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

Risk Assessment Report

Tildipirosin

(Veterinary Medicinal Products)

Food Safety Commission of Japan (FSCJ)
November 2019

ABSTRACT

FSCJ conducted a risk assessment of tildipirosin (PMT) (CAS No. 328898-40-4), a macrolide antimicrobial agent, using a written application for the marketing approval of zuprevo 40 injection that is a veterinary medicinal product composing of PMT as the major component.

FSCJ considered PMT to be quickly absorbed after oral ingestion and the potential of the repeated dose to results a remarkable accumulation to be little, based on the data of the ADME studies in various animals. The parameters related the ADME such as Cmax and AUC were lower in rats than in dogs suggesting interspecies difference of the ADME.
Data from the intramuscular administration study in pigs suggested that the concentration remained rather constant for relatively long time after the administration. The biodistribution in pigs was high in the kidneys, liver and lung. Data on metabolism of PMT after the intramuscular administration suggested involvement of Cytochrome P450 system in the liver, similar to other macrolide antimicrobial agents as metabolic detoxication of PMT by conjugation.
In data on residue, the concentration of PMT decreased in each tissues by time, but PMT was detected in the liver and kidneys throughout the study period (up to 32 days after the administration).
FSCJ judged that PMT has no genotoxicity relevant to human health, based on the negative results in all genotoxicity studies, such as in vitro reverse mutation test, gene mutation test, chromosomal aberration test and in vivo micronucleus test. Hence, the acceptable daily intake (ADI) for PMT could be specified.
Although no carcinogenicity study on PMT was conducted, no change inducible neoplastic response was observed in subacute toxicity study in dogs and rats and in 55-week chronic toxicity study in dogs. In addition, PMT has no genotoxicity relevant to human health. Hence, carcinogenicity potential of this product to human through foods is considered negligible as long as it is appropriately used.

FSCJ specified the toxicological ADI to be 0.03 mg/kg bw/day applying the safety factor of 200 to the LOAEL of 6 mg/kg bw/day obtained in 13-week subacute toxicity study in dogs.
Microbiological ADI was estimated to be 0.28601 mg/kg bw/day.

FSCJ specified the ADI of PMT as 0.03 mg/kg bw/day as the toxicological ADI is smaller than the microbiological ADI.

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical endpoints[1]
Rat	28-day subacute toxicity study	0, 25, 100, 400	25 (LOAEL) Increased locomotor activity
	13-week subacute toxicity study	0, 20, 60, 400	20 (LOAEL) Increased locomotor activity, decreased gripping power
	Two-generation reproductive toxicity study	0, 20, 80, 320	Parents: 20 Vacuolation of follicular cells in the thyroid Reproductive activity: 80 Reduced testicular sperm counts, decreased litter size Offspring: 80 Retarded eruption of incisor
	Developmental toxicity study	0, 30, 120, 480	Dams: 120 Decreased feed consumption Offspring: 120 Decreased fetal weight Teratogenicity: Negative
Rabbit	Developmental toxicity study	0, 10, 30, 90	Dams: 30 Suppressed body weight Decreased feed consumption Fetauses: 30 Low fetal weight, increased findings of skeletal mutation Teratogenicity: Negative
Dog	4-week subacute toxicity study	0, 20, 60, 180	20 Cell vacuolation in various tissues/organs
	13-week subacute toxicity study	0, 6, 20, 60	6 (LOAEL) Emotional instability, tremor, weird sounds

[1] Major adverse effect observed at LOAEL

	55-week acute toxicity study	0, 2, (4), 10, 50 (oral administration)	10 Changes of blood chemical parameters, increases in organ weight, cell vacuolation in various tissues/organs
Toxicological ADI (mg/kg bw/day)			0.03 mg/kg bw/day
The critical study for setting Toxicological ADI			13-week subacute toxicity study (dogs) LOAEL: 6 mg/kg bw/day SF: 200
Microbiologicall ADI (mg/kg bw/day)			0.28601 mg/kg bw/day
The critical study for setting Microbiological ADI			A geometric mean MIC_{50} 5.2 μg/mL
ADI (mg/kg bw/day)			0.03 mg/kg bw/day