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

Risk Assessment Report

Tolfenamic acid

(Veterinary Medicinal Products)

Food Safety Commission of Japan (FSCJ)
May 2016

ABSTRACT

FSCJ conducted a risk assessment of tolfenamic acid (CAS No. 13170-19-5), an anti-inflammatory drug, based on the submitted documents including original research papers[1-3], together with reference to the reports from the European Medical Agency (EMEA) and the Australian government.

The data used in the assessment include pharmacokinetics (rats, rabbits, dogs, cattle, pigs and humans), metabolism (rats, rabbits, dogs, cattle, pigs and humans), residues (cattle and pigs), genotoxicity, acute toxicity (mice, rats, rabbits and dogs), subacute toxicity (mice, rats, rabbits, dogs and miniature pigs), chronic toxicity/carcinogenicity (mice and rats), as well as reproductive and developmental toxicity (rats and rabbits).

No genotoxicity relevant to human health were suggested by the various genotoxicity studies on tolfenamic acid. Therefore, an acceptable daily intake (ADI) is possible to be established for the toxicity.

Major adverse effects of tolfenamic acid were observed on GI tract (erosions and ulcers).
No carcinogenicity was observed in repeated dose toxicity studies in mice and rats.

Prolonged gestation period, delayed delivery and dystocia were observed in rat reproductive and developmental toxicity study as well as toxicity studies, in which maternal rats were given the drug from day 15 or day 17 of gestation through lactating periods. No adverse effects, however, were observed at doses below 12 mg/kg bw/day in these studies. No teratogenicity was observed in a toxicity study, in which rats were given the drug from day 7 to day 17 of gestation, and also in developmental toxicity studies in rabbits.

The lowest no-observed-adverse-effect level (NOAEL) was 1 mg/kg bw/day, based on the necrosis of GI mucosal epithelium in a one-month subacute toxicity study in rabbits, the adverse effect observed at the lowest dose among the toxicity studies.

FSCJ thus specified the ADI of 0.01 mg/kg bw/day for tolfenamic acid by applying a safety factor of

100 to the NOAEL of 1 mg/kg bw/day in the one-month subacute toxicity study in rabbits.

References

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2. Ozaki M, Kunikane K, Igarashi Y, Tsushima K, Sato S, Kawabe K, Hiyama T, Tosaka K. Toxicity study of N-(2-Methyl-3-Chlorophenyl)-anthranilic acid (GEA6414), a new anti-inflammatory agent. Journal of the Medical Society of Toho University. 1983; 29(6): 851-855

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