FOOD SAFETY

doi: 10.14252/foodsafetyfscj.2015015s

Metoclopramide

Summary

Food Safety Commission of Japan

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment of metoclopramide (CAS No. 364-62-5) as a veterinary medicinal product used to gastrointestinal motility disorder, based on the documents submitted from the Ministry of Health, Labour and Welfare (MHLW). Various *in vivo* and *in vitro* genotoxicity studies suggested no apparent genotoxicity of metoclopramide relevant to human health. No carcinogenicity study nor the detail of chronic toxicity study was available, but metoclopramide is unlikely a genotoxic carcinogen. FSCJ concluded, therefore, that the acceptable daily intake (ADI) for metoclopramide can be specified. The lowest value among no-observed-adverse-effect levels (NOAELs) and lowest-observed-adverse-effect levels (LOAELs) in various toxicological studies was 0.5 mg/kg bw/day in a 6-month subacute toxicity study in dogs (LOAEL), as a toxic indicator of clinical signs including restlessness. FSCJ considered it appropriate to apply an additional safety factor of 10 on the specification of the ADI based on the LOAEL, taking into account of the lack of carcinogenicity tests, reproductive toxicity tests and neurotoxicity tests, and insufficient data of chronic toxicity tests. Accordingly, the specified ADI is 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 in a 6-month subacute toxicity study in dogs.

Conclusion in Brief

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment of metoclopramide (CAS No. 364-62-5) as a veterinary medicinal product used to gastrointestinal motility disorder, based on the documents* submitted from 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).

Positive results were obtained in chromosomal aberration, gene mutation and micronucleus tests in mammalian cells, whereas negative results were obtained with bacterial reverse mutation tests, and DNA damage tests (alkaline-elution) and the unscheduled DNA synthesis tests in mammalian cells, and also *in vivo* DNA double-strand break tests using rats, and micronucleus tests using rats and mice. These data suggest no apparent genotoxicity of metoclopramide relevant to human health. No carcinogenicity study nor the detail of chronic toxicity study was available, but metoclopramide is unlikely a genotoxic carcinogen as described above. FSCJ concluded, therefore, that the acceptable daily intake (ADI) for metoclopramide can be specified.

Published online: 29 September 2015
This is an English translation of excerpts from the original full report (June 2015−FS/474/2015). Only original Japanese texts have legal effect.
The original full report is available in Japanese at http://www.fsc.go.jp/fsciis/attachedFile/download?retrievalId=kya20130130026&fileId=201
Acknowledgement: FSCJ wishes to thank the members of Expert Committee on Veterinary Medicinal Products for the preparation of this report.
Suggested citation: Food Safety Commission of JAPAN. Metoclopramide: Summary. Food Safety. 2015; 3 (3): 110–111. doi:10.14252/foodsafetyfscj.2015015s

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* The assessment was requested by MHLW to re-evaluate the provisional maximum residue limits for agricultural chemicals in foods developed at the time of the introduction of the "positive list" system in 2006.

The following documents were submitted from MHLW: the results of various studies in the previous application documents on approval and re-evaluation** of the related veterinary medicinal products according to the Pharmaceutical Affairs Law***; the results of the additional studies (genotoxicity and residue tests) for this assessment; the information on the metoclopramide-containing human drugs.

** The term of "re-evaluation" is provided by the Pharmaceutical Affairs Law***. According to the law, the "re-evaluation" of veterinary medicinal products is established to review the quality, efficacy and safety of drugs approved in the past based on current medical and pharmaceutical scientific standards.

*** The Pharmaceutical Affairs Law was renamed on November 25, 2014, "Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics".