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

Risk Assessment Report

Mosapride (Second edition)

(Veterinary Medicinal Product)

Food Safety Commission of Japan (FSCJ)
July 2022

ABSTRACT

The FSCJ conducted a risk assessment of a gastroprokinetic agent, mosapride (CAS No. 112885-41-3), based on application documents for approval of manufacturing and marketing a veterinary medicinal product. In the revision for this second edition, the additional test results of pharmacokinetics and residual studies in cattle were submitted in line with the application for approval of manufacturing and sales of oral gavage formulation for cattle (Pronamide powder 2% for cattle) containing mosapride citrate as an active substance.

The test results used in the assessment include the data on pharmacokinetics (rats, dogs, monkeys, cattle, horses and humans), residues (cattle and horses), genotoxicity, acute toxicity (mice, rats and dogs), subacute toxicity (rats and dogs), carcinogenicity (mice and rats), reproductive toxicity (rats and rabbits), pharmacological effects and others.

All genotoxicity studies showed negative results. Although tumors were found in hepatocytes and thyroid follicular epithelium in a carcinogenicity study using mice and rats, the expression of these tumors was deemed to be due to non-genetic toxic mechanisms and there would be a threshold dose. Therefore, the FSCJ ascertained that an acceptable daily intake (ADI) could be specified for mosapride.

Based on these results, mosapride and metabolite M-1 were specified as the relevant substances for the residue definition of dietary risk assessment.

The lowest no-observed-adverse-effect level (NOAEL) obtained from all the studies was 2 mg/kg bw per day, owing to the symptom of swelling hepatocytes of the female rats in a 26-week subacute toxicity study (the first study). Meanwhile, in a longer period of a 104-week carcinogenicity study in rats, the effect on hepatocytes in the liver was observed similarly to the 26-week subacute toxicity study, and the NOAEL of 3 mg/kg bw per day was identified. The FSCJ determined that the NOAEL of 3 mg/kg bw per day identified in the 104-week carcinogenicity study should be appropriate for the NOAEL of this formulation, considering the following reasons:
- Extension of the administration period did not strengthen effects on hepatocytes.
- Pharmacokinetics study revealed differences in metabolite between male and female rats, which indicated that the effects of this formulation on females last longer than those on males, and the effects on hepatocytes were identified in female rats.

- The common dosage ratio of the 104-week carcinogenicity study is smaller than that of the 26-week subacute toxicity study (the first study).

Although no NOAEL was identified in male rats [the lowest-observed-effect-level (LOAEL) of 10 mg/kg bw per day] in that study, the FSCJ viewed that the NOAEL of 3 mg/kg bw per day identified in female rats could be applied to male rats. The rationale for this NOAEL is that the male is deemed to be less affected by this formulation than the female from the result of pharmacokinetics study and no effect was observed at the dose of 3 or 2 mg/kg bw per day in a 13-week or a 26-week (the first study) subacute toxicity studies.

Given the above, the FSCJ specified an ADI of 0.03 mg/kg bw per day (for mosapride citrate) by applying a safety factor of 100 to the NOAEL of 3 mg/kg bw per day identified in the 104-week carcinogenicity study in rats. [1]

[1] The ADI was initially specified in October, 2014 (first edition).