FOOD SAFETY

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Triptorelin Acetate

Summary

Food Safety Commission of Japan

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment of triptorelin acetate (CAS No. 140194-24-7), which is intended for use in a single fixed-time insemination by synchronizing estrus cycles of weaned sows, based on the documents for the import tolerance application. FSCJ recognize none of adverse effects of triptorelin acetate on human health through dietary exposure, because of the lack of genotoxicity relevant to human health and negligible oral bioavailability due to the degradation in the digestive tract. FSCJ thus judged it unnecessary to establish an acceptable daily intake (ADI) for triptorelin acetate.

Conclusion in Brief

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment of triptorelin acetate (CAS No. 140194-24-7), which is intended for use in a single fixed-time insemination by synchronizing estrus cycles of weaned sows, based on the documents for the import tolerance application.

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

In pharmacokinetic studies of triptorelin in pigs, plasma triptorelin concentrations were decreased to levels below the detection limit within thirty-six hours (in all the pigs) after the intravenous administration, and within eight hours (in all the pigs except one outlier) after the intravaginal administration.

Rises in serum luteinizing hormone (LH) concentration, the most sensitive effect of triptolelin, were observed after the single intravenous administration in rats, as well as after the single intravaginal administration in pigs, whereas no change was observed in serum LH concentration after the single gavage administration in rats. The absence of LH release stimulation after the gavage administration is reasonably explained by the degradation of triptorelin, a decapeptide, in the digestive tract. Judging from the negligible oral bioavailability, effects of triptolelin are unlikely through foods.

So far no genotoxicitic study had been conducted for triptorelin acetate. However, the experiments with triptorelin pamoate showed no genotoxicity. In addition, triptorelin is degraded prior to the absorption and thus unlikely to show the genotoxicity *in vivo*. Thus, triptorelin acetate is considered to show no genotoxicity relevant to human health.

No oral toxicity studies on toxicity of triptorelin acetate was reported in carcinogencity or reproductive developmental toxicity. Two 45-day subacute toxicity studies in rats with subcutaneous or gavage administration were reported, and serum hormone concentrations including LH levels were measured in both studies. LH levels were clearly elevated

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two hours after administration at doses of 4μg/kg bw/day and the higher in the subcutaneous toxicity study. Other sex hormone levels were declined and various adverse changes in reproductive organs were observed at the termination at the same doses. No toxicological effect or hormonal alteration was, however, observed up to 4μg/kg bw/day, the highest dose tested, in the oral toxicity study. These results indicate no apparent toxicological and pharmacological effects after the oral administration of triptorelin.

In conclusion, FSCJ recognize none of adverse effects of triptorelin acetate on human health through dietary exposure, because of the lack of genotoxicity relevant to human health and negligible oral bioavailability due to the degradation in the digestive tract. FSCJ thus judged it unnecessary to establish an acceptable daily intake (ADI) for triptorelin acetate.