Date: October 21, 2022

FREEDOM OF INFORMATION SUMMARY

Import Tolerance

VMF 006-250

monepantel

Cattle

monepantel sulfone (the marker residue): 7 parts per million (ppm) in cattle fat, 2 ppm in cattle liver, 1 ppm in cattle kidney and 0.3 ppm in cattle muscle

Petitioner:

Elanco US Inc.

Table of Contents

I. GENERAL INFORMATION

A. File Number

VMF 006-250

B. Petitioner

Elanco US Inc.
2500 Innovation Way
Greenfield, IN 46140

C. Drug Established Name

monepantel

D. Pharmacological Category

Antiparasitic

E. Species/Class

Cattle

F. Import Tolerances for Drug Residues in Edible Tissues

monepantel sulfone (the marker residue): 7 parts per million (ppm) in fat, 2 ppm in liver, 1 ppm in kidney, and 0.3 ppm in muscle

II. HUMAN FOOD SAFETY

A. Antimicrobial Resistance

The Agency evaluated the need to address the impact of the use of monepantel on antimicrobial resistance among bacteria of public health concern in or on monepantel-treated cattle. After reviewing information (literature, data, etc.) both submitted by the sponsor and available in the public domain, the Agency determined:

1) Monepantel is not regularly considered to have properties that would exert pressure towards the emergence or selection of resistant bacteria of public health concern in food-producing animals,
2) Monepantel is not used to treat gastroenteritis or other bacterial diseases in humans,
3) Monepantel (or a similar class representative) is not under development to treat a bacterial disease in humans, and
4) Monepantel is not indicated for a bacterial disease in a food-producing animal species.

Therefore, the Agency determined that a microbial food safety (antimicrobial resistance) assessment was not needed for this import tolerance for monepantel.

B. Toxicology

Toxicity studies considered in the human food safety assessment of monepantel are listed below:

- 90-day oral toxicity study followed by a 4-week recovery period in the Wistar rat (Study No. 858125)
- 13-week oral toxicity study in the CD-1 mice (Study No. 858126)
- 13-week oral toxicity study followed by a 4-week recovery period in Beagle dogs (Study No. 29215 TCC)
- 52-week oral toxicity study in Beagle dogs (Study No. 30240 TCC)
- 52-week oral toxicity study in Wistar rats (Study No. AHC-210225)
- Prenatal developmental oral toxicity study in the Han Wistar rat (Study No. 858651)
- Prenatal developmental oral toxicity study in the Himalayan Rabbit (Study No. 858649)
- Two generation reproduction oral toxicity study in the Han Wistar rat (Study No. A02970)
- Mutagenicity test using *Salmonella typhimurium* (Study No. 0512002)
- Chromosome aberration test with cultured human peripheral blood lymphocytes (Study No. 0512102)
- Bone marrow micronucleus test by oral route in mice (Study No. 30319 MAS)
- Ames test (Study No. 0413029)
- Micronucleus test *in vitro* using TK6 cells (Study No. 0414029)
- 78-week oncogenicity study in CD-1 mice (Study No. A23207)
- 104-week oncogenicity study in Wistar rats (Study No. A23218)

Center for Veterinary Medicine (CVM) evaluated the full toxicology study reports of these studies when establishing import tolerances for monepantel sulfone in edible tissues of sheep. The Freedom of Information Summary for the establishment of import tolerances in sheep edible tissues, VMF 005-967, dated January 19, 2016, contains a summary of these studies and CVM's evaluation. An Acceptable Daily Intake (ADI) of 30 µg/kg body weight (bw)/day was established based on the No-Observed-Effect Level (NOEL)/No-Observed-Adverse-Effect Level (NOAEL) of 3 mg/kg bw/day in a one-year toxicity study in dogs and a safety factor of 100. Based on this ADI, the safe concentrations for total residues of monepantel are determined to be 6 ppm for muscle, 18 ppm for liver, 36 ppm for kidney, and 36 ppm for fat, using food consumption factors of 300 g, 100 g, 50 g, and 50 g for these tissues respectively.

The Joint Food Agricultural Organization (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (JECFA) established an ADI of 0-20 µg/kg bw (WHO Technical Report Series (TRS) No. 969, 2012; WHO TRS No. 988, 2014; WHO TRS No. 1008, 2018). The ADI established by JECFA is lower than the ADI determined by CVM. Therefore, the safe concentrations calculated based on the JECFA ADI were used to derive the import tolerances.

C. Residue Chemistry

1. Summary of Residue Chemistry Studies

An evaluation of monepantel in cattle was performed at the 85th JECFA meeting (2017). The JECFA review of the studies below was used as a basis for establishing an import tolerance (FAO JECFA Monograph 21, 2018).

a. Total Residue and Metabolism Study

Total Radioactive Residue (TRR) Depletion and Metabolism of [^{14}C]-Monepantel Following Oral Administration to Beef Cattle (Study No. 286778)

Systemic absorption of monepantel was relatively high, with total radiolabeled residues reaching peak concentrations at 24 hours after dosing. About 21% of the dose was eliminated in the urine over three days. Approximately 36% of the dose was eliminated in feces. About 60% of the dose was recovered in excreta over three days, with the remaining material distributed in the tissues. Total residues depleted most slowly from renal fat followed by liver, kidney, and muscle (Table 1). Fat is established as the target tissue. The major metabolite identified was monepantel sulfone.

Table 1. Mean TRR (µg equiv/kg; mean ± standard deviation) in edible tissues of beef cattle (FAO JECFA Monograph 21, 2018).

Day	Fat	Liver	Kidney	Muscle
3	7373 ± 1164	2677 ± 256	1315 ± 328	201 ± 26
7	2636 ± 466	1587 ± 136	531 ± 86	80 ± 39
14	1019 ± 107	843 ± 42	246 ± 25	28 ± 10
21	362 ± 182	725 ± 177	111 ± 51	11 ± 4

b. Comparative Metabolism Study

Metabolite Profiling and Covalent Binding of [^{14}C] Monepantel in Rat, Bovine, and Sheep Hepatocytes (Study No. 151639)

The metabolism of monepantel in intact rat, cattle and sheep hepatocytes was investigated. Incubations were profiled by HPLC and profiles were similar across the tested species. The results of the *in vitro* study were consistent with those in the total residue and metabolism study (Study No. 286778).

c. Tissue Residue Depletion Studies

Residue depletion data are not needed for establishing an import tolerance because a withdrawal period is not assigned. However, the studies listed below provide supporting information about the depletion of monepantel from cattle.

(1) Depletion of Residues of Monepantel Sulfone in Edible Tissues of Beef Cattle Following Three Oral Administrations 21 Days Apart of Zolvix at 3.75 mg monepantel/kg bw (Study No. NAH-13-069)

The maximum monepantel sulfone residues were observed in the Day 4 samples. While initial residues in renal fat were highest, by the later sampling times, residues were highest in subcutaneous fat.

(2) Depletion of Residues of Monepantel Sulfone to Limit of Quantification in Edible Tissues of Beef Cattle Following Three Oral Administrations 21 Days Apart of Zolvix at 3.75 mg monepantel/kg bw (Study No. NAH-13-090)

The maximum monepantel sulfone residues were observed in the Day 21 samples. At the final sampling time (Day 85), all residues were below the method limit of quantitation (LOQ = 5 parts per billion (ppb)).

2. Target Tissue and Marker Residue

The target tissue is fat. The marker residue is monepantel sulfone.

3. Import Tolerances

We assign import tolerances of 7 ppm monepantel sulfone in cattle fat, 2 ppm monepantel sulfone in cattle liver, 1 ppm monepantel sulfone in cattle kidney and 0.3 ppm monepantel sulfone in cattle muscle, harmonized with Codex international standards.

4. Withdrawal Period

A withdrawal period is not assigned when establishing an import tolerance.

D. Analytical Method for Residues

1. Description of the Analytical Method

A validated LC-MS/MS method for measuring monepantel sulfone in cattle edible tissues was provided.

2. Availability of the Analytical Method

The validated analytical method for analysis of residues of monepantel sulfone is on file at the Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855. To obtain a copy of the analytical method, please submit a Freedom of Information request to: https://www.accessdata.fda.gov/scripts/foi/FOIRequest/requestinfo.cfm.

III. AGENCY CONCLUSIONS

The Center for Veterinary Medicine assigns import tolerances of 7 ppm monepantel sulfone in cattle fat, 2 ppm monepantel sulfone in cattle liver, 1 ppm monepantel sulfone in cattle kidney and 0.3 ppm monepantel sulfone in cattle muscle. The data submitted in support of establishment of the import tolerances for monepantel in cattle satisfy the requirements of section 512(a)(6) of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 510, Subpart C.