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

Risk Assessment Report

Cephapirin

(Veterinary Medicinal Products)

Food Safety Commission of Japan (FSCJ)
September 2018

ABSTRACT

FSCJ conducted a risk assessment of cephapirin (CAS No. 21593-23-7), an antimicrobial, based on EMEA evaluation reports of cephapirin benzathine (CAS No.94768-37-6) and cephapirin sodium (CAS No. 24356-60-3), the attached documents of the application for reevaluation for a veterinary medicinal product.

Data used in the assessment include pharmacokinetics (mice, rats, dogs, cattle and humans), residues (cattle), acute toxicity (mice and rats), subacute toxicity (rats and dogs), reproductive developmental toxicity (rats), genotoxicity and pharmacological effects.

Data of all *in-vitro* genotoxicity studies were negative, except some positive data on cephapirin sodium and cephapirin benzathine from *in-vitro* studies. Moreover, data from *in-vivo* mouse micronucleus test with intraperitoneal administration was negative even at high doses. Hence, FSCJ considered that cephapirin has no genotoxicity relevant to human health, thus it is possible to specify an ADI for cephapirin.

Major adverse effect observed in various toxicity studies was suppressed body weight.
In reproductive developmental toxicity studies, piloerection and/or alopecia was observed in dams but not teratogenicity.
Although carcinogenicity was not studied, precancerous change was not observed in the subacute toxicity study. On the basis of this fact and EMEA evaluation report, FSCJ judged that an ADI can be specified for cephapirin by applying an additional safety factor.
FSCJ specified a toxicological ADI for cephapirin as 0.023 mg/kg bw/day, by applying a safety factor of 1,000 (consist of an additional safety factor of 10 for lack of data on chronic toxicity and carcinogenicity) to the NOAEL of 22.6 mg (titer)/kg bw/day which was obtained in a 13-week subacute toxicity study in rats.
Microbiological ADI was estimated to be 0.002 mg/kg bw/day.
FSCJ specified the ADI of cephapirin as 0.002 mg/kg bw/day as the microbiological ADI is smaller than the toxicological ADI.

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

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day) and Critical endpoints[1]
Rat	4-week subacute toxicity study	0, 30, 100, 300, 1 000 (sodium salt) (gavage administration)	300 (294 as cephapirin) Fatty change in the liver (M)
	4-week subacute toxicity study	0, 10, 50, 200, 1 000 (benzathine salt) (gavage administration)	200 (150 as cephapirin) Urinalysis findings, changes of blood biochemical parameters, changes in the weight of organs, histopathological findings (M/F)
	13-week subacute toxicity study	0, 22.6 (M) or 23.8 (F) (sodium salt) (Dietary)	22.6 ~ 23.8 (as cephapirin) No effects of the administration
	Developmental toxicity study	0,10, 100, 1 000 (benzathine salt) (gavage administration)	Dams：10 (7.51 as cephapirin) Piloerection, alopecia, decreased food consumption, suppressed body weight. Fetuses：1 000 (751 as cephapirin) No effects of the administration
Dog	13-week subacute toxicity study	0, 20 (sodium salt) (oral administration)	20 (as cephapirin) No effects of the administration
Toxicological ADI (mg/kg bw/day)			0.023 NOAEL：22.6 SF：1 000
The critical study for setting Toxicological ADI			13-week subacute toxicity study in rats
Microbiological ADI (mg/kg bw/day)			0.00196
The critical study for setting Microbiological ADI			The value was specified according to the VICH guideline based on MICcalc of cephapirin against human clinically isolated strains which was obtained in the Comprehensive survey of the emerging problems for ensuring food safety of FY 2006.
ADI (mg/kg bw/day)			0.002

[1] Major adverse effect observed at LOAEL