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

Risk Assessment Report

Metoclopramide
(Veterinary Medicinal Products)

Food Safety Commission of Japan (FSCJ)
June 2015

ABSTRACT

FSCJ conducted a risk assessment of metoclopramide (CAS No. 364-62-5), one of the antistomach and preparations, antidiarrhoics, based on a set of data submitted to the Ministry of Health, Labour and Welfare (MHLW).

The data used in the assessment include pharmacokinetics (mice, rats, rabbits, dogs, cattle, pigs and humans), residues (cattle and pigs), genotoxicity, acute toxicity (mice, rats, rabbits and dogs), subacute toxicity (rats, rabbits and dogs), and reproductive and developmental toxicity (mice and rats).

In vitro studies using mammal-derived cells, which are chromosomal aberration tests, gene mutation tests and micronucleus tests, were positive. However, some other *in vitro* data of bacterial reverse mutaton tests, and DNA damage tests and the unscheduled DNA synthesis tests in mammal-derived cells, and *in vivo* DNA double-strand break tests using rats, and micronucleus tests using rats or mice were negative. From these data, we considered that metoclopramide has no genotoxicity relevant to human health. Carcinogenicity study was not conducted, but a chronic toxicity study was tested as reference data. FSCJ concluded, therefore, that metoclopramide is not a genotoxic carcinogenic even if it has a carcinogenic potential, and the acceptable daily intake (ADI) for metoclopramide can be specified, on the basis of the genotoxicity data.

The lowest no-observed-adverse-effect level (NOAEL) or the lowest-observed-adverse-effect level (LOAEL) in various toxicological studies was the LOAEL of 0.5 mg/kg bw/day in a 6-month subacute toxicity study in dogs, as a toxic indicator of clinical signs such as restlessness.

FSCJ considered it appropriate to specify the ADI based on the LOAEL, and also to apply an additional safety factor of 10, because of the adopted LOAEL value, insufficient data of chronic toxicity tests, as well as lack of carcinogenicity tests, reproductive toxicity tests and neurotoxicity tests. Accordingly, FSCJ specified the ADI of 0.0005 mg/kg bw/day for metoclopramide, applying a safety factor of 1,000 (10 for species difference, 10 for individual difference and 10 for the additional factor) to the LOAEL of 0.5 mg/kg bw/day.