.1. Elaboration of MRLs

The data on manganese residues in tissues, including injection sites, following subcutaneous use in cattle show that residue levels were highest at the first sampling time point after administration, i.e. at 8 hours after administration. By 24 hours after administration residue levels were around or below the

limit of detection of the method (2 to 3 mg/kg) in all tissues including injection site. These levels are within the normal range of manganese levels reported in the literature.

Calculation of theoretical daily intake of residues

As it is not realistic to assume that an animal would be slaughtered within a day of treatment with manganese carbonate, it was considered acceptable to use the 24 hours timepoint as the basis for the evaluation of the theoretical daily intake of residues. As it is considered that manganese residues in tissues and milk will be at background levels at this timepoint, it is concluded that ingestion of tissues and other food commodities derived from cattle treated with medicinal products containing manganese carbonate will be well within the normal range of expected dietary exposure. However, even using the 8 hour timepoint, the levels of manganese would be within average intake levels for consumers, should they ingest 300 gram of injection site meat.

It is concluded that parenterally administered manganese carbonate in cattle does not represent a human health risk, and that therefore there is no need for control of residues in tissues or milk from treated animals. Consequently, parenteral use does not impact on the 'no MRLs required' status, and the existing provision "for oral use only" can be deleted.

3.2. Considerations on possible extrapolation of MRLs

In line with Article 5 of Regulation (EC) No 470/2009 the CVMP considered the possibility of extrapolating its recommendation on maximum residue limits for manganese carbonate in bovine species 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
All food producing species	Yes	The data reviewed for the current application demonstrate that, following parenteral administration to cattle, residue levels are only briefly elevated, returning rapidly to background levels. Although there were no specific pharmacokinetic data in other food producing species, the pharmacokinetics of this simple substance is not expected to be significantly different in cattle and other species. The recommendation for bovine species can be extrapolated to 'all food producing species' without compromising the safety of the consumer.

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

Having considered that:

- the establishment of an ADI for manganese was not considered necessary;
- manganese is an essential element, and a normal component of the human diet;
- the dietary exposure to manganese resulting from parenteral use of manganese carbonate in cattle is well within the range of the normal dietary intake levels;

- residues of manganese carbonate depleted to background or undetectable levels in all edible tissues including injection sites by 24 hours after parenteral treatment, whereas it is reasonable to assume that animals are sent to slaughter at longer time intervals after treatment;
- a similar pattern of exposure can be expected following parenteral administration of manganese carbonate in different species;

the Committee recommends the extension of maximum residue limits for manganese carbonate to include parenteral use, and the amendment of table 1 of the Annex to 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
Manganese carbonate	NOT APPLICABLE	All food producing species	No MRL required	NOT APPLICABLE	NO ENTRY	Alimentary tract and metabolism / mineral supplements

4. Background information on the procedure

Submission of the dossier	03 February 2012
Steps taken for assessment of the substance	
Application validated:	15 February 2012
Clock started:	16 February 2012
CVMP opinion adopted:	12 July 2012
Commission request for reconsideration of opinion	29 November 2012
Revised CVMP opinion adopted:	10 January 2013