This is provisional English translation of an excerpt from the original full report.

Risk Assessment Report

Valnemulin

(Veterinary Medicinal Products)

Food Safety Commission of Japan (FSCJ)
September 2018

ABSTRACT

FSCJ conducted a risk assessment of valnemulin (CAS No. 101312-92-9), pleuromutilin (Pleuromulin) antibiotics, based on various documents.
In this assessment, FSCJ added reference information and revised description adjustment using the documents and new findings attached to the applications presented for conducting re-evaluation of veterinary medicinal products which contain this substance as an active substance (Econor 1 % Premix and 10 % Premix).

Data used in the assessment include pharmacokinetics (rats, dogs and pigs), residues (pigs), acute toxicity (mice and rats), sub-acute toxicity (mice, rats, dogs and pigs), reproductive developmental toxicity (mice, rats and rabbits), genotoxicity and microbiological effects.

No effect on reproductivity and teratogenicity were observed in toxicity studies. Although chronic toxicity/carcinogenicity study was not conducted, this substance was judged to have no genotoxicity relevant to human health based on the results of genotoxicity study. Considering the results of other toxicity studies, properties of this substance, and the evaluation by EMA that concluded the carcinogenicity study was unnecessary, FSCJ judged that the acceptable daily intake (ADI) for valnemulin could be specified applying the additional safety factor if a carcinogenicity study was not conducted.

The minimum no-observed-adverse-effect level (NOAEL) in the toxicological studies was 8 mg/kg body weight/day obtained in a 13-week subacute toxicity study in rats.

Microbiological ADI was estimated to be 0.00795 mg/kg bw/day based on MIC_{50} (0.053 μg/ml) by the equation of CVMP (The Committee for Medicinal Products for Veterinary Use in EMA). This ADI is equal to toxicological ADI (0.008 mg/kg bw/day) that was estimated by tentatively applying a safety factor of 1,000 on the premise that chronic toxicity/carcinogenicity study was not conducted, thus the toxicological safety is considered to be sequred sufficiently.
Hence, FSCJ specified the ADI of valnemulin as 0.008 mg/kg bw/day.

Table 1. *Levels relevant to toxicological evaluation of Valnemulin*

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical endpoints
Rats	Developmental toxicity study	0, 10, 30, 100	Dams: 10 Fetuses: 10 Dams: Suppressed body weight and decreased feed consumption Fetuses: Delayed ossification No teratogenicity was observed.
	13-week subacute toxicity study	0, 8, 16, 32, 64	8 Toxic sign was similar to the above study, the liver lesiones. (No effects on the thyroid)
	Two-generation reproductive toxicity study	0, 8, 40, 200 (→160)	Dams: 40 Dams: Suppressed body weight, convulsion, the liver lesiones
	Developmental toxicity study	0, 25, 75, 225	75 Dams: Maternal toxicity Fetuses: Wavy Ribs, delayed ossification No teratogenicity was observed
Dogs	13-week subacute toxicity study	0, 10, 30, 100	30 Severe convulsion, suppressed body weight, a high AP-value
Toxicological ADI			—
The critical study for setting Toxicological ADI			13-week sub-acute toxicity study in rats
Microbiological ADI			0.00795 mg/kg bw/day
The critical study for setting Microbiological ADI			geometric mean MIC_{50} excluding the non-sensitive strain 0.053 mg/mL (CVMP equation)
ADI			0.008 mg/kg bw/day