8. Monepantel

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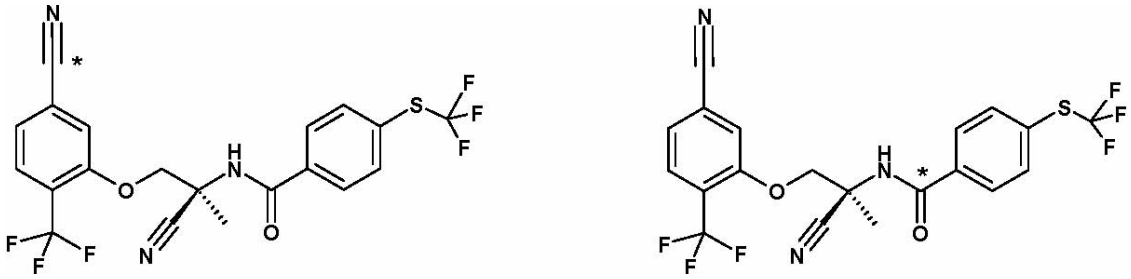
Identity

IUPAC Name: N-[(1S)-1-Cyano-2-(5-cyano-2-trifluoromethyl-phenoxy)-1-methyl-ethyl]-4-trifluoromethylsulfanyl-benzamide

Synonyms: N-[2-(5-cyano-2-trifluormethyl-phenyloxy)-1-(S)-1-cyano-1-methyl-ethyl]-4-trifluoromethylthio-benzoic amide, Zolvix

Chemical Abstracts Service Number: 887148-69-8



Molecular formula: $C_{20}H_{13}F_6N_3O_2S$

Molecular weight: 473.4

Background

Monepantel (CAS No. 887148-69-8) is a member of the amino-acetonitrile derivative anthelmintics. Monepantel causes a paralysis of gastrointestinal nematodes by binding to a unique receptor. It is administered as an oral drench to control gastrointestinal nematodes (roundworms) in sheep.

Monepantel was previously reviewed by the Committee at its Seventy-fifth Meeting (FAO, 2011), which established an ADI of 0–20 µg/kg bw, corresponding to an upper bound of acceptable intake of 1200 µg/day for a 60 kg person. The Committee recommended MRLs, determined as monepantel sulfone, in sheep tissue of 300 µg/kg in muscle, 700 µg/kg in kidney, 3000 µg/kg in liver and 5500 µg/kg in fat. Because sufficient data were available to calculate median residue values, the EDI approach was used. Using the model diet and marker to total residue ratio of 1 for muscle and 0.66 for fat, liver and kidney, and after applying a correction factor of 0.94 to account for the mass difference between monepantel sulfone (the marker residue) and monepantel, the EDI calculated is 201 µg/person per day, which represents 17% of the upper bound of the ADI.

At the Twentieth Session of the Codex Committee on Residue of Veterinary Drugs in Food (CCRVDF), concerns were raised that the recommended MRLs were significantly lower than those already established in some countries and could create trade problems (FAO/WHO, 2012). It was also noted that the recommended MRLs were not consistent with

the withdrawal times in some countries. The CCRVDF discussed higher MRLs, recognizing that it was within the purview of the Codex Committee, as risk managers, to modify the MRLs recommended by JECFA. Some Delegations did not consider advancing higher MRLs appropriate without an evaluation of their safety by JECFA, in recognition of JECFA's role as risk assessor for Codex. The CCRVDF agreed to request that JECFA evaluate the safety of the proposed higher MRLs in light of the information provided by the Committee. Specifically, JECFA was asked to consider if higher MRLs (Muscle, 700 µg/kg; Liver, 5000 µg/kg; Kidney, 2000 µg/kg; Fat, 7000 µg/kg) are compatible with the ADI and consistent with the JECFA process for the derivation of MRLs.

Current evaluation

No new data or studies were provided for the current evaluation. A summary of global approvals, the MRLs assigned by regulatory authorities, and associated withdrawal periods is provided in Table 8.1 (Novartis, 2013).

Table 8.1. Currently approved MRLs and withdrawal periods for Monepantel, all based on Monepantel sulfone as Marker Residue

Country or region	MRLs (µg/kg)	Withholding period (days)
European Union	Fat 7000 Liver 5000 Kidney 2000 Muscle 700	7
Argentina		7
Chile		7
Uruguay		7
Brazil		7
Republic of South Africa		10
New Zealand		7
Australia		14
Switzerland		7
Japan (Import tolerance only)	As above plus "Other edible tissues 7000"	N/A (Import tolerance only)

The MRLs and withdrawal period in New Zealand were confirmed by that country (New Zealand, 2013).

The information provided in response to the re-evaluation request noted that the MRLs proposed by the 75th Meeting of JECFA are lower than those established in the countries where monepantel is approved. Additionally, based on the residue studies provided in the original dossier, the proposed MRLs would be violated if animals were slaughtered at the established withholding periods in all of the countries listed in Table 8.1, except for Australia and the Republic of South Africa.

The MRLs listed in Table 8.1 would lead to a theoretical consumption of 84% of the ADI (Novartis, 2013). The EDI was described as being "…considerably lower." Neither the EDI nor the ADI referenced in this comment were provided.

Appraisal

The summary of global approvals clearly indicates the conditions of use for monepantel in several countries or regions of the world. It also includes the applicable MRLs and withdrawal times. Absent from the information is the assigned ADI that underpins these MRL assignments in Table 8.1.

EDI calculations based on the evaluation of the 75th JECFA and the EDI that would be consistent with the shortest identified withdrawal times in Table 8.1 are summarized in Tables 8.2 and 8.3.

Table 8.2. EDI based on median residues at Day 13 (1)

Tissue	Median	Consumption	MR:TR	Monepantel parent: Monepantel sulfone	Total
Muscle	76	0.3	1	0.94	21
Liver	595	0.1	0.66	0.94	85
Kidney	169	0.05	0.66	0.94	12
Fat	1156	0.05	0.66	0.94	82
TOTAL					**201**

NOTES: (1) Day 13 is the withdrawal day used by the 75th JECFA in its EDI calculation.

Table 8.3. EDI based on median residues at Day 7 (1)

Tissue	Median	Consumption	MR:TR	Monepantel parent: Monepantel sulfone	Total
Muscle	152	0.3	1	0.94	43
Liver	1295	0.1	0.66	0.94	184
Kidney	406	0.05	0.66	0.94	29
Fat	2620	0.05	0.66	0.94	187
TOTAL					**443**

NOTES: Day 7 is the shortest withdrawal period identified for monepantel approvals in Table 8.1.

The upper bound of the ADI assigned by JECFA is 1200 µg/day for a 60 kg person. The EDI, based on median residues at Day 13, is approximately 17% of the JECFA assigned ADI. The EDI based on median residues at Day 7, the shortest assigned withdrawal time cited in Table 8.1, is approximately 37% of the JECFA assigned ADI.

Maximum Residue Limits

In recommending MRLs for monepantel in sheep, the Committee considered the following factors:

- An ADI of monepantel of 0–20 µg/kg bw was previously established by the Committee, corresponding to an upper bound of the acceptable intake of 1200 µg/day for a 60 kg person.
- Monepantel is extensively metabolized.
- The metabolite monepantel sulfone is the marker residue in tissues.
- Fat contains the highest concentration of monepantel sulfone at all sampling times, followed by liver, then kidney and muscle. Liver and fat can serve as the target tissues.
- The ratios of the concentration of marker residue to total residues (MR:TR) are 1.0 in muscle and 0.66 in fat, liver and kidney.
- A validated analytical method for the determination of monepantel sulfone in edible sheep tissues (liver, kidney, muscle and fat) is available and may be used for monitoring purposes.
- MRLs were calculated on the basis of the upper limit of the one-sided 95% confidence interval over the 95th percentile of residue concentrations (UTL 95/95).

Consistent with the shortest withdrawal time assigned in Member States with an approved use of monepantel, the Committee recommended MRLs determined as monepantel sulfone, expressed as monepantel, in sheep tissue of 500 µg/kg in muscle, 1700 µg/kg in kidney, 7000 µg/kg in liver and 13 000 µg/kg in fat. Using the model diet and marker residue to total residue ratio of 1.00 for muscle and 0.66 for fat, liver and kidney, and

applying a correction factor of 0.94 to account for the mass difference between monepantel sulfone (the marker residue) and monepantel, the EDI is 443 µg/person per day, which represents 37% of the upper bound of the ADI.

Table 8.4. Calculation of the estimated daily intake (EDI)

Tissue	Median residue	Standard Food Basket (kg)	MR:TR ratio	Monepantel parent: Monepantel sulfone		Estimated Daily Intake (µg)
Muscle	152	0.3	1	0.94		43
Liver	1295	0.1	0.66	0.94		184
Kidney	406	0.05	0.66	0.94		29
Fat	2620	0.05	0.66	0.94		187
					EDI	**443**
					As % of ADI	37%

NOTES: MR:TR ratio is the ratio of marker residue to total residues (MR:TR).

References

FAO. 2011. Monepantel. *In*: Online Edition: "Residues of some veterinary drugs in foods and animals" Residue Monograph 12-2012. Available at http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-vetdrugs/en/ Accessed 2014-05-10.

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Novartis. 2013. Monepantel CODEX MRLs: re-evaluation at the Seventy-eighth Meeting of the Joint FAO/WHO Committee on Food Additives (JECFA): Data in support of higher MRLs. See: http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-vetdrugs/en/