European Medicines Agency
Veterinary Medicines and Inspections

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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE

NORGESTOMET

SUMMARY REPORT (2)

1. Norgestomet is a synthetic derivative of progesterone with improved oral activity due to its 17α-acetate side chain. In veterinary medicine norgestomet is used for the synchronisation of oestrus in cattle. It is administered as a subcutaneous ear implant (containing 3 mg norgestomet; to be removed after 9 to 10 days), in combination with a single intramuscular injection containing 3 mg norgestomet and 5 mg oestradiol valerate. The injection is to be given immediately after application of the implant. Norgestomet is not used in human medicine.

   Norgestomet is currently included in Annex III of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Norgestomet	Norgestomet	Bovine	0.5 µg/kg 0.5 µg/kg 0.5 µg/kg 0.5 µg/kg 0.15 µg/kg	Muscle Fat Liver Kidney Milk	Provisional MRLs expire on 1.1.2008. For therapeutic and zootechnical purposes only

   Additional data on the validation of the routine analytical method for tissues and milk of bovine species were provided at the request of the Commission.

2. In a battery of animal test models it was shown that norgestomet possesses progestagenic activity without oestrogenic and androgenic side effects, and that norgestomet is more potent and orally more active than progesterone. An overall oral pharmacological hormonal NOEL of 1 µg norgestomet/kg bw/day was established for endometrial proliferation in the uterus of female juvenile, oestrogen pre-treated rabbits and monkeys (based on amenorrhoea in an 84-day oral test with doses of 0, 1 or 10 µg/kg bw/day). In the test for establishing the pharmacological hormonal NOEL in rabbits 3 metabolites of norgestomet and an extract of polar (unidentified) metabolites were shown to possess less than 1 % up to 10 % of the progestagenic activity of norgestomet.

3. Pharmacokinetic studies with ^{3}H-norgestomet were performed in heifers after intravenous administration and after recommended treatment (subcutaneous ear implant in combination with an intramuscular injection). After intravenous administration, elimination half-lives in plasma were in the range of 2.5 to 5.2 days. The major route of elimination was via the bile (35 % within 12 hours). Within 10 days after intravenous treatment 28 % was excreted in faeces and 10 to 20% in urine. After recommended treatment, plasma peak levels were reached within 2 to 6 hours after application of implant and injection, with plasma elimination half-lives of 4.3 to 9.5 days after removal of the implant. Elimination was mainly via faeces (97 % within 18 days after treatment).

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In heifers, norgestomet was extensively metabolised into mainly polar metabolites. In plasma, urine and bile, norgestomet and three metabolites (norgestomet with a degraded pregnane chain, norgestomet of which the 17α-acetyl chain was hydrolysed, and this latter metabolite reduced at the 20-position) were identified. The greater part (75 %) of the polar metabolites, of which only a small fraction were glucuronide- or sulphate conjugates, could not be identified. The 3 metabolites and an extract of the unidentified metabolites were shown to have no or little progestagenic activity (see paragraph 2). This demonstrates that norgestomet follows the general breakdown pattern of progesterone-like substances, leading to loss of progestagenic activity.

In pharmacokinetic studies with cows after recommended treatment (ear implant left in place for 10 days in combination with a single intramuscular injection) with the commercial product, mean peak plasma levels of norgestomet (approximately 0.15 µg/l) were reached within 1 to 6 hours after application of implant and injection. The plasma levels remained at this level for 1 day, and decreased thereafter to 0.012 µg/l immediately after the removal of the implant (approximately 5 minutes) and decreased further to pre-treatment values (0.008 µg/l) within 1 day after removal.

4. The acute oral toxicity of norgestomet is low. The oral LD_{50} in rats was greater than 2 g/kg bw.

5. The repeated dose toxicity of norgestomet was tested in a 13-week oral rat study and a 13-week oral dog study (both at doses of 0, 0.05, 0.25 or 2 mg norgestomet/kg bw/day). At all doses tested, effects directly related to the pharmacological activity of norgestomet were found in rats (changes in ovarian and uterus weight, mammary proliferation, prostatic atrophy, changes in uterus, ovarian and vaginal morphology) and dogs (mammary proliferation). No NOEL could be established from these studies.

6. In an oral 2-generation reproduction study rats received 0, 0.0001, 0.001, 0.01, 0.1 or 1 mg norgestomet/kg bw/day by gavage. The NOEL for maternal toxicity was 0.01 mg/kg bw/day, based on a slightly increased incidence of endometritis. The NOEL for reproductive toxicity was also 0.01 mg/kg bw/day, based on increased post-implantation loss and consequently a decreased number of pups *post-partum*.

7. A teratogenicity study in rats (receiving oral doses of 0, 0.1, 1 or 10 mg norgestomet/kg bw/day on day 7 to 16 of gestation) revealed no embryotoxic or teratogenic effects. The NOEL for maternal toxicity was 1 mg/kg bw/day, based on reduced food intake.

8. In both *in vitro* (gene mutation test with *Salmonella typhimurium*, chromosomal aberration test in human peripheral lymphocytes, a gene mutation test in mouse lymphoma cells) and *in vivo* (micronucleus test in rats) mutagenicity studies, norgestomet tested negative. As norgestomet can be considered a non-genotoxic compound, carcinogenicity studies are not deemed necessary.

9. Between 1997 and 1999, new data became available on the genotoxicity and carcinogenicity of steroid hormones, although not including norgestomet. These data were also reviewed and discussed by the Joint FAO/WHO Committee on Food Additives (JECFA) in 1999, by the Scientific Committee on Veterinary Measures Relating to Public Health (SCVPH) of the European Commission in 1999 and by the International Agency for Research on Cancer (IARC) in 1999. Upon evaluation of these data, mainly concerning 17ß-oestradiol, the CVMP concluded that steroid hormones are devoid of genotoxic activity *in vivo* and that these compounds exert their (possible) carcinogenic action only after prolonged exposure and at levels considerably higher than those required for a physiological (hormonal) response. Hence, the previous conclusions with respect to genotoxicity and carcinogenicity could be endorsed.

10. The effect of norgestomet on the menstrual cycle was investigated in two studies with in total 23 healthy normally ovulating women. In both studies the subjects received oral doses of 0.04, 0.2 or 1 mg norgestomet/day during a complete menstrual cycle. The highest dose tested (equivalent to 16.7 µg/kg bw/day) seemed to have no effect on progesterone, oestradiol, oestrone, luteinizing hormone and follicle-stimulating hormone levels in blood, and did not inhibit ovulation. However, as the full study reports were not available, this apparent pharmacological hormonal NOEL in humans can not serve as basis for the ADI.

11. The overall toxicological NOEL was 0.01 mg/kg bw/day derived from the reproductive toxicity study in rats. As pharmacological (hormonal) effects of norgestomet were observed at lower doses than the toxicological effects it is more appropriate to base the ADI on the lowest oral pharmacological hormonal NOEL of 1 µg/kg bw/day observed in rabbits and monkeys. Using a safety factor of 100, an ADI of 0.01 µg/kg bw (equivalent to 0.6 µg for a 60 kg person) can be established for norgestomet.

12. In a radiometric tissue residue study with ^{3}H-norgestomet heifers received the recommended treatment. Three animals/group were slaughtered at 0, 2, 4, or 8 days after removal of the implant. In liver, the highest non-volatile residue level was found immediately after removal of the implant (22 µg equivalents/kg), thereafter declining via 6.6 µg equivalents/kg at 2 days and 3.7 µg equivalents/kg at 4 days to 1 µg equivalents/kg at 8 days withdrawal. Non-volatile residues in kidney, fat, and non-injection site muscle were much lower (3.3, 1.5 and 0.3 µg equivalents/kg, respectively, at 0 days withdrawal, declining to 1, 0.2 and 0.2 µg equivalents/kg, respectively, at 8 days withdrawal. Although in this study the ^{3}H-label was easily exchanged, it was demonstrated that use of the more appropriate ^{14}C-label was not possible due to lack of sufficient specific activity. The parent compound norgestomet was not determined in this study and information about injection site residues was limited.

13. In a non-radiolabelled tissue residue study, cows were administered the commercial product at the recommended treatment. Groups of 4 cows were slaughtered at 0, 2, 5, or 8 days after removal of the implant, and norgestomet residues were determined in tissues using an LC-MS-MS method.

    Immediately after removal of the implant, highest mean levels of the parent drug were found in fat (0.37 µg/kg), followed by injection site muscle (0.09 µg/kg), kidney (0.07 µg/kg) and liver (0.05 µg/kg). Norgestomet levels in liver and fat declined quickly to below their respective limit of quantifications of 0.03 and 0.07 µg/kg in most samples at 2 days withdrawal. Norgestomet levels in kidney declined more gradually via 0.05 µg/kg at 2 days to at or below the limit of quantification of 0.03 µg/kg at 5 and 8 days after administration.

    In injection site muscle norgestomet levels showed no apparent decline, as the levels were in the range from below limit of quantification (0.07 µg/kg) to 0.15 µg/kg at 2, 5 and 8 days withdrawal. In non-injection site muscle, norgestomet was not detectable at any time point (limit of quantification 0.07 µg/kg).

14. In a non-radiolabelled milk residue study 6 lactating cows were given the commercial product at the recommended treatment. Norgestomet residues in milk were determined using a radioimmunoassay-method. The highest mean norgestomet concentration (0.138 µg/l) was found at 2 days following application of implant and injection, declining gradually to 0.008 µg/l at removal of the implant. Similar results were obtained in another non-radiolabelled milk residue study in eight lactating cows using the same product and treatment. In this study the norgestomet residues in milk were determined using an LC-MS method.

15. Norgestomet was considered the most suitable marker residue because it could be measured in all bovine tissues and milk and it is the residue with the highest hormonal activity.

    The ratio of marker to total residue was calculated by combining the results of the radiolabel study and the non-radiolabel study. The ratio was 0.23 for muscle, 0.26 for fat, 0.003 for liver, and 0.03 for kidney. The ratio of marker to total residues could not be established in milk, because no information on total residues in milk was available. However, based on the ratios observed in muscle and fat, the ratio in milk was estimated at 0.25.

16. For the routine determination of norgestomet residues in bovine tissues and milk an LC-MS method has been provided. The method was described in an internationally recognised format (ISO 78/2), and completely validated. The limits of quantification are 0.1 µg/kg for muscle, fat, liver, and kidney, and 0.075 µg/kg in milk.

Conclusions and recommendation

Having considered that:

- A pharmacological ADI of 0.01 µg/kg bw (0.6 µg/person) has been established,
- Norgestomet was considered the marker residue,
- The ratio of marker to total residues was 0.23 for muscle, 0.26 for fat, 0.003 for liver, and 0.03 for kidney. The ratio of marker to total residues was not established in milk, but was estimated at 0.25,
- The average activity of metabolites was 4 % of that of the parent,
- A fully validated LC-MS method is available for monitoring the marker residue in bovine tissues and milk;

the Committee for Medicinal Products for Veterinary Use recommends the inclusion of norgestomet in Annex I of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Norgestomet	Norgestomet	Bovine	0.20 µg/kg 0.20 µg/kg 0.20 µg/kg 0.20 µg/kg 0.12 µg/kg	Muscle Fat Liver Kidney Milk	For therapeutic and zootechnical purposes only

Based on these MRLs, and taking into account the activity of metabolites, the maximum intake of residues is 0.59 µg/day, i.e. 98 % of the ADI.