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Risk assessment report

Melengestrol Acetate (Veterinary Medicinal Products)

Summary

Food Safety Commission of Japan

Food Safety Commission of Japan (FSCJ) conducted a risk assessment of melengestrol acetate (MGA, CAS No. 2919-66-6), a synthetic hormone, based on results from various studies. MGA was recognized to have no genotoxicity relevant to human health, and it enabled FSCJ to specify an acceptable daily intake (ADI) in the assessment. *In vitro* studies using various human hormone-receptors showed that MGA exerts biological action primarily as progestogens and secondarily as glucocorticoids. Major adverse effects of MGA observed were mammary gland hyperplasia, endometrial hyperplasia, and a lack of corpora lutea, accompanying the elevated level of serum prolactin. Increased incidence of mammary gland tumor was observed in C3Han/f mice at the dose of 1.5 mg/kg bw/day in a carcinogenicity study. The increase was presumably due to MGA-induced hyperprolactinemia, but not a direct effect of MGA from the experiment, using a prolactin inhibitor. Inhibitions of estrus and ovulation, in addition to dystocia, were observed in female animals in the reproductive and developmental toxicity studies. Malformations such as cleft palate, clubfoot, umbilical hernia, and defective skeletal ossification were observed in rabbits at doses of 0.8 and 1.6 mg/kg bw/day in a developmental toxicity study. However, these were likely due to the corticosteroidal (glucocorticoid) action of MGA. The no-observed-adverse-effect level (NOAEL) was obtained from a rhesus monkey study given orally 1.5 µg/kg bw/day of MGA over the one menstrual-cycle. The value was, however, the result of the study using the large common ratio of 10. In another study, the lowest-observed-adverse-effect level (LOAEL) of 5 µg/kg bw/day, obtained from a cynomolgus monkey given MGA over the three menstrual-cycles. The LOAEL value was estimated close to the biological threshold, because of no obvious hormonal disorders despite of minimal change of menstrual cycle. Therefore, FSCJ considered it appropriate to specify an ADI on the basis of the LOAEL obtained from a cynomolgus monkey study over the three menstrual-cycles, and to add an additional safety factor of 2. Consequently, FSCJ specified the ADI of 0.025 µg/kg bw/day by applying a safety factor of 200 to the LOAEL of 5 µg/kg bw/day in a cynomolgus monkey study over the three menstrual-cycles.

Conclusion in Brief

Food Safety Commission of Japan (FSCJ) conducted a risk assessment of melengestrol acetate (MGA, CAS No. 2919-66-6), a synthetic hormone, based on results from various studies.

The data used in the assessment include pharmacokinetics (rabbits, cattle and humans), residues (cattle), genotoxicity, acute toxicity (mice, rats and rabbits), subacute toxicity (mice, rats, rabbits and dogs), chronic toxicity/carcinogenicity (mice and dogs), reproductive toxicity (rats, rabbits, dogs and cattle) and hormonal activity (mice, monkeys and cattle).

Based on the results from various genotoxicity studies, MGA was recognized to have no genotoxicity relevant to human health, and it enabled FSCJ to specify an acceptable daily intake (ADI) in the assessment.

In vitro studies using various human hormone-receptors showed that MGA exerts biological action primarily as pro-

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gestogens and secondarily as glucocorticoids.

Major adverse effects of MGA observed were mammary gland hyperplasia, endometrial hyperplasia, and a lack of corpora lutea, accompanying the elevated level of serum prolactin. Increased incidence of mammary gland tumor was observed in C3Han/f mice at the dose of 1.5 mg/kg bw/day in a carcinogenicity study. The increase was presumably due to MGA-induced hyperprolactinemia, but not a direct effect of MGA from the experiment, using a prolactin inhibitor. Inhibitions of estrus and ovulation, in addition to dystocia, were observed in female animals in the reproductive and developmental toxicity studies. Malformations such as cleft palate, clubfoot, umbilical hernia, and defective skeletal ossification were observed in rabbits at doses of 0.8 and 1.6 mg/kg bw/day in a developmental toxicity study. However, these were likely due to the corticosteroidal (glucocorticoid) action of MGA.

FSCJ considered that MGA's hormonal action in non-human primates is the most reliable indicator for the determination of the endpoint.

The no-observed-adverse-effect level (NOAEL) was obtained from a rhesus monkey study given orally 1.5 µg/kg bw/day of MGA over the one menstrual-cycle. The value was, however, the result of the study using the large common ratio of 10. In another study, the lowest-observed-adverse-effect level (LOAEL) of 5 µg/kg bw/day, obtained from a cynomolgus monkey given MGA over the three menstrual-cycles. The LOAEL value was estimated close to the biological threshold, because of no obvious hormonal disorders despite of minimal change of menstrual cycle.

Therefore, FSCJ considered it appropriate to specify an ADI on the basis of the LOAEL obtained from a cynomolgus monkey study over the three menstrual-cycles, and to add an additional safety factor of 2.

Consequently, FSCJ specified the ADI of 0.025 µg/kg bw/day by applying a safety factor of 200 to the LOAEL of 5 µg/kg bw/day in a cynomolgus monkey study over the three menstrual-cycles.

Table 1. *Levels relevant to toxicological evaluation of MGA*

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)
Mouse	10-day subacute toxicity study	0.033, 0.166, 0.33, 1.3, 3, 5, 7.5 (Oral administration)	4.2 (Minimum effective dose) Abnormal estrous cycle
	20-day subacute toxicity study (the 1st study)	0, 0.25, 0.5, 2.5, 5, 10, 15, 20, 25, 40 (Dietary administration)	N/A Mammary gland development in the control group of C3Han/f mice
	20-day subacute toxicity study (the 2nd study)	0, 0.5, 1.5, 2.5, 5, 10, 25 (Dietary administration) + MEA	N/A Increased serum prolactin concentrations and mammary gland development
	20-21day subacute toxicity study	0, 0.05, 0.25, 0.5, 1.5, 2.5, 5, 25 (Dietary administration)	1.5 Increased body weight
	30-day subacute toxicity study	0, 1, 3, 10, 30 (Gavage administration)	1 Absence of corpora lutea
	24.5-month carcinogenicity study	0, 0.017, 17 (Dietary administration)	- A slight and nonsignificant increase in the incidence of mammary adenocarcinomas
	27-month carcinogenicity study	0, 0.5, 1, 1.5, 2.5, 5, 10, 15, 25 (Dietary administration)	1 Increase in mammary tumor incidence
	29-month carcinogenicity study	0, 0.5, 1.5, 2.5, 5, 10, 25 (Dietary administration) + MEA 100 mg/animal /day (Subcutaneous administration)	0.5 Increase in mammary tumor
	33-month carcinogenicity study	0, 0.017, 17 (Dietary administration)	- Increase in the incidence of mammary adenocarcinomas
Rat	28-day subacute toxicity study	0, 1, 3, 10 (Gavage administration)	N/A Decreased weights of the adrenals, ovaries, and testes
	90-day subacute toxicity study (the 1st study)	0, 0.015, 0.15, 0.3 (Dietary administration)	0.015 (Minimum effective dose) Histopathological change (Enlarged mammary glands)
	90-day subacute toxicity study (the 2nd study)	0, 0.055 (Dietary administration)	N/A Decreased weights of the adrenals, ovaries, and uterus
	One-generation reproductive toxicity study	0, 0.03, 0.06, 0.13, 0.25, 1 (Dietary administration)	0.03 Reproductive toxicity
	Developmental toxicity study (the 1st study)	2 (Subcutaneous administration)	N/A
	Developmental toxicity study (the 2nd study)	0, 15, 25, 50, 100 (Subcutaneous administration)	N/A Lack of information on the toxicokinetics of the sustainable release formulation

Table 1. *Levels relevant to toxicological evaluation of MGA (continued)*

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)
Rabbit	22-day subacute toxicity study	20 (Intramuscular administration)	N/A Increased Chol and Glu, elevated LDH and ALP levels, enlarged liver, muscular atrophy and atrophic change of adrenals, glycogen deposits, swollen hepatocytes with glycogen deposits and cytoplastic vacuole, decreased granulation of the zona glomerulosa of the adrenals
	Developmental toxicity study (the 1st study)	0, 0.016, 0.064, 0.16, 0.4, 0.8, 1.6, 3.2, 6.4 (Dietary administration)	Offspring: 0.4 Developmental toxicity (Decreased number of live fetuses and mean litter and fetal weights)
	Developmental toxicity study (the 2nd study)	0, 25, 50 (Intramuscular administration) 0, 5, 15 (Intramuscular administration)	N/A Lack of information on the toxicokinetics of the sustainable release formulation
Dog	29-day subacute toxicity study	0, 1, 3, 10 (Oral administration)	N/A Slight decrease in body weights, increase in absolute/relative liver weights, and reduction in adrenal weights, cells with a pale cytoplasm that did no stain for fat in the liver, renal tubular epithelium, and zona fasciculata of the adrenals
	Two-year chronic toxicity study	0, 0.001, 0.002, 0.008/0.004 (Oral administration)	0.001 Effects on endocrine organs
	One-generation reproductive toxicity study (the 1st study)	0.001, 0.005, 0.01, 0.02, 0.04, 0.08 (Oral administration)	N/A Insufficient data to specify a NOAEL
	One-generation reproductive toxicity study (the 2nd study)	0.1/body (Oral administration)	N/A Increased body weight of fetus
	One-generation reproductive toxicity study (the 3rd study)	0, 0.001, 0.002, 0.008/0.004 (Oral administration)	0.002 Fertility of dams (Disturbance of the estrous cycle and dystocia)
Monkey	One-menstrual-cycle study (the 1st study)	0, 0.0015, 0.015, 0.075, 0.15 (Oral administration)	0.0015 Suppression of ovulation
	One-menstrual-cycle study (the 2nd study)	0, 0.0025, 0.005, 0.01 (Oral administration)	N/A AUC for LH was decreased
	Three-menstrual-cycle study	0, 0.005, 0.01, 0.025 (Oral administration)	0.005 (Minimum effective dose) Changes in menstrual cycle
Cattle	16-day administration study	0.00016, 0.00031, 0.00063, 0.0013, 0.0025, 0.005, 0.01, 0.02 (Dietary administration)	N/A Disturbance of the estrous cycle
	Administration study (the 2nd study)	0, 0.0018 (Dietary administration)	N/A Hormonal response observed at higher doses
	One-generation reproductive toxicity study (the 1st study)	0, 0.002 (Dietary administration)	- No abnormality observed
	One-generation reproductive toxicity study (the 2nd study)	0, 1 mg/head (Dietary administration)	- No abnormality observed

Table 1. *Levels relevant to toxicological evaluation of MGA (continued)*

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)
Toxicological ADI			0–0.03 µg/kg bw/day Minimal effects on menstral cycle in monkeys Lowest LOEAL: 5 µg/kg bw/day SF: 200
The critical study for setting the ADI			Three menstrual-cycle study in monkeys
ADI			0–0.03 µg/kg bw/day

-, NOEL could not be specified