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

Risk Assessment Report

Mosapride

(Veterinary Medicinal Products)

Food Safety Commission of Japan (FSCJ)
October 2014

ABSTRACT

FSCJ conducted a risk assessment of mosapride citrate hydrate (CAS No. 112885-42-4), an agent affecting digestive organs, based on documents including a written application for marketing approval of a new veterinary medicinal product.

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

All the data were negative in studies on genotoxicity of mosapride citrate hydrate. Although hepatocellular tumors and tumors of follicular thyroid epithelial cells were induced in a carcinogenicity study in rats and mice, it was considered that genotoxic mechanism was not involved and a threshold dose exsitsed in the tumor induction. Therefore, FSCJ judged that an acceptable daily intake (ADI) for mosapride citrate hydrate could be specified.

The lowest no-observed-adverse-effect level (NOAEL) in the toxicological studies was 2 mg/kg bw/day for hepatocellular swelling in a 26-week subacute toxicity study in rats. However, effects on the hepatocyte similar to that observed in the 26-week subacute toxicity study were observed in a carcinogenicity study in rats administered for longer period (104 weeks), and the NOAEL of 3 mg/kg bw/day has been established for the effects.
FSCJ judged it appropriate to determine that the NOAEL of 3 mg/kg bw/day observed in a 104-week carcinogenicity study is the NOAEL of mosapride citrate hydrate based on the following evidences:

1. the effects on hepatocytes had not been enhanced by elongating the duration of administration,
2. the effects had been detected in female rats where the effects of this agent seems to last longer than in males because of the differences in metabolism between the sexes indicated by pharmacokinetic study in rats, and
3. common ratio of the dose in a 104-week carcinogenicity study was smaller than that in 26-week subacute toxicity study.

The NOAEL in male rats was not obtained in this carcinogenicity study [a lowest-observed-adverse-effect level (LOAEL) 10 mg/kg bw/day]. However, FSCJ considered that 3.0 mg/kg bw/day, which is the NOAEL obtained in female rats, could be regarded as a NOAEL for male rats, since pharmacokinetic study suggested that male rats are less sensitive to this medicinal agent than female rats, and no adverse effects were observed in the dose of 3 or 2 mg/kg body weight/day in 13-week or 26-week subacute toxicity study.

Consequently, FSCJ established an acceptable daily intake (ADI) of 0.03 mg/kg bw/day by applying a safety factor of 100 (10 for species difference, 10 for individual difference) to the NOAEL obtained in the 104-week carcinogenicity study in rats.