doi: 10.14252/foodsafetyfscj.2015003s

Mosapride

Summary

Food Safety Commission of Japan

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment of mosapride citrate (CAS No. 112885-42-4), a gastrointestinal agent, based on documents including a written application for marketing approval of a new veterinary medicinal product. Although hepatocellular and thyroid follicular cell tumors were induced in carcinogenicity studies in rats and mice, no genotoxicities were suggested in all the studies of mosapride citrate. The involvement of genotoxic mechanism is thus unlikely. Therefore, an acceptable daily intake (ADI) for mosapride citrate is able to be specified. In a 26-week subacute toxicity study using both sexes of rats, the no-observed-adverse-effect level (NOAEL) and the lowest-observed-adverse-effect level (LOAEL) values were obtained, respectively, to be 2 mg/kg bw/day and 10 mg/kg bw/day for the female, and to be 10 mg/kg bw/day and 50 mg/kg bw/day for the male. However, hepatocellular swelling observed in the female in the 26-week subacute toxicity study was also observed in the 104-week carcinogenicity study in the male given 10 mg/kg bw/day (lowest dose) and in the female given 30 mg/kg bw/day. Liver altered foci were observed in the female given 10 mg/kg bw/day (LOAEL), and the NOAEL value for the female was 3 mg/kg bw/day. Lowest values for all the hepatic lesion was 10 mg/kg bw/day for the female on both the 26-week and 104-week studies. A clear sex-related difference was observed in the plasma levels of mosapride in rats, in which the higher levels were observed in the female. The result, together with the data on the 26-week study, suggests that the NOAEL value in the male rats is unlikely to be lower than 3 mg/kg bw/day. FSCJ judged it appropriate to adopt this value as the NOAEL for the ADI of mosapride citrate, based on the following reasons: 1) The clear sex-related difference was observed in the plasma levels of mosapride in rats, in which the higher levels were observed in the female; and 2) The common ratio of the dose was smaller in the 104-week carcinogenicity study than that in the 26-week subacute toxicity study. Consequently, FSCJ established an ADI of 0.03 mg/kg bw/day, 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.

Conclusion in Brief

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment of mosapride citrate (CAS No. 112885-42-4), a gastrointestinal agent, based on documents including a written application for marketing approval of a new veterinary medicinal product.

The data used in the assessment include the data on 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.

Published online: 30 March 2015
This is an English translation of excerpts from the original full report (October 2014−FS/790/2014). 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=kya20140325242&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. Mosapride: Summary. 2015; 3 (1): 32–33. doi:10.14252/foodsafetyfscj.2015003s

Although hepatocellular and thyroid follicular cell tumors were induced in carcinogenicity studies in rats and mice, no genotoxicities were suggested in all the studies of mosapride citrate. The involvement of genotoxic mechanism is thus unlikely. Therefore, an acceptable daily intake (ADI) for mosapride citrate is able to be specified.

In a 26-week subacute toxicity study using both sexes of rats, the no-observed-adverse-effect level (NOAEL) and the lowest-observed-adverse-effect level (LOAEL) values were obtained, respectively, to be 2 mg/kg bw/day and 10 mg/kg bw/day for the female, and to be 10 mg/kg bw/day and 50 mg/kg bw/day for the male. However, hepatocellular swelling observed in the female in the 26-week subacute toxicity study was also observed in the 104-week carcinogenicity study in the male given 10 mg/kg bw/day (lowest dose) and in the female given 30 mg/kg bw/day. Liver altered foci were observed in the female given 10 mg/kg bw/day (LOAEL), and NOAEL value for the female was 3 mg/kg bw/day. Lowest values for all the hepatic lesion was 10 mg/kg bw/day for the female on both the 26-week and 104-week studies. A clear sex-related difference was observed in the plasma levels of mosapride in rats, in which the higher levels were observed in the female. The result, together with the data on the 26-week study, suggests that the NOAEL value in the male rats is unlikely to be lower than 3 mg/kg bw/day.

FSCJ judged it appropriate to adopt this value as the NOAEL for the ADI of mosapride citrate, based on the following reasons:

1. The clear sex-related difference was observed in the plasma levels of mosapride in rats, in which the higher levels were observed in the female, and
2. The common ratio of the dose was smaller in the 104-week carcinogenicity study than that in the 26-week subacute toxicity study.

Consequently, FSCJ established an ADI of 0.03 mg/kg bw/day, 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.