



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/CVMP/741250/2011
Committee for Medicinal Products for Veterinary Use

European public MRL assessment report (EPMAR)

Monepantel (caprine and ovine milk)

On 29 April 2013 the European Commission adopted a Regulation¹ establishing a maximum residue limit for monepantel in caprine and ovine milk, valid throughout the European Union. This maximum residue limit was based on the favourable opinion and assessment report adopted by the Committee for Medicinal Products for Veterinary Use.

Monepantel is intended for treatment and control of gastrointestinal roundworms (nematodes) in sheep and goats. The proposed use in sheep and goats is as a single oral drench of 2.5 and 3.75 mg/kg bw, respectively.

Maximum residue limits had previously been established for monepantel in ovine and caprine tissues. Novartis Animal Health Inc. submitted an application for the establishment of a maximum residue limit in milk to the European Medicines Agency on 30 August 2011.

Based on the original and complementary data in the dossier, the Committee for Medicinal Products for Veterinary Use recommended, on 16 May 2012, the establishment of a maximum residue limit for monepantel in ovine and caprine milk.

Subsequently the Commission recommended, on 8 March 2013, that a maximum residue limit in ovine and caprine milk be established. This recommendation was confirmed on 29 March 2013 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 29 April 2013.

¹ Commission Implementing Regulation (EU) No 394/2013, O.J. 118, of 30.04.2013



Summary of the scientific discussion for the establishment of MRLs

Substance name:	Monepantel
Therapeutic class:	Antiparasitic agents/Agents acting against endoparasites/ anthelmintic
Procedure number:	EU/11/195/NOV
Applicant:	Novartis Animal Health Inc
Target species:	Ovine (milk)
Intended therapeutic indication:	Monepantel is intended for treatment and control of gastrointestinal roundworms (nematodes)
Route(s) of administration:	Oral solution

1. Introduction

Monepantel (CAS NO 887148-69-8) is the S-enantiomer of N-[(1S)-1-Cyano-2-(5-cyano-2-trifluoromethyl-phenoxy)-1-methyl-ethyl]-4-trifluoromethylsulfanyl-benzamide.

Monepantel is an anthelmintic intended for treatment and control of gastrointestinal roundworms (nematodes) in sheep and goats. The proposed use in sheep and goats is as a single oral drench of 2.5 and 3.75 mg/kg bw, respectively.

Monepantel was previously assessed by the CVMP and a toxicological ADI of 0.03 mg/kg bw (i.e 1.8 mg/person) was established

Currently monepantel is included in 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
Monepantel	Monepantel sulfone	Ovine, caprine	700 µg/kg 7000 µg/kg 5000 µg/kg 2000 µg/kg	Muscle Fat Liver Kidney	Not for use in animals producing milk for human consumption	Antiparasitic agents/Agents acting against endoparasites

Novartis Animal Health Inc submitted to the European Medicines Agency the application for the extension of maximum residue limits to ovine milk on 30 August 2011.

2. Scientific risk assessment

2.1. Safety assessment

The CVMP has previously assessed the consumer safety of monepantel and a toxicological ADI of

0.03 mg/kg bw (i.e 1.8 mg/person) was established based on the NOAEL of 3 mg/kg bw/day based on increased alkaline phosphatase activity and elevated liver weights associated with hepatocellular hypertrophy, seen in a one-year dog study and applying a safety factor of 100. Therefore, no further assessment regarding the consumer safety of the substance is required for the purpose of this extension application.

2.2. Residue assessment

In the establishment of MRLs in ovine meat the pharmacokinetics was described in detail for both target species and laboratory animals. The metabolic pathways in non-lactating sheep are well understood. Monepantel is rapidly oxidised to the sulfoxide and then into the sulfone, which is the predominant metabolite. Slower oxidative mechanisms convert the sulfone into a further oxidized metabolite, and the metabolites are also cleaved into fragments, representing either of the two phenyl rings. The cleaved metabolites were only observed in excreta. A unique cyclised metabolite was observed in variable, but overall small quantities in both sheep fat and in rat fat. The major elimination pathway is via the faeces, with a significant contribution by urine, and about 90% of the dose is excreted within 2-3 weeks.

For the establishment of an MRL in milk, a GLP absorption, distribution, metabolism and excretion study was carried out in lactating sheep to investigate the excretion via milk and the nature of metabolites in milk. A single oral dose of [¹⁴C]-monepantel at 3.75 mg/kg in a commercial formulation was administered to four lactating sheep, two high yielding and two low yielding. The residue depletion in blood, milk and cream was determined by measuring total radioactive residues (TRR) in specimens collected over a period of 5 weeks.

Milk and cream specimens of interest and containing sufficient levels of radioactivity were subjected to metabolite profiling. The metabolite pattern in milk was very similar to the one found in muscle and fat in a previous study with non-lactating sheep. Monepantel sulfone was by far the most prominent metabolite accounting for 84 to 92% of the total residue. Monepantel was a minor constituent and was present only at the early time points. Monepantel sulfoxide (an intermediate in the formation of the sulfone) was also found but only at lower levels and only at the early time points. There was another minor metabolite with an unusual cyclic structure, which was found in fat and (at much lower levels) also in muscle in a previous study. The metabolite depleted over time, but slightly more slowly than the major metabolite monepantel sulfone. The radioactivity was readily extractable with organic solvent from cream. The metabolite pattern was very similar to the one found in the respective milk specimens. The residues of monepantel and monepantel sulfone found with the non-radiolabelled analytical methods were compared to the total radioactive residues values. At day 14 the parent compound was not found in milk but 75.8 µg of monepantel sulfone/l were found in milk at day 20. The percentage of the administered dose excreted via milk ranged from 6.5 to 14.4%. From this sheep study tissue data were also provided. At 35 days residues in muscle were between 4 and less than 10 µg equivalent monepantel/kg, in fat between 27 and 76 µg equivalent monepantel/kg, in kidney less than 10 µg equivalent monepantel/kg and between 20 and 50 µg equivalent monepantel/kg in liver.

A pilot non-GLP milk residue depletion study in lactating Merino sheep was carried out. Three Merino ewes with suckling lambs were administered a commercial preparation at the highest recommended dose rate of 3.75 mg/kg, and milk samples were collected every 12 hours for the first 6 days, then once daily for the next 3 days and then every second day, for a total collection period of 2 weeks. Whole milk samples were analysed for monepantel and its sulfone by an LC-MS/MS method. Mean residues of the sulfone metabolite and the parent drug decline from 5790/1145, 4417/485, 2467/153

to 511/11 µg/l at 12, 24, 48 hours and 7 days respectively. Very low residues were observed in the corresponding skim milk fraction, indicating the lipophilic nature of the analytes.

As for tissues, the marker residue for milk is monepantel sulfone as it represents the majority of the total residue. The ratio of marker to total residue was established as 0.87.

2.2.1 Monitoring or exposure data

No monitoring or exposure data other than that described elsewhere in this report are available.

2.2.2 Analytical method for monitoring of residues

An analytical LC-MS/MS method is proposed as the regulatory method for determination of monepantel sulfone in ovine milk. Detection is by tandem mass spectrometry and quantification is achieved by comparing the ratio of analyte/internal standard responses to those of the calibration curve.

The assessment of the method took into account that the validation has been performed in accordance with the current requirements of Volume 8 of the Rules Governing Medicinal Products in the European Union and, considering that ovine milk is considered a minor use commodity, the guideline on safety and residue data requirements for veterinary medicinal products intended for minor uses or minor species (EMEA/CVMP/SWP/66781/2005) was also considered for the evaluation.

The method has been validated in a range corresponding to 50 to 1500 µg/l monepantel sulfone in milk. The validated limit of quantification is 68 µg/kg (equivalent to 68 ng/ml).

The relevant EU reference laboratory was consulted on the analytical method and agreed that the analytical method can be considered to be satisfactorily validated.

2.2.3 Findings of EU or international scientific bodies

Monepantel was reviewed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2011, which recommended maximum residue limits of monepantel in ovine tissues at the following levels: 300 µg/kg in muscle, 5500 µg/kg in fat, 3000 µg/kg in liver and 700 µg/kg in kidney. The 20th Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) proposed higher MRLs as established in some countries, e.g. in the EU, and recommended requesting JECFA to evaluate the safety of the proposed higher MRLs. JECFA did not recommend MRLs 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 type of substance therefore no data were required.

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

Maximum residue limits for monepantel are currently established for edible ovine and caprine tissues. The current evaluation concerns an extension to dairy animals and the establishment of a maximum residue limit for ovine milk. In deriving a maximum residue limit for milk consideration was given to

the need to reserve a portion of the ADI for possible future uses of the substance that might lead to residues in other food commodities, i.e. eggs and honey. However, it is accepted that due to the limited spectrum of activity of monepantel towards parasites, with only some gastrointestinal nematodes being sensitive, it is very unlikely that monepantel will ever find a use in the treatment of hens or bees. It is therefore concluded that there is no need to maintain an unused portion of the ADI.

3.3. Elaboration of MRLs

Monepantel MRLs are established in ovine fat, liver, kidney and muscle as 7000, 5000, 2000 and 700 µg/kg, respectively. The marker residue is monepantel sulfone, which represents 68, 68, 68 and 94% respectively of total residues.

Since the ADI is 0.03 mg/kg (1.8 mg per person), these MRLs account for 84% of the permitted theoretical consumer intake. The remaining 16% of the ADI (0.288 mg per person) can therefore be allocated to milk.

The nominal consumption of milk is 1.5 kg per day. Therefore, the safe concentration of total residues in milk is 192 µg/kg. Taking account of the ratio of marker to total residues of 0.87 and correcting for molecular weight differences between the marker residue and the parent compound, this value translates to monepantel sulfone concentration of 178 µg/kg. An MRL of 170 µg/kg is therefore recommended for milk.

Calculation of theoretical daily intake of residues

The existing MRLs for tissues combined with the recommended MRL for milk results in a theoretical daily intake calculated as follows:

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	700	0.94*f	209
Fat	0.05	7000	0.68*f	482
Liver	0.10	5000	0.68*f	689
Kidney	0.05	2000	0.68*f	138
Milk	1.50	170	0.87*f	275
Estimated total daily intake µg/person				1792
ADI (µg/person)				1800

*f: correction factor for molecular weight, marker to parent, 473/505

The theoretical consumer intake of total residues represents 99.6 % of the ADI.

It is noted that the portion of the ADI available limits the MRL value that can be recommended for milk, and is likely to result in a very long withdrawal for milk.

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 recommended maximum residue limit for monepantel in ovine milk 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' milk	Yes	<p>MRLs have already been established in goat tissues.</p> <p>Existing data indicate that the pattern of metabolites seen in rats, dogs and sheep is similar with the predominant metabolite being the sulfone. Based on this existing inter-species metabolism data, and that sheep and goats are related species (ruminants), the assumption can reasonably be made that the sulfone metabolite will be the predominant metabolite in the goat's milk and consequently it is accepted as the marker residue for goats' milk as it is in sheep's milk. Although no specific pharmacokinetic or residue data were available for goats and therefore the ratio of marker to total residues could not be derived, the limitations resulting from lack of species specific data are compensated for by the fact that consumption of goats' milk, and consequently exposure to residues in goats' milk is limited.</p> <p>The analytical method developed for the monitoring of residues in sheep's milk has been demonstrated to be applicable to goats' milk.</p> <p>The MRL recommended for sheep's milk can also be recommended for goats' milk without compromising the safety of the consumer.</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 chickens. 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>Furthermore, given the limited spectrum of activity of monepantel towards parasites, its use in chickens is considered unlikely.</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, dogs and sheep 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.</p> <p>No data are available to demonstrate that the analytical method proposed for monitoring of residues is applicable for monitoring of residues in horses.</p>
Rabbits	No	<p>Although existing data indicate that the pattern of metabolites seen in rats, dogs and sheep 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. As the marker residue established in ovine species is not the parent compound, species specific data would be needed to confirm that monepantel sulphone would also be a suitable marker residue for monitoring of residues in fin fish.</p> <p>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>Furthermore, given the limited spectrum of activity of monepantel towards parasites, its use in honey bees is considered unlikely.</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

Having considered that:

- an ADI of 0.03 mg/kg bw (i.e. 1.8 mg/person) has previously been established for monepantel;
- the sulfone metabolite was retained as the marker residue for ovine milk;
- the ratio of marker to total residue in ovine milk was 0.87;
- based on existing inter-species metabolism data and on the fact that sheep and goats are related species, it is accepted that the marker residue and the ratio of marker to total residues established in ovine milk can also be applied to caprine milk;
- an analytical method for monitoring of residues in ovine milk is available and validated according to the requirements of Volume 8 of the Rules Governing Medicinal Products in the European Union and the guideline on safety and residue data requirements for veterinary medicinal products intended for minor uses or minor species (EMA/CVMP/SWP/66781/2005);
- the analytical method for monitoring of residues in ovine milk has been demonstrated to be applicable for goats' milk also;

the Committee recommends the establishment of maximum residue limits for monepantel in ovine and caprine milk 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
Monepantel	Monepantel sulfone	Ovine, caprine	700 µg/kg 7000 µg/kg 5000 µg/kg 2000 µg/kg 170 µg/kg	Muscle Fat Liver Kidney Milk		Antiparasitic agents/Agents against endoparasites

4. Background information on the procedure

Submission of the dossier	30 August 2011
Steps taken for assessment of the substance	
Application validated:	13 September 2011
Clock started:	14 September 2011
List of questions adopted:	12 January 2012
Consolidated response to the list of questions submitted:	16 February 2012
Clock re-started:	17 February 2012
CVMP opinion adopted:	16 May 2012