14 April 2011
EMA/CVMP/306267/2011
Veterinary Medicines and Product Data Management

Committee for Medicinal Products for Veterinary Use

European public MRL assessment report (EPMAR)

Monepantel (ovine and caprine species)

On 13 April 2011 the European Commission adopted a Regulation[1] for the extension of provisional maximum residue limits for monepantel in caprine species, valid throughout the European Union. Maximum residue limits for monepantel had previously been established for ovine species and provisional maximum residue limits had been established for caprine species with an expiry date of 1 January 2011[2]. 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 use in ovine and caprine species for the treatment and control gastrointestinal roundworms (nematodes), as an oral solution.

Novartis Animal Health Inc submitted the original application for the establishment of maximum residue limits to the European Medicines Agency on 31 January 2008.

Based on the original and complementary data in the dossier, the Committee for Medicinal Products for Veterinary Use concluded that monepantel should be included in Annex I of Council Regulation (EEC) No 2377/90 for ovine species and Annex III of Council Regulation (EEC) No 2377/90 for caprine species.[3] This recommendation was confirmed on 8 May 2009 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 8 June 2009.

Novartis Animal Health Inc submitted a request for extension of the provisional MRLs for caprine species on 12 July 2010. The request was reviewed by the Committee for Medicinal Products for Veterinary Use, which subsequently recommended extension of the provisional MRLs to the European Commission. This recommendation was confirmed on 12 February 2011 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 13 April 2011.

[1] Commission Regulation (EU) No 362/2011, O.J. L 100, of 14.04.2011

[2] Commission Regulation (EU) No 478/2009,O.J. L 144, of 09.06.2009

[3] Annexes to Regulation (EEC) No 2377/90 were repealed by Commission Regulation (EU) No 37/2010, O.J. L15, of 20.01.2010

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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:	EU/08/163/NOV
Applicant:	Novartis Animal Health Inc
Target species:	Caprine, ovine
Intended therapeutic indication:	Treatment and control 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 body weight, respectively.

Monepantel is currently included in Commission Regulation (EU) No 37/2010[4] as indicated in the following table:

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Monepantel	Monepantel-sulfone	Ovine	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
		Caprine	700 µg/kg 7000 µg/kg 5000 µg/kg 2000 µg/kg	Muscle Fat Liver Kidney	Provisional MRLs expire on 1.1.2011 Not for use in animals producing milk for human consumption.	Antiparasitic agents/Agents acting against endoparasites

Novartis Animal Health has requested an extension to the provisional MRLs in caprine species in order to complete the scientific studies requested by the Committee.

The scientific assessment previously carried out by the Committee leading to the recommendation for the establishment of MRLs in ovine species and of provisional MRLs in caprine species is reported in the paragraphs below, and has been adapted taking into consideration the provisions set out in Regulation (EC) No 470/2009.

[4] OJ No L 15 of 20.01.2010

2. Scientific risk assessment

2.1. Safety assessment

2.1.1. Overview of pharmacological properties

Pharmacodynamic properties including mode of action

Monepantel is specific towards the ACR-23 protein which belongs to a nematode-specific subfamily of nicotinic acetylcholine receptor. This receptor is not present in mammals, which would explain the low activity of monepantel in organisms other than nematodes.

Safety pharmacological studies in rats indicate that monepantel does not exert effects on the cardio-vascular system, the respiratory tract or gastro-intestinal tract at a dose of 2000 mg/kg bw, and nor does it exert neurobehavioural effects at this dose.

Pharmacokinetic properties (in laboratory animals)

In rats the bioavailability based on 14C-monepantel was approximately 30 % after a single oral dose of 2.5 mg/kg bw. The terminal elimination of radioactivity from plasma occurred roughly monoexponentially with half-lives between 40 and 60 hours. The oral bioavailability of parent monepantel was estimated to be 9.4 % indicating that a part of the absorbed oral dose is eliminated by first-pass metabolism. Monepantel was excreted mainly via the faeces (70 to 97 %) within 3 days. Metabolite profiles in faeces showed mainly unchanged parent (25 % of the mean daily dose) and the metabolite M3 (hydoxylated sulfone, 52 % of the daily dose).

After repeated daily oral administration of 10 mg/kg bw for seven days, the major part of the administered radioactivity was recovered in faeces (60 to 80 %) and some in urine (3 to 6 %). Females showed a somewhat slower metabolism/elimination than males. Absolute residue concentrations were generally highest in the liver and fat, followed by adrenals, pancreas and ovaries. Concentrations were low in blood and muscle and intermediate in kidney. The residue levels in organs and tissues were generally higher in females than in males.

In all tissues residues were characterized as mainly parent drug and the sulfone metabolite. In addition three minor metabolite fractions and a further five very minor fractions were detected in tissues.

In dogs, no formal metabolism study has been undertaken, but pharmacokinetic data for non-radioactive monepantel after intravenous, oral and dermal administration were available. The parent compound was observed initially but depleted relatively quickly from blood. The sulfone metabolite was the dominant metabolite, appearing later and depleting rather slowly compared to in rats and sheep. The sulfone metabolite was seen to accumulate in dogs, while it did not accumulate in rats or sheep, but this accumulation was not related to the cytotoxicity seen in repeated dose studies in dogs.

In vitro studies using liver microsomes were performed to determine the intrinsic clearance of parent compound in mouse, rat, dog and human, with a view to monitoring a possible relationship between toxicological response and metabolic stability of parent compound in various species and to comparing the interspecies pattern and nature of metabolites. High intrinsic clearance values of monepantel (at 1 µmol/l) were observed in liver microsomes of rat and man whereas only moderate values were determined in liver microsomes of mouse and dog. The pattern of metabolites in incubations at 10 µmol/l monepantel were comparable between the four species. However, an additional minor metabolite (P32.5) was formed in rat and human microsomes. Data from in vivo studies show that this metabolite is not present in edible sheep tissues. A number of weaknesses were noted with this study, including the fact that microsomes from only male mice, rats and dogs were used, while data from *in vivo* studies show that female rats metabolise/eliminate monepantel more slowly than males.

An additional *in vitro* study was performed using dog and human microsomes. One of the intentions of this study was to investigate whether the dog is an inappropriate species for an extrapolation of toxicological findings to humans. Biotransformation rates of monepantel were determined based on calculated half-lives of the parent compound and were shown to be twice as high in dogs as in human donors. This was suggested to reflect a pharmacokinetic difference pointing to a specific toxicological sensitivity in the dog.

However, the data generated by the in vitro studies were not considered sufficient, on their own, to allow firm mechanistic conclusions to be drawn. A number of shortcomings were noted with the studies, including the fact that while the proposed biotransformation pathways in rats include several sulfotransferase-mediated steps, the in vitro metabolism studies concentrated on metabolite patterns arising from microsomal proteins and did not examine cytosolic enzymes which would include sulfotranferases.

2.1.2. Calculation of pharmacological ADI

Specific studies to establish a pharmacological ADI were not conducted. Safety pharmacological studies mentioned above and results from oral acute and subchronic toxicology studies suggested that monepantel does not exert significant secondary pharmacological activity on major organ systems. Therefore, the establishment of a pharmacological ADI was not considered relevant for the safety assessment of the substance.

2.1.3. Overview of toxicology

Single-dose toxicity

The results of single oral dose studies in rats indicated low acute toxicity of monepantel. Following oral as well as dermal administration, the lethal dose was greater than the limit dose of 2000 mg/kg bw in rats. No substance-related effects were identified on respiration rate, body temperature, blood pressure or heart rate. Monepantel was considered to possess low acute toxicity.

Tolerance in target species

Target animal safety studies were conducted in sheep at 50, 75, 100 and 125 mg/kg bw (33 times the maximum recommended dose of 3.75 mg/kg bw). At 125 mg/kg there was a transient decrease of appetite, slight increases in fluoride oxalate glucose, serum glucose and urea concentrations, a slight trend towards increased alanine aminotransferase concentrations, and slightly decreased haemoglobin concentrations. At 100 mg/kg, only the slightly decreased haemoglobin concentration could be considered treatment-related. It was concluded that the sheep tolerated single dose levels of up to 33 times the maximum therapeutic dose very well, without toxicologically significant changes in any of the observed parameters.

Repeated dose toxicity

Rats

Three repeated dose toxicity studies have been carried out in rats. Consistent with the pharmacokinetic data, female rats were generally more sensitive than male rats.

The first study was a 4 week non-GLP study in which animals (5 per sex per dose) were exposed to monepantel in the diet at 0, 1000, 4000 and 12000 mg/kg feed corresponding to 0, 90, 350, or 1000 mg monepantel/kg bw/day. The compound was clinically well tolerated at all concentrations. Increased cholesterol, triglycerides and phospholipids indicating changes in lipid metabolism and increased liver weights were seen at all dose levels in females and at 4000 and 12000 mg/kg feed in

males. Centrilobular hypertrophy of the liver and follicular hypertrophy of the thyroid were observed at all dose levels. No NOEL could be set.

The second rat study was a 13-week GLP study. Monepantel was administered in the diet at 0, 50, 200, 1000 or 12000 mg/kg feed corresponding to 0, 4, 15, 75 and 900 mg/kg bw/day (10 animals per sex per dose). No clinical signs were observed and no differences in body weight were detected. The main targets were the liver and lipid metabolism. Small changes were observed in plasma glucose, phospholipids, triglycerides, bilirubin, and albumin in the highest dose groups (1000 and 12000 mg/kg feed) and mainly in females. Liver weights were increased in females at 1000 and 12000 mg/kg feed. Centrilobular hepatocellular hypertrophy was present in 3 of 10 females at 1000 mg/kg feed and in all females at 12000 mg/kg feed. A NOEL of 15 mg/kg bw/day (200 mg/kg feed) was determined.

The third study in rats was a 52-week GLP compliant study. Monepantel was administered in the diet at 0, 50, 200, 1000 or 12000 mg/kg feed corresponding to 0, 2.7/3.4, 10.7/14, 54/67 and 656/778 mg/kg bw/day for males/females (20 animals per sex per dose). There were no clinical signs and no effects on food consumption or body weights that were related to treatment. In clinical chemistry, increased protein, albumin and globulin levels, and decreased glucose levels were considered possibly treatment related at 12000 mg/kg feed. Increased cholesterol, triglycerides and phospholipids were observed at 12000 mg/kg feed. Elevated liver weights were observed at 1000 and 12000 mg/kg feed. It was concluded that effects on lipid metabolism, plasma proteins and liver weight were the main effects at the high dose. There was no indication of proliferative lesions. A NOEL of 14 mg/kg bw/day (200 mg/kg feed) was established.

Mice

A repeated dose (GLP) toxicity study over 3 months was carried out in mice. Mice were exposed to monepantel in the feed at 0, 30, 120, 600 or 6000 µg/kg feed, corresponding to 0, 5, 18, 100 or 1000 mg/kg bw/day, respectively (10 animals per sex per dose). No treatment-related clinical signs of toxicity and no significant differences in body weight or food consumption were observed. In clinical chemistry changes were observed in bilirubin, cholesterol, alkaline phosphatase, aspartate transaminase and alanine transaminase at 600 and 6000 mg/kg feed. Microscopic changes were observed in the liver at 600 and 6000 mg/kg feed and consisted of predominantly centrilobular fatty change. A NOAEL of 18 mg/kg (120 mg/kg feed) was retained.

Dogs

Three repeated-dose, GLP compliant toxicity studies have been carried out in dogs. In the first study animals were dosed with 0, 5000, 15000 and 40000 mg/kg feed (161/184, 566/561, 1217/1472 mg/kg bw/day males/females) for 4 weeks (2 animals per sex per group). Treatment was well tolerated despite some body weight loss in males in the high dose group. Increased alkaline phosphatase activities and adrenal weights at all dose levels and increased liver weights in females given 40000 mg/kg feed were not associated with histological correlates and no other parameter indicative of potential liver damage was effected. Lower thymus weights and thymus involution were noted in the high dose group. No NOEL could be established as effects were seen at all dose levels.

In the second study dogs (4 dogs per sex per group) received monepantel for 13 weeks in the feed at 0, 300, 3000, or 30000 mg/kg feed (9.9/10.7, 97/107, 963/1176 mg/kg bw/day males/females). Food consumption was not affected by treatment but a lower body weight gain was recorded in females given 30000 mg/kg feed during the treatment period. Treatment related changes in alkaline phosphatase values were noted in all groups but the biochemical parameters alanine transaminase and aspartate transaminase were not affected. In the highest dose group in females, gamma-glutamyl transpeptidase was increased. Higher liver weights were recorded at all concentrations in both sexes at the end of the treatment period. No treatment-related necropsy findings were noted. Upon microscopic

examination treatment-related changes were noted in the liver (hepatocellular hypertrophy, biliary proliferation, brown pigments in Kupffer cells and hepatocytes), small intestine (dilatation of glands) and pancreas (increased apoptosis) in the various groups. An increased incidence and/or severity was seen for hepatocellular lesions at 3000 and 30000 mg/kg feed in both sexes. The bile duct proliferation, the brown pigment in hepatocytes/Kupffer cells and the increase in alkaline phosphatase activity could all be related to potential liver cholestasis. One female showed a slight hypertrophy as well as higher liver weight and increased alkaline phosphatase at 300 mg/kg feed. Findings in the pancreas and small intestine were seen in all dose groups. A NOEL could not be set as effects were seen at all dose levels.

The third study in dogs was conducted over 52 weeks. Monepantel was administered in the diet at 0, 100, 300 or 3000 mg/kg feed corresponding to 0, 3/3, 8/10 and 91/99 mg/kg bw/day for males/females (4 animals per sex per dose). Reduced body weight gain was recorded in animals at 3000 mg/kg feed. Higher alanine transaminase (both sexes) and gamma-glutamyl transpeptidase (males only) activities, lower total protein, albumin and calcium levels and lower albumin/globulin ratios were noted at 3000 mg/kg feed. At the concentration of 300 mg/kg feed, lower albumin levels and albumin/globulin ratio were observed in females. At all feeding levels, effects on alkaline phosphatase activity and liver weights associated with hepatocellular hypertrophy indicated the liver as the main target organ. Elevated adrenal weights associated with cortical cell hypertrophy and elevated thyroid weights without a histopathological correlate were seen in the mid and high dose groups. Brown pigmentation in hepatocytes and Kupffer cells as well as increased proliferation of smooth endoplasmic reticulum membranes, dilated intestinal glands (probably related to increased turnover of goblet cells and mucosa production and secretion), minimal increase of brown pigmentation in tubular cells of kidney, and increased apoptosis of pancreas acinar cells were also observed at the lowest dose but were also seen in the control groups. Microscopic examination showed bile duct hyperplasia in the liver of both sexes at 3000 mg/kg feed. No proliferative pre-neoplastic lesions were observed. While a dose related response was evident for the liver effects, particularly the increase in alkaline phosphatase activity, the overall conclusion from the statistical analyses (using analysis of variance) was that the effects were not statistically significant at the lowest dose of 3 mg/kg bw/day. Based on this, a NOAEL of 3 mg/kg bw/day was established.

Reproductive toxicity, including developmental toxicity

In a GLP compliant study monepantel was administered orally to 2 successive generations (F0 and F1) of male and female rats by admixture in the diet at 0, 200, 1500, and 12000 mg/kg feed (10/32, 82/245, and 650/2000 mg/kg bw/day in males/females). There was no mortality and no treatment related clinical signs. Food consumption and body weights were similar in all groups. Mating, fertility, conception and gestation were all 100 %. Precoital time and gestation length were not affected. Implantations, post implantation loss, viability index, and weaning index were all unaffected. Sperm analysis did not reveal any difference between control and dosed males. Increased adrenal weights and relative liver weights were observed at 1500 and 12000 mg/kg feed in P and F1 females. Liver weights were also increased at 12000 mg/kg feed in F1 and F2 pups. No treatment-related changes were noted in macropathology. Histopathological evaluation revealed centrilobular hepatocellular hypertrophy and cortical cell hypertrophy of the zona glomerulosa in the adrenal glands of P and F1 females at 1500 and 12000 mg/kg feed. A NOEL of 200 mg/kg feed corresponding to 32 mg/kg bw/day was established.

In a GLP compliant oral gavage embryo/foetal development study in rats, monepantel administered at doses of 0, 100, 300 and 1000 mg/kg bw/day (during gestation day 6 through 20, with 22 animals per dose) caused no adverse effect on embryonal and foetal development. NOELs for maternal and foetal toxicity and for teratogenicity were 1000 mg/kg bw/day.

Similarly, in a GLP compliant oral gavage embryo/foetal development study performed in rabbits administered doses of 0, 100, 300 and 1000 mg/kg bw/day (during gestation day 6 through 27, with 20 animals per dose), no adverse effect on embryonal and foetal development was observed. NOELs for maternal and foetal toxicity were 1000 mg/kg bw/day. Monepantel did not show any teratogenic potential under the conditions of the study.

Genotoxicity

Monepantel was tested in a comprehensive series of mutagenicity test systems with studies performed under GLP conditions. Negative results were obtained in the Ames' assay, in the *in vitro* chromosomal aberration test and in the *in vitro* micronucleus test. Additionally the *in vivo* micronucleus assay in mice revealed negative results. Taking together all data from *in vitro* and *in vivo* mutagenicity tests there was no indication of mutagenic activity of monepantel.

The sulfone metabolite was tested in the Ames' assay (GLP compliant) and in the *in vitro* micronucleus test (TK6 cells). Results did not indicate that the sulfone metabolite has mutagenic potential.

Carcinogenicity

Two GLP compliant carcinogenicity studies have been conducted, one in rats and one in mice. In rats monepantel was administered in the diet at 0, 100, 1000 or 12000 mg/kg feed corresponding to 0, 4.6/5.6, 47/57 and 578/707 mg/kg bw/day in males/females (50 rats per sex per group). No specific clinical signs could be observed and linked with the treatment. A consistently slightly lower mean body weight development in females fed with 12000 mg/kg was considered to be test item-related but non-adverse because of the low magnitude of the change. Slightly increased liver, kidney and heart weights were recorded in females fed with 1000 or 12000 mg/kg. In the absence of any correlating microscopic findings, these effects were considered to be possibly test item-related but non-adverse. The incidence, onset and location of palpable nodules/masses did not distinguish test item-treated rats from their respective controls. Similarly, the incidence of histopathological lesions did not indicate any effect of treatment. Monepantel was not considered to be carcinogenic in rats.

In mice, an 18-month carcinogenicity study was conducted. Monepantel was administered in the diet at 0, 10, 30, 120 or 500 mg/kg feed corresponding to 0, 1.5, 5, 20 or 69/92 (males/females) mg/kg bw/day (50 mice per sex per group). No specific clinical signs could be observed and linked with the treatment. A statistically significant increase in absolute and relative liver weights was noted in females at 120 and 500 ppm. Microscopically, increased incidences and severities of fatty liver were noted in males and females at 120 and 500 ppm. Due to the mostly macrovesicular appearance of fatty liver, this alteration was considered to be indicative of increased lipid metabolism or decreased availability of transporter mechanisms. No further indicator of adverse liver injury was recorded and hence, this lesion was deemed to be an adaptive, metabolic response rather than an adverse effect. In addition, indicators of microvesicular steatosis were not seen. There was no indication of an oncogenic potential of monepantel in this study.

Studies of other effects including immunotoxicity and neurotoxicity

Monepantel was not irritating in an acute dermal irritation test in rabbits. In the local lymph node assay monepantel did not induce delayed contact hypersensitivity. An acute eye irritation test in rabbits showed that monepantel is a slight irritant.

Effects on biochemical liver parameters and thyroid hormones in female rats were investigated due to the increased thyroid weights and follicular cell hypertrophy in rats. Due to the lack of plasma hormone changes of TSH, T3 and T4 a rat specific mechanism on the liver-pituitary-thyroid-axis could not be confirmed. Additionally, increased thyroid weights were seen in dogs. Therefore, effects on the thyroid were considered relevant for human safety assessment.

Based on structure-activity modelling the potential toxicological properties of the impurity AHC 2155367 (N-[2-(5-cyano-2-trifluormethyl-phenyloxy)-1-(S)-1-cyano-1-methyl-ethyl]-4-chloro-benzoic amide), specified at ≤0.5 %, did not raise a specific toxicological concern in addition to that relevant to the parent compound.

Mutagenicity studies with the sulfone metabolite did not show any mutagenic potential, as reported in the *Mutagenicity* section, above.

2.1.4. Calculation of the toxicological ADI or alternative limit

Toxicity of monepantel when repeatedly administered with the daily diet was shown to be generally low to moderate in laboratory animals up to the highest concentrations tested. The main target organ was the liver in all species investigated. The NOEL in the rat was 14 mg/kg and the NOAEL in the mouse was 18 mg/kg. The dog was shown to be the most sensitive species, with a NOAEL set at 3 mg/kg bw/day based on increased alkaline phophatase activity and elevated liver weights associated with hepatocellular hypertrophy, seen in the one year study. Based on this NOAEL and applying the standard uncertainty factor of 100 to account for inter and intra-species variability, a toxicological ADI of 0.03 mg/kg bw (1.8 mg/person) was established.

2.1.5. Overview of microbiological properties of residues

No data were provided but as microbiological effects are not expected for this type of substance this is acceptable.

2.1.6. Calculation of microbiological ADI

No microbiological ADI was calculated as microbiological effects are not expected for this type of substance.

2.1.7. Observations in humans

No information available.

2.1.8. Findings of EU or international scientific bodies

No evaluations by other international committees were available.

2.1.9. Overall conclusions on the ADI

The toxicological endpoint was considered the most relevant for the safety assessment of monepantel. Consequently, the toxicological ADI of 0.03 mg/kg bw (1.8 mg/person) was retained as the overall ADI for monepantel.

2.2. Residues assessment

2.2.1. Pharmacokinetics in target species

A GLP study investigating the absorption, distribution, metabolism and elimination (ADME) of radiolabelled monepantel following oral dosing of 5 mg/kg bw in sheep was conducted. Radioactivity was predominantly excreted through the faeces with a significant contribution from urinary elimination. Faecal excretion was high in the first 3 days (about 30 %), but then slowed, with about 2 to 3 weeks required for 90 % elimination.

Highest residues in edible tissues were found in the fat and liver. Muscle had the lowest residues. The approximate total radioactive residue proportions were 100 (fat) : 50 (liver) : 20 (kidney) : 10 (muscle) : 1 (blood) : 1 (plasma).

In sheep the metabolism is similar to that described in rat. Metabolism first involves oxidation of the parent to the transient sulfoxide M1, with rapid oxidation to the sulfone M2. The predominant metabolite is the sulfone. There is a further slow oxidation to M3. The other route involves cleavage to yield the phenol M4, together with its sulfate conjugate M5.

2.2.2. Residue depletion studies

Three depletion studies (2 in lambs and 1 in sheep) with single administration of unlabelled monepantel have been performed. Monepantel was administered at the proposed maximum dose rate of 3.75 mg/kg bw. In the first study, lambs were slaughtered at 7, 18, 29 and 40 days (8 animals at each time point) and in the second study at 7, 19, 29, 40, 70 and 77 days after administration. In the final study sheep were slaughtered at 7, 18, 29, 35, 70, 120 and 127 days after administration. In all studies residues were highest in fat followed by liver, kidney and muscle.

The unlabelled analytical method used in these studies was the proposed regulatory method for the sulfone metabolite with a limit of quantification of 50 µg/kg. Additional solid phase extraction clean-up was used to lower the limit of quantification to 10 µg/kg, and hence increase the number of quantifiable values for statistical purposes.

Selection of marker residue and target tissues

Based on the results of the ADME-14C-metabolism-study the sulfone metabolite of monepantel was selected as the marker residue. This sulfone metabolite represented a large and relatively constant fraction of total residues in all tissues (approximately 90 % in muscle, approximately 60 % in other tissues) and marker to total residue ratios were determined over a wide time period (2 to 35 days). The following ratios of marker to total residues, established at day 7, were selected for calculation of the daily intake of residues: 0.94 for muscle and 0.68 for fat, liver and kidney. While no tissue data are available between time of dosing and day 2 post treatment plasma profiles of the parent compound and the sulfone metabolite demonstrated that the sulfone metabolite becomes the more dominant compound in blood and therefore is expected to dominate in the tissues.

2.2.3. Monitoring or exposure data

Not provided.

2.2.4. Analytical method for monitoring of residues

A validated HPLC method with UV detection for determination of the sulfone metabolite of monepantel in tissues (fat, liver, kidney and muscle) of sheep is available according to the current requirements of Volume 8 of The Rules Governing Medicinal Products in the European Union. The limits of quantification for ovine tissues were 51 µg/kg for fat, 56 µg/kg for liver, 13 µg/kg for kidney and 15 µg/kg for muscle.

2.2.5. Findings of EU or international scientific bodies

No evaluations by other international committees were available.

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

None.

3.3. Elaboration of MRLs

Based on the residue distribution in tissues and residue depletion data MRL values of 7000, 5000, 2000 and 700 µg/kg can be recommended for fat, liver, kidney and muscle, respectively.

No data were available for milk therefore the use should be restricted to non lactating animals.

Calculation of theoretical daily intake of residues

Tissue	Consumption/ day (kg)	Proposed MRLs (µg/kg)	Ratio of marker to total residues from day 7 after dosing (ADME study)	Daily intake of residues (µg)
Muscle	0.3	700	*f*0.94*	*219*
Fat	0.05	7000	*f*0.68*	*482*
Liver	0.1	5000	*f*0.68*	*689*
Kidney	0.05	2000	*f*0.68*	*138*
Estimated total daily intake (µg/person)	0.5			1518
ADI (µg/person)				1800

f: Correction for molecular difference parent/marker: 473/505=0.94

The theoretical consumer intake of total residues represents 84 % of the ADI.

3.4. Considerations on possible extrapolation of MRLs

According to the Note for Guidance on the Risk Analysis Approach for Residues of Veterinary Medicinal Products in Food of Animal Origin (EMEA/CVMP/187/00-Final), the MRLs established for sheep may be extrapolated to goats if the data indicate that the marker residue established in sheep is also appropriate for goats and if the regulatory method established is appropriate for monitoring residues in goat tissue. 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, the assumption can reasonably be made that the sulfone metabolite will be the predominant metabolite in the goat and consequently it is accepted as the marker residue for goats as well as for sheep. However, further data should be provided to demonstrate that the regulatory method is applicable in goats.

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;
- at day 7 after administration the ratios of marker to total residue were 0.94, 0.68, 0.68, and 0.68 in muscle, fat, liver, and kidney respectively;
- ovine MRLs and the marker residue can be extrapolated to the goat species since metabolism data in sheep and all laboratory species provide clear evidence that the sulfone metabolite is the predominant metabolite of monepantel, and it is therefore reasonable to assume that this will be the case for the goat species as well;
- an analytical method for monitoring residues from sheep tissues validated according to the current requirements of Volume 8 is available;
- the applicability of the analytical method to goat tissues was not demonstrated;
- a study to demonstrate the applicability of the analytical method to goat tissues is currently ongoing;

The Committee, having considered the request and in accordance to Article 14(4) of Regulation 470/2009 recommends, by consensus the extension of the time period applying for the provisional MRLs in accordance with the following table:

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Monepantel	Monepantel-sulfone	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. Provisional MRLs expire on 1.1.2012	Antiparasitic agents/Agents acting against endoparasites

4. List of questions

1. In accordance with the CVMP Note for Guidance on the Risk Analysis Approach for Residues of Veterinary Medicinal Products in Food of Animal Origin (EMEA/CVMP/187/00-Final) the applicant is requested to demonstrate that the analytical method proposed for sheep is applicable to goat tissues.

5. Glossary

ADI – Acceptable daily intake

HPLC – High performance liquid chromatography

MRL – Maximum residue limit

NOAEL – No observed adverse effect level

NOEL – No observed effect level

6. Background information on the procedure

Submission of the dossier:	31 January 2008
Steps taken for assessment of the substance:	
Application validated:	14 February 2008
Clock started:	15 February 2008
List of questions adopted:	14 May 2008
Consolidated response to list of questions submitted:	13 October 2008
Clock re-started:	14 October 2008
CVMP opinion adopted:	12 November 2008
Request for extension of provisional MRLs for goats	12 July 2010
CVMP opinion	15 September 2010