

Risk Assessment Report: Veterinary Medicinal Products

Prednisolone

Summary

Food Safety Commission of Japan

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment of prednisolone (CAS No. 50-24-8), a steroidal anti-inflammatory agent, using the evaluation reports of EMA (EMEA) and documents for the re-evaluation* of veterinary medicinal products. All the genotoxicity studies *in vivo* were negative, although some of *in vitro* genotoxicity studies showed positive results. Prednisolone was thus judged to have no genotoxicity relevant to human health. FSCJ concluded it possible to specify an acceptable daily intake (ADI) of prednisolone. Major adverse effects of prednisolone observed are reduced counts of leukocyte and decreased weights of the thymus, spleen and adrenal gland. Slight decreases were also observed on bone marrow cells. There is no substantial evidence to suggest the carcinogenicity of prednisolone. Prednisolone treatment resulted in an increased rate of embryonal resorption and a decrease of fetal body weights in a developmental toxicity study in rats. No teratogenicity was observed. FSCJ specified an ADI of 0.00025 mg/kg bw/day (0.25 µg/kg bw/day) for prednisolone applying a safety factor of 1,000 to the LOAEL of 0.25 mg/kg bw/day obtained from the LOAEL of prednisone in 18-month carcinogenicity study in mice.

Conclusion in Brief

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment of prednisolone (CAS No. 50-24-8), a steroidal anti-inflammatory agent, using the evaluation reports of EMA (EMEA) and documents for the re-evaluation* of veterinary medicinal products.

The data used in the assessment include pharmacokinetics and metabolism (rats, rabbits, dogs, cattle, horses, pigs and humans), residues (cattle, pigs and horses), genotoxicity, acute toxicity (mice and rats), subacute toxicity (rats, dogs, rabbits and Guinea pigs), chronic toxicity/carcinogenicity (rats), reproductive and developmental toxicity (rats, rabbits, hamsters and humans), and others.

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Prednisolone treatment resulted in an increased rate of embryonal resorption and a decrease of fetal body weights in a developmental toxicity study in rats. No teratogenicity was observed.

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This is an English translation of excerpts from the original full report (March 2016–FS/133/2016). Only original Japanese texts have legal effect.

The original full report is available in Japanese at <http://www.fsc.go.jp/fscjis/attachedFile/download?retrievalId=kya20140325011&fileId=201>

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Reduced counts of leukocyte, a common effect of glucocorticoids, was observed at a dose of 0.6 mg/kg bw/day in a subacute toxicity study in rats. The experimental details of this study were, however, obscure and thus not used for ADI specification. A lowest value of no-observed-adverse-effect level (NOAEL) was obtained as 3 mg/kg bw/day on the embryonal resorption rate and fetal body weight in rat developmental toxicity study among various toxicology studies of prednisolone. Thus, the NOAEL was not feasible due to the presence of the effect at 0.6 mg/kg bw/day described above. Instead, the low-observed-adverse-effect level (LOAEL) of prednisone, an equipotent prednisolone, was 0.25 mg/kg bw/day, based on atrophy and degeneration of the adrenal cortex in 18-month carcinogenicity study in mice. FSCJ adopted this LOAEL of prednisone as for the LOAEL of prednisolone.

FSCJ applied an additional safety factor of ten for an ADI specification of prednisolone from following reasons:

- 1) Typical toxicity of glucocorticoid effect was observed as endpoint in 18-month carcinogenicity study,
- 2) Although only the LOAEL was obtained in the male of this study, the NOAEL was obtained in the female,
- 3) Substantial levels of endogenous glucocorticoids are circulating in the body. No additional factor more than ten is thus necessary even though the possible existence of intrinsic actions between endogenous and exogenous corticoids.

In conclusion, FSCJ specified an ADI of 0.00025 mg/kg bw/day (0.25 µg/kg bw/day) for prednisolone applying a safety factor of 1,000 to the LOAEL of 0.25 mg/kg bw/day obtained from the LOAEL of prednisone in 18-month carcinogenicity study in mice.

- * The term of “re-evaluation” is provided by “Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics”. According to the act, 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.