FOOD SAFETY

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Orbifloxacin

Summary

Food Safety Commission of Japan

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment of orbifloxacin (CAS No.113617–63-3), a family of synthetic antimicrobial agents of fluoroquinolones, based on a written application for the marketing approval of new veterinary medicinal products and its attached documents. All the *in vivo* data were negative in studies on genotoxicity of orbifloxacin, although some *in vitro* data were positive. Therefore, FSCJ concludes that orbifloxacin has no genotoxicity relevant to human health. Orbifloxacin showed photogenotoxicity *in vitro* and *in vivo* through the indirect action to DNA, suggesting that orbifloxacin has no photogenotoxicity relevant to human health. No carcinogenicity was observed in a 2 year carcinogenicity study in rats. From the results of toxicity studies, FSCJ judged it appropriate to use a lowest-observed-adverse-effect level (LOAEL) of 12.5 mg/kg bw/day observed in a 30-day subacute toxicity study in dogs, and to specify the toxicological ADI as 0.013 mg/kg bw/day, applying a safety factor of 1000 to this LOAEL. Microbiological ADI was estimated to be 0.012 mg/kg bw/day based on the VICH (the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products) guideline 36. FSCJ specified the ADI of orbifloxacin as 0.012 mg/kg bw/day which is smaller than the toxicological ADI.

Conclusion in Brief

FSCJ conducted a risk assessment of orbifloxacin (CAS No.113617–63-3), a family of synthetic antimicrobial agents of fluoroquinolones, based on a written application for the marketing approval of new veterinary medicinal products and its attached documents.

Data used in the assessment includes pharmacokinetics (mice, rats, pigs and cattle), residues (pigs and cattle), genotoxicity, acute toxicity (mice and rats), subacute toxicity (rats and dogs), carcinogenicity (rats), reproductive and developmental toxicity (rats and rabbits), and microbiological effects.

All the *in vivo* data were negative in studies on genotoxicity of orbifloxacin, although some *in vitro* data were positive. Therefore, FSCJ concluded that orbifloxacin has no genotoxicity relevant to human health. Orbifloxacin showed photogenotoxicity *in vitro* and *in vivo* through the indirect action to DNA, suggesting that orbifloxacin has no photogenotoxicity relevant to human health.

No carcinogenicity was observed in a 2 year carcinogenicity study in rats. Hence, FSCJ concludes that an acceptable daily intake (ADI) can be specified.

From the results of toxicity studies, FSCJ judged it appropriate to use a lowest-observed-adverse-effect level (LOAEL) of 12.5 mg/kg bw/day observed in a 30-day subacute toxicity study in dogs, and to specify the toxicological ADI as 0.013 mg/kg bw/day, applying a safety factor of 1000 to this LOAEL. This safety factor of 1000 was composed of

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10 for species difference, 10 for individual difference, and 10 for additional factors due to usage of LOAEL, short period of the rational study, and insufficient findings in chronic toxicity and carcinogenicity tests.

Microbiological ADI was estimated to be 0.012 mg/kg bw/day based on the VICH (the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products) guideline 36.

FSCJ specified the ADI of orbifloxacin as 0.012 mg/kg bw/day as the microbiological ADI is smaller than the toxicological ADI.