15 November 2016
EMA/CVMP/351687/2016
Committee for Medicinal Products for Veterinary Use

European public MRL assessment report (EPMAR)

Monepantel (bovine species)

On 17 October 2016 the European Commission adopted a Regulation[1] establishing maximum residue limits for monepantel in bovine species, valid throughout the European Union. These maximum residue limits were based on the favourable opinion and the assessment report adopted by the Committee for Medicinal Products for Veterinary Use.

Monepantel is intended for the treatment of parasitic roundworms (nematodes) in bovine species, to be administered as a single oral drench at a maximum dose of 3.75 mg/kg bw.

Maximum residue limits had previously been established[2] in ovine and caprine species. Novartis Animal Health UK Limited (subsequently acquired by Eli Lilly and Company Limited) submitted to the European Medicines Agency an application for the extension of maximum residue limits to bovine species, on 15 January 2015.

Based on the original and complementary data in the dossier, the Committee for Medicinal Products for Veterinary Use recommended, on 19 May 2016, the extension of maximum residue limits for monepantel to bovine tissues.

Subsequently the Commission recommended on 7 September 2016 that maximum residue limits in bovine species are established. This recommendation was confirmed on 28 September 2016 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 17 October 2016.

[1] Commission Implementing Regulation (EU) No 2016/1834, O.J. L 280, of 17 October 2016
[2] Commission Implementing Regulation (EU) No 394/2013, O.J. 118, of 30 April 2013

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Summary of the scientific discussion for the establishment of MRLs

Substance name:	Monepantel
Therapeutic class:	Antiparasitic agents / Agents (acting) against endoparasites
Procedure number:	EMEA/V/MRL/003200/EXTN/0003
Applicant:	Novartis Animal Health UK Ltd (subsequently acquired by Eli Lilly and Company Ltd)
Target species applied for:	Bovine tissues and milk
Intended therapeutic indication:	Treatment of parasitic roundworms
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. It is an anthelmintic used for the treatment of gastrointestinal roundworms (nematodes) in sheep and goats.

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 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
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

Novartis Animal Health UK Ltd (subsequently acquired by Eli Lilly and Company Ltd) submitted an application under Article 3 of Regulation (EC) No 470/2009 for the extension of maximum residue limits to bovine species to the European Medicines Agency, on 15 January 2015. The substance is intended for the treatment of parasitic roundworms (nematodes), to be administered as a single oral drench at a maximum dose of 3.75 mg/kg bw.

2. Scientific risk assessment

2.1. Safety assessment

The CVMP previously assessed the consumer safety of monepantel and established a toxicological ADI of 0.03 mg/kg bw (i.e 1.8 mg/person) as the overall ADI. The ADI was derived from a 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.

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

No pharmacokinetic study in cattle has been provided but the bioavailability and the rate of excretion has been addressed as part of the radiolabelled metabolism/depletion study, reported in section 2.2.2.

2.2.2. Residue depletion studies

Radiolabelled studies

Four groups of beef cattle, 3 animals per group, were treated with monepantel at a dose level of 3.75 mg monepantel/kg bw. Each animal was treated with a single oral dose of [^{14}C]monepantel on study day 0.

Urine and faeces samples were collected from one group of animals at 24 hour intervals until 3 days after administration. Blood samples were collected from a second group of animals at selected time points until 21 days after administration and were used to generate plasma data.

One group of animals was euthanised at each of 3, 7, 14 and 21 days after administration. Following euthanasia, liver, kidney, loin muscle, renal fat, bile and whole blood were collected and retained. Radioactivity was determined in all samples by liquid scintillation counting, either by direct counting, solubilisation or combustion. Selected samples were subject to extraction and profiling by HPLC with either on-line or fraction collection liquid scintillation counting. Metabolite identification was done by co-chromatography with authentic standards of monepantel, monepantel sulfone and the cyclic metabolite previously found in sheep tissues and milk.The mean dose level achieved for all animals (excluding animal 11M) was 3.80 mg monepantel/kg bw, with an overall range of 3.76-3.86 mg monepantel/kg bw. One animal (11M) received an elevated dose level of 4.70 mg monepantel/kg bw as a result of complications at the first dose attempt. Residue data were linearly corrected back to the target dose in the statistical evaluation, which is acceptable in this narrow dose range.

[^{14}C]Monepantel is rapidly absorbed from the gastro-intestinal tract and distributed to tissues. Mean monepantel equivalent concentrations in plasma peaked at 24 hours with mean concentration of 0.268 mg equivalents/kg. Total radioactive residue levels then declined steeply thereafter and had halved by between 48 hours and 72 hours after administration. From 96 hours after administration, the rate of decline was lower.

Elimination was mainly through faeces (36% of dose) with a significant amount through urine (21% of dose).

The drug was distributed principally to the fat, with progressively smaller amounts in liver, kidney and muscle. Depletion of total radioactive residues occurred in all tissues from 3 to 21 days after administration.

As in sheep, the major metabolite in tissues was monepantel sulfone, being 30 to 84% of the tissue residue at 3 days after administration. A remarkably low extraction ratio of approximately 63% of total radioactive residues was found in liver at day 3 and 13% at day 21. It was noted that the level of extractable liver residues was lower in cattle than in sheep, and this was argued to be related to differences in the rate of metabolism between cattle and sheep.

A pilot GLP absorption, distribution, metabolism and elimination (ADME) study was conducted in one lactating dairy cow with [^{14}C]monepantel at an oral dose of 10 mg/kg monepantel in a predecessor formulation similar to the commercial formulation. The cow was kept in a metabolism crate for the collection of urine and faeces until sacrifice at day 21. Blood samples were collected at regular intervals. Milk was collected every 12 hours until sacrifice, when samples of edible tissues and bile were collected. Radioactivity was determined in all samples by liquid scintillation counting, either by direct counting, solubilisation or combustion. Selected whole milk samples were separated into cream and skim milk.

The total recovery of radioactivity via excretion was higher than 92% of the administered dose, with urine, faeces and milk accounting for 34%, 48% and 11% of the dose, respectively.

Maximum total radioactive residues in urine and faeces were observed in the 24 to 48 hour pools, and then decreased steadily. Maximum milk total radioactive residues (about 9000 µg/kg equivalents) were observed in the 36 hours milk sample, with steady decline thereafter. The radioactivity was concentrated in the cream (fat) fraction with very little in the skim milk fraction. Monepantel sulfone accounted for about 90% of milk total radioactive residues between 4 and 7 days. Since the study only comprises one animal it is considered supportive but cannot be accepted as a basis for setting a MRL for milk.

Non-radiolabelled studies

A tissue residue study was conducted with 20 young Angus cross cattle of mixed sex. Cattle were treated with monepantel orally three times, 21 days apart at a nominal dose of 0.15 ml/kg bw (3.75 mg monepantel/kg bw). Following the third treatment, animals were progressively sacrificed at the following times: 4, 7, 10 and 13 days. Tissue specimens were collected (muscle, kidney, liver, renal fat and subcutaneous fat) and analysed for monepantel sulfone residues. For all tissue types, the limit of quantification (LOQ) was 5 µg/kg.

Additionally, blood samples were collected following each treatment to assess possible accumulation of monepantel and monepantel sulfone. Blood specimens were collected after 1st, 2nd and 3rd treatments at predefined intervals between 4 hours and 20 days. Blood concentrations were determined for monepantel and monepantel sulfone using a validated LC-MS/MS method. The LOQ was 0.25 ng/ml for monepantel and monepantel sulfone.

The blood profiles of the animals were compared following repeated administration and no accumulation of monepantel and monepantel sulfone in blood was evident.

The maximum monepantel sulfone residues observed were 4110, 4680, 1090, 478 and 231 µg/kg for subcutaneous fat, renal fat, liver, kidney and muscle, respectively at day 4. These concentrations depleted steadily and maximum residues observed were 1720, 770, 146, 61.8 and 22.8 µg/kg for subcutaneous fat, renal fat, liver, kidney and muscle, respectively at day 13. The half-life estimates for muscle, kidney, liver, renal and subcutaneous fat were 2.8, 2.7, 2.7, 2.9 and 5.1 days, respectively.

Selection of marker residue and ratio of marker to total residues

Monepantel sulfone is the predominant moiety found in bovine tissues and is therefore retained as the marker residue.

As the theoretical maximum daily intake based on total radioactive residues at 3 days is below the ADI, data from day 3 were used in the calculation of the ratio of marker to total residues (MR:TR). The following ratios were derived: liver 0.30; kidney 0.55; muscle 0.67 and fat 0.84.

2.2.3. Monitoring or exposure data

No monitoring or exposure data relevant to the use of monepantel in cattle were available in addition to the data presented elsewhere in the residues section of this report.

2.2.4. Analytical method for monitoring of residues

Bovine tissues:

The proposed regulatory analytical method for monepantel sulfone in bovine muscle, fat, liver and kidney is based on extraction and protein precipitation with acetonitrile and the sample extracts are analysed by gradient LC-MS/MS. The method has been satisfactorily validated with respect to specificity, accuracy, precision, linearity, LOQ, LOD, stability of matrix and extracts. The validation ranges were 5 - 1750 µg/kg for muscle, 5 - 17500 µg/kg for fat, 5 -12000 µg/kg for liver, and 5 - 5000 µg/kg for kidney. The LOQ was 5 µg/kg for all tissues. The method is considered validated according to the requirements of Volume 8 of the Rules Governing Veterinary Medicinal Products in the EU.

Bovine milk:

An analytical method for monitoring of residues in milk has been provided. The method was previously accepted for monitoring monepantel sulfone residues in ovine and caprine milk and has now been revalidated for use in bovine milk. The proposed regulatory method for analysis of monepantel sulfone in bovine milk is based on extraction and protein precipitation with acetonitrile followed by solid phase extraction. The sample extracts are analysed by gradient LC-MS/MS using an internal standard. The method has been satisfactorily validated in the range 50 – 1500 µg/kg for bovine milk and the LOQ is 50 µg/kg.

The relevant European Reference laboratory has reviewed the proposed analytical methods and considered that overall the methods are fit-for-purpose.

2.2.5. Findings of EU or international scientific bodies

No relevant evaluations by other EU or international scientific bodies relating to residues of monepantel in cattle were identified. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has evaluated monepantel and recommended the establishment of MRLs in ovine species.

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 and therefore no data were required.

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

The available data were not sufficient to allow a recommendation for an MRL for milk. As a consequence the use of monepantel in cattle should be restricted to animals not producing milk for human consumption.

No other relevant factors were identified for consideration of the risk management recommendations.

3.3. Elaboration of MRLs

Based on the marker residue data at day 4 and the ratios of marker to total residues at day 3, the following MRL values are derived:

Tissue	**MRL**
Muscle	300 µg/kg
Fat	7000 µg/kg
Liver	2000 µg/kg
Kidney	1000 µg/kg

The available data were not sufficient to allow a recommendation for an MRL for milk.

Calculation of theoretical daily intake of residues

Edible tissue or products	**Daily consumption (kg)**	**MRL proposal (µg/kg)**	**Ratio of marker to total residue and correction for mol wt[#]**	**Total residue intake (µg)**
Muscle	0.30	300	0.67 * 0.94	125
Fat	0.05	7000	0.84 * 0.94	390
Liver	0.10	2000	0.30 * 0.94	625
Kidney	0.05	1000	0.55 * 0.94	85
Estimated total daily intake (µg/person)				1225
Total % of ADI				68

[#]*Correction for molecular difference parent/marker: 473/505 = 0.94*

Based on the above figures the maximum theoretical consumer intake represents 68% of the ADI (of 1800 µg/person). When intake derived from consumption of ovine milk is also considered, the theoretical maximum daily intake represents approximately 83% of the ADI.

3.4. Considerations on possible extrapolation of MRLs

In line with Article 5 of Regulation (EC) No 470/2009, and taking account of the established maximum residue levels in ovine and caprine species, the CVMP considered the possibility of extrapolating its recommendation on maximum residue limits for monepantel in bovine species to other food producing species and commodities. However, since there is a large species variation in tissue distribution, as well as in elimination rate of monepantel between sheep and cattle, no extrapolation to other animal species is recommended.

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 by the CVMP for monepantel,
- monepantel sulfone was retained as the marker residue,
- the following ratios of marker to total residues are established based on total residue levels at day 3: liver 0.30; kidney 0.55; muscle 0.67 and fat 0.84,
- a validated analytical method for the monitoring of residues of monepantel in edible bovine tissues is available,
- the available data did not allow derivation of an MRL for milk,
- as a maximum residue limit in milk cannot be derived, use of the substance should be limited to animals not producing milk for human consumption,

the Committee recommends the establishment of maximum residue limits for monepantel in accordance with the following table:

Pharmaco-logically active substance	**Marker residue**	**Animal species**	**MRLs**	**Target tissues**	**Other provisions**	**Therapeutic classification**
Monepantel	Monepantel sulfone	Bovine	300 µg/kg 7000 µg/kg 2000 µg/kg 1000 µg/kg	Muscle Fat Liver Kidney	Not for use in animals producing milk for human consumption	Antiparasitic agents / Agents (acting) against endoparasites

Based on the recommended maximum residue limits the theoretical intake of residues from bovine tissues represents approximately 68% of the ADI. When intake derived from consumption of ovine milk is also considered, the theoretical maximum daily intake represents approximately 83% of the ADI.

4. Background information on the procedure

Submission of the dossier	15 January 2015
Steps taken for assessment of the substance	
Application validated:	04 February 2015
Clock started:	05 February 2015
List of questions adopted:	04 June 2015
Consolidated responses to list of questions received	17 November 2015
Clock restarted:	23 November 2015
List of outstanding issues adopted:	21 January 2016

Clock re-started:	20 April 2016
CVMP opinion adopted	19 May 2016