The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines Evaluation Unit

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

MEDROXYPROGESTERONE ACETATE

SUMMARY REPORT

1. Medroxyprogesterone acetate is a synthetic analogue of the natural steroid hormone progesterone. Medroxyprogesterone acetate is biologically and pharmacologically active after oral and parenteral administration, the latter route leading to long-acting and high effectiveness. In veterinary medicine medroxyprogesterone acetate is only used for synchronization and induction of oestrus in sheep (as intravaginal sponge) at a dose of 60 mg medroxyprogesterone acetate (= 1 sponge)/animal. In human medicine, medroxyprogesterone acetate is used as a contraceptive, as a cytostaticum in antitumour therapy and for the treatment of hormonal and gonadal disorders.

2. Medroxyprogesterone acetate exhibits pharmacological actions that resemble those of natural progesterone, but medroxyprogesterone acetate has the advantage of being orally active, due to its resistance to (first-pass) metabolic breakdown. Medroxyprogesterone acetate is a potent progestin, but also has effects that resemble other steroid functions (e.g. androgenic and anti-androgenic, and corticoid effects). Generally, medroxyprogesterone acetate exerts effects on tissues and/or organs of the reproductive system and its function(s). Medroxyprogesterone acetate also influences several enzymes, e.g. drug metabolizing enzymes in the liver and ß-glucuronidase in the kidney. Another action of medroxyprogesterone acetate is its interference with membrane stuctures, which supports the use of medroxyprogesterone acetate in antitumour therapy.

3. The pharmacodynamic activity of medroxyprogesterone acetate was tested in the Clauberg-McPhail test, in which the degree of endometrium proliferation is a measure of the progestational action of a compound. The oral NOEL for medroxyprogesterone acetate in this study was 0.03 mg/kg bw/day.

4. After oral treatment with medroxyprogesterone acetate, peak plasma levels are reached within 1-4 hours in humans, dogs and monkeys, and 18 hours in sheep. After intravaginal treatment, peak plasma levels are observed at 1 day in women and at 1-3 days in cows. Following intramuscular administration to humans, dogs and monkeys, medroxyprogesterone acetate is slowly released from the injection site, resulting in low but persistent drug levels in the circulation. Compared to intramuscular administration, the oral bioavailability is 54% and 85% in monkeys and dogs, respectively. In humans, approximately 50% of an oral dose is absorbed when compared with intramuscular administration.

   Elimination of medroxyprogesterone acetate after intramuscular application is prolonged up to 6 to 10 times in comparison to oral administration. Medroxyprogesterone acetate and metabolites are mainly excreted in faeces after oral or parenteral administration in most of the species studied. Faecal excretion was 77%, 75%, 55% and 44% of the dose in sheep, dog, monkey and human, respectively. Medroxyprogesterone acetate is also excreted into milk.

   In urine from humans and dogs, some metabolites were identified (accounting for only 10% of all urinary metabolites), but little is known of the metabolism of medroxyprogesterone acetate.

   In sheep treated intravaginally with a sponge, medroxyprogesterone acetate concentrations are highest and most persistent in fat, while lower levels are found in liver and muscle.

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5. The acute oral toxicity of medroxyprogesterone acetate is very low (LD_{50} in rats greater than 10,000 mg/kg bw). In mice, the LD_{50} after intravenous administration is 376 mg/kg bw.

6. Repeated dose toxicity studies in rats, rabbits, dogs and monkeys are available in which medroxyprogesterone acetate was administered intramuscularly or orally. Although most studies were conducted prior to implementation of GLP and were described in a rather limited way, they clearly show that pharmacological effects of medroxyprogesterone acetate are evoked at lower doses than toxicological effects. In dogs and rats treated orally with 3, 10, or 30 mg medroxyprogesterone acetate/kg bw/day for 181 and 190 days, respectively, medroxyprogesterone acetate was relatively nontoxic, but did induce hormonal effects at all dose levels. The same was observed after intramuscular administration of 3, 10 or 30 mg medroxyprogesterone acetate/kg bw (3-monthly injections of a depot-formulation) to monkeys, rabbits and dogs, where medroxyprogesterone acetate was also nontoxic but pharmacologically active at all tested doses. Observed hormonal effects included endocrine-related organ weight changes and related histopathological lesions (e.g. adrenal atrophy).

7. Medroxyprogesterone acetate exerts signs of toxicity or reduced function on the reproductive system, dependent on dosage and time of exposure. In dogs and sheep it was shown that treated animals return to normal reproductive performance after cessation of treatment. In order to establish effects on the reproductive ability of the pups, dogs were treated orally with 1, 10 or 50 mg medroxyprogesterone acetate/kg bw/day for 35 days starting on day 22 of gestation. Due to a masculinizing effect of medroxyprogesterone acetate, the reproductive ability was strongly affected at 50 mg/kg bw, but only slightly at 10 mg/kg bw. No effects were noted at 1 mg/kg bw.

8. After subcutaneous and intramuscular administration of medroxyprogesterone acetate to rabbits, embryotoxicity was noted and cleft palate was induced in a dose-related manner. The latter can be explained by the corticoid action of medroxyprogesterone acetate, which is known from general literature. In the rabbit studies no effects were observed at a dose level of 1 mg medroxyprogesterone acetate/kg bw/day (subcutaneous). Studies with primates showed that single intramuscular doses of up to 10 mg medroxyprogesterone acetate/kg bw during organogenesis did not induce any malformations.

9. Medroxyprogesterone acetate was negative in Ames tests, a DNA damage/alkaline elution assay in Chinese hamster lung fibroblasts and an *in vivo* micronucleus test (via intraperitoneal route). Positive results were reported only in an indicator test (SCE-test) and an inappropriately conducted Ames test. Because medroxyprogesterone acetate does not contain a structural alert, and for structural analogues of medroxyprogesterone acetate no genotoxicity was observed in a range of mutagenicity tests, medroxyprogesterone acetate is considered a non-genotoxic compound.

10. The carcinogenicity of medroxyprogesterone acetate was tested after intramuscular administration to mice (18-months), rats (2-years), monkeys (10-years) and dogs (7-years). The results were negative for rats, mice and monkeys. The positive results in dogs (mammary glands) can be discarded because dogs are extremely sensitive to progestagenic substances and, therefore, the dog is considered not to be a suitable test animal. In 2/16 monkeys dosed with 150 mg medroxyprogesterone acetate/kg bw (50 times the human dose) endometrial carcinoma was observed.

11. An increased risk of breast cancer has been observed in recent users of depot medroxyprogesterone acetate (DMPA) and in users of depot medroxyprogesterone acetate under 35 years of age. However, from several epidemiological multicenter studies that have been carried out with depot medroxyprogesterone acetate in various parts of the world (many of which were conducted under the auspices of the World Health Organization), it can be concluded that the long-term use of depot medroxyprogesterone acetate (intramuscular injections of 3 mg medroxyprogesterone acetate/kg bw, every 3 months for several years) does not increase the overall risk on breast, cervical, ovarian or liver cancer. The data provided evidence that depot medroxyprogesterone acetate protects against endometrial cancer.

12. From a broad database on effects in various human populations (including children with precocious puberty), post-menopausal women turned out to be most sensitive to the effects of medroxyprogesterone acetate. An oral dose of 1 mg medroxyprogesterone acetate per day is the minimally effective dose, as observed by the occurrence of minimal withdrawal bleeding.

13. From the toxicity data provided, an overall oral NOEL of 1 mg/kg bw/day can be established for medroxyprogesterone acetate, resulting in a toxicological ADI of 0.01 mg/kg bw/day (equivalent to 600 µg/day for a 60 kg person). However, as pharmacological effects of medroxyprogesterone acetate are evoked at lower doses than toxicological effects, it is more appropriate to establish a pharmacological ADI for medroxyprogesterone acetate. Based on the pharmacological NOEL of 0.03 mg/kw bw/day (as found in the Clauberg-McPhail test) and a safety factor of 100, a pharmacological ADI of 0.3 µg /kg bw/day (equivalent to 18 µg /day for a 60 kg person) can be established for medroxyprogesterone acetate.

14. Residue data with sheep have been provided after intravaginal administration of the commercial product (containing 60 mg medroxyprogesterone acetate/sponge; the sponge remains *in situ* for 13 days). Residues in plasma and tissues were determined by means of radioimmunoassay after withdrawal times of 2 hours, 2 and 5 days. During treatment, in plasma of both treated and control animals immunoreactive medroxyprogesterone acetate-like material was detected (3-4.3 µg/l). After removal of the sponge medroxyprogesterone acetate was no longer detectable in plasma (less than 3 µg/l). Mean tissue residues were highest in fat (greater than 20 µg /kg at 2 hours after sponge removal, declining to 14 µg/kg at 2 days and approximately 7.5 µg /kg at 5 days after sponge removal). Lower levels were found in liver and muscle (approximately 2 and 1 µg/kg respectively at 2 hrs and 2 days after sponge removal, declining to less than 1 µg/kg at 5 days after sponge removal). In kidney, levels were less than 1 µg/kg at all time points.

15. Milk residue data have been provided after intravaginal treatment of sheep with the commercial product. Milk samples were taken during and after treatment and residues were determined by means of radioimmunoassay. Medroxyprogesterone acetate concentrations in milk varied from 1.75-6 µg/l during presence of the sponge, rapidly declining to control values (0.5-3.75 µg/l) after removal of the sponge.

16. The residue data indicate a rapid depletion of medroxyprogesterone acetate from tissues and milk of sheep. Even when taking the maximum individual tissue and milk concentrations during and after treatment, the consumer intake of residues represents only 60% of the pharmacological ADI.

Conclusions and recommendation

Having considered the criteria laid down by the Committee for the inclusion of substances into Annex II of Council Regulation (EEC) No 2377/90, and in particular that :

- medroxyprogesterone acetate is used only for zootechnical purposes (namely induction and synchronization of oestrus), once a year in the breeding season,
- the animals are unlikely to be sent for slaughter during or immediately after treatment,
- medroxyprogesterone acetate is rapidly absorbed and excreted;

the Committee considers that there is no need to establish an MRL for medroxyprogesterone acetate and recommends its inclusion in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Medroxyprogesterone acetate	Ovine	For intravaginal use for zootechnical purposes only