The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines and Inspections

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

DESLORELIN ACETATE

SUMMARY REPORT

1. Deslorelin (CAS Number: 57773-65-6) is a nonapeptide analogue of the natural gonadotrophin releasing hormone (GnRH). Compared to the natural GnRH, deslorelin has chemical modifications in the amino acid composition at positions 6 and 9/10. It has the following amino acid sequence: 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-tryptophyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide. Deslorelin is intended for induction and timing of ovulation in oestrous mares. It is recommended to be used as a single subcutaneous short term implant containing 2.1 mg deslorelin acetate.

2. Like GnRH, GnRH analogues control the release of pituitary gonadotrophins such as luteinising hormone (LH) and follicle stimulating hormone (FSH). The removal of the C-terminal glycine in natural GnRH and substitution of the 6-position L-glycine with an amino acid of D- configuration is said to be responsible for enhanced biological activity of the analogue. When administered as a single dose, GnRH analogues stimulate the release of LH and FSH. This effect is assumed to be the most sensitive and relevant pharmacodynamic response. The stimulatory effect of short-term administration of deslorelin on luteinizing hormone has been demonstrated in oestrous mares**.** In contrast, multiple doses or continuous low level dosing may cause an inhibition of LH and FSH synthesis and secretion in a dose dependent manner. This inhibition is thought to arise from desensitisation of receptors responsible for gonadotrophin release, loss of pituitary receptor binding capacity and a dose and time-dependent depletion of pituitary gonadotrophins. These effects provide the pharmacological basis of the medicinal applications of GnRH analogues in gynaecological, endocrine conditions and in oncology in humans.

3. Limited information on pharmacokinetics was available from subcutaneous studies in horses and a subcutaneous and oral study in dogs. In these studies, deslorelin activity was measured via LH or FSH response in plasma. In horses following single subcutaneous administration of the projected 2.1 mg deslorelin implant (about 3.5 µg/kg bw), blood concentrations of LH and FSH peaked at around 12 hours after implantation (LH approximately 12.2 to 95.5 µg/l and FSH about 36 to 59.7 µg/l). At 24 hours concentrations had significantly fallen from peak levels and returned to pre-treatment levels within 72 to 96 hours. These data suggested rapid absorption and elimination of the compound. In the oral studies in prepubertal Beagle dogs, a relatively large dose of 100 µg/kg bw (6 animals per sex) showed no clearly discernible increase in plasma LH concentration or in AUC of LH compared to controls over the 4 hour observation period while subcutaneous administration of the same dose resulted in a more than 3-fold increase of LH basal levels at 15 to 30 min after injection already. Following subcutaneous dosing, LH concentrations were only measured over a relatively short period (30 minutes). Therefore no overall AUC could be estimated and the relative degree of oral versus subcutaneous bioavailability could not be calculated. Nonetheless, the oral dog data indicated that oral bioavailability of the substance, if at all, is relatively poor.

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The pharmacokinetic results for deslorelin appear to be fully consistent with literature information on other GnRH analogues. Generally, the oral bioavailability of this class of peptides in laboratory species and also in humans is very limited due to metabolism and inactivation in the gastrointestinal tract and poor absorption through mucous membranes. Oral bioavailability in humans was estimated to be less than 1 %. For example, in humans, the chemically very closely related peptide leuprolide given orally at 2 mg/person (about 33 µg/kg bw) did not increase plasma LH and FSH. Only at a dose of 10 mg/person (about 167 µg/kg bw) was the LH/FSH response measurably increased (around 1 to 6 hours post dose). Similarly, oral administration of buserelin to humans at 600 µg did not result in increased urinary and plasma LH concentrations. Metabolism of GnRH and analogues can be expected to occur by enzymatic breakdown into the individual amino acid components. Plasma half-lives as determined for parenteral routes of administration are relatively short and have been estimated being in the range of 1 to 3 hours. Generally, synthetic GnRH agonists appear to be more resistant to degradation than the natural parent compound GnRH.

4. Conventional oral single dose toxicity studies with deslorelin were not available. There was also no information on oral single dose toxicity for other GnRH analogues.

5. Oral repeated dose toxicity and developmental toxicity studies have not been carried out with deslorelin. Published information on oral repeated dose toxicity studies or oral reproductive or teratogenicity studies for other GnRH analogues is not available.

6. Genotoxicity studies were not carried out and are not deemed necessary considering the nature of the substance. In literature, peptidic substances such as deslorelin have not been associated with genotoxicity.

7. No carcinogenicity studies were available. Related compounds like buserelin have not been reported to be carcinogenic following long-term parenteral treatment of rats.

8. No studies on other effects as immunotoxicity, etc and microbiological properties have been carried out.

9. Considering the chemical nature of the substance, its particular conditions of use and its limited or absent systemic activity by the oral route of exposure, there is no need to specify an ADI.

10. In humans, deslorelin has been tested extensively for treatment of children with precocious puberty (4 µg/kg bw, subcutaneously, daily over several years) and also for treatment of prostate cancer (250 to 500 µg/kg bw subcutaneously, daily over 2 years). Deslorelin is currently being tested in trials for the treatment of menorrhagia, fibroids and endometriosis. In healthy males stimulation of LH and FSH was observed after single subcutaneous administration of 20 µg deslorelin. Following repeated dosing, adverse reproductive effects such as decrease or loss of fertility have been noted after daily subcutaneous administration of 50 µg deslorelin and higher doses for up to 10 weeks. These effects were shown to be reversible.

11. Conventional residue depletion studies in horses were not carried out. Peak concentrations of LH in mares at 12 hours post implantation of deslorelin and absence of hormonal effects after 72 to 96 hours suggested rapid release from injection sites and effective inactivation or elimination of the substance. As administration of the substance will be occasionally as a single, short-term acting dose to selected mares at oestrus, accumulation of residues in horse tissues is not an issue. These circumstances of use suggest that human exposure to potential residues in horse meat is an acute rather than a chronic event. A worst case exposure estimate illustrated that even in the case of consumption of meat from treated animals immediately after dosing, consumer risk from residues is negligible: The mean residue concentration in the horse after absorption of the full parenteral dose (2.1 mg/500 kg bw) can amount to about 4 µg/kg bw (assuming approximately homogeneous distribution). This concentration is corresponding to a theoretical intake of about 2 µg deslorelin/60 kg person in the usual 500 g standard meat portion or 0.033 µg/kg bw which is 3000 times below the oral deslorelin dose of 100 µg/kg bw that was shown to be virtually inactive in dogs. A large safety margin therefore exists even for horse meat immediately after dosing.

Conclusions and recommendation

Having considered that,

- deslorelin is a peptidal substance chemically closely related to the natural occurring GnRH, which has been assessed previously and included in Annex II for all food producing species,
- deslorelin is intended for only single dose, occasional treatment, of individual horses, as an aid to breeding,
- deslorelin is expected to be quickly degraded and eliminated in the target animal,
- oral bioavailability in humans is considered negligible,
- deslorelin treated animals are unlikely to be sent for slaughter immediately after treatment,

the Committee for Veterinary Medicinal Products concludes that there is no need to establish an MRL for deslorelin in horses and recommends its inclusion in Annex II of Council Regulation (EEC) No. 2377/90 in accordance with the following table:

Pharmacologically active substance	Animal species	Other provisions
Deslorelin acetate	*Equidae*	