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

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

LECIRELIN (LE)

SUMMARY REPORT

1. Lecirelin (6-(3-methyl-d-valine)-9-(N-ethyl-L-prolynamide)-10-deglycinamide) luteinizing hormone releasing factor, is a synthetic hypothalamic gonadotropin releasing hormone (GnRH) analogue. Lecirelin is a nonapeptide, while the natural compound is a decapeptide; moreover the glycine aminoacid in the 6th position has been substituted by leucine.

2. The drug is intended for the induction of ovulation in cows, mares and rabbits, both for treatment of such conditions as ovarian cysts and for improvement of conception rates. The recommended dosing regime is a single or repeated twice intramuscular treatment with 50-100 µg (cow, mare) or 0.5-0.8 µg (rabbit) of active compound.

3. The pharmacodynamic action is based on the release of DH and FSH from the pituitary gland, elicited for a longer (approximately double) time as compared to the natural GnRH. Treatment with lecirelin also increases slightly the plasma levels of 17-beta oestradiol and progesterone, while no significant effects on testosterone have been observed in bulls.

4. Pharmacokinetics studies carried out in rats, cattle, cows, sheep, rabbits, as well as humans treated with a closely related compound, showed a complete disappearance from plasma and target tissues (hypophysis, testicles, uterus) within 24 hours. The plasma half-life is species-related, being lower in rats (40-60 minutes) than in sheep (50-140 minutes).

5. Degradation of GnRH analogues takes places in the liver as well as in the target tissue. No traces of intact peptide were found within 60 minutes in rat liver and kidney after an intravenous treatment with a closely related analogue. The first metabolic step is cleavage at the N-terminal through pyroglutamyl-amino-peptidase pyroglutamic histidine bridge; then in the liver only, enzymes completely degrade the compound. The main excretory route is through the urine.

6. No deaths or clinical signs were induced by lecirelin following a single subcutaneous or intramuscular treatment of 0.25 mg/kg in rats and $\underline{<}$ 1.05 mg/kg in mice: however, in female rats congestion of uterus and ovaries was observed. A single intramuscular injection of < 1.000 and 25 µg in cows and rabbits, respectively, induced no unwanted secondary effects, either local or systemic.

7. When 50 µg were administered intramuscular to dairy cows, lecirelin was below the limit of detection at 1-12 hours after treatment, using either HPLC (limit : 5 µg/ml) and RIA (limit : 5 pg/ml).

8. Like other peptide compounds, lecirelin will be largely digested. Therefore the compound is expected to show little activity upon oral administration as compared to parenteral treatment. The pharmacokinetics data show a short half-life and a rapid clearance. In fact, cleavage of the amino acid component by digestive enzymes will lead to complete inactivation. To summarise, it is most unlikely that any consumer would be exposed to even small amounts of lecirelin, considering also that the drug is intended for use in breeding animals. As a result of these considerations, there is no need to define an ADI and, therefore, to establish MRLs and the substance is recommended for entry into Annex II of Council Regulation (EEC) Nº 2377/90 for use in cattle, horses and rabbits.

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