The European Agency for the Evaluation of Medicinal Products

EMEA/MRL/019/95-FINAL

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

BUSERELIN

SUMMARY REPORT

1. Buserelin (D-Ser (Bu^t)^6 Pro^9 Net LHRH acetate) is a synthetic hypothalamic gonadotropin releasing hormone (GN-RH, LH-RH) analogue.

2. Buserelin is intended for the induction of ovulation in cows, mares and rabbits, both for the treatment of ovarian disorders such as ovarian cysts and for the improvement of conception rates. The recommended dosage regime is a single or repeated twice i.m., s.c. or i.v. treatment with 0.02 mg (cows), 0.04 mg (mares) and 0.8 µg (rabbits) of the active compound.

3. The pharmacodynamic action of buserelin corresponds to that of natural LH-RH in stimulating the pituitary release of LH and FSH and, secondarily, secretion of gonadal steroids. Its LH releasing activity is, depending on the route and time of administration, about 18 to 322 times higher in comparison to that of the natural compound.

   Repeated administration of high buserelin doses or continuous i.v. infusion result in an inhibition of the secretion of gonadotrophins and/or gonadal steroids which is due to pituitary desensitisation and loss of gonadal LH- and prolactin receptors The suppressive effects are both dose- and time-dependent and are reversible.

   Studies on secondary effects of buserelin on the cardiovascular or renal system, blood glucose, central nervous system or motility of smooth muscles were negative.

   In humans, buserelin was shown to be biologically inactive following oral or sublingual single or repeated twice doses of 5 mg or 0.5 mg/person.

4. Pharmacokinetic studies were carried out in vivo (rats, guinea pigs, rabbits and cows) and in vitro. Following i.v. application buserelin is rapidly eliminated from blood circulation with an initial half life of 5 minutes (rats) or 12 minutes (guinea pigs). The compound accumulates in the pituitary gland, liver and kidneys, where it is enzymatically degraded into smaller peptide fragments with negligible biological activity. The main excretory route is through the urine.

   In the target species cows and rabbits buserelin was rapidly eliminated from plasma following i.v. application.

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In milk buserelin concentrations following an iv. dose of 10 mg peaked at 1 h post dose (ca. 10 µg/l) and decreased to pre-treatment values within 10 to 24 h.

5. In a single dose toxicity study performed in rats and mice, no deaths or clinical signs were observed following i.v. application of 500 µg/kg b.w (mice) and 1000 µg/kg b.w. (rats).

6. Repeated dose toxicity studies were carried out in rats and dogs. Repeated s.c. administration of high buserelin doses resulted in a dose-dependent marked depression in pituitary and gonadal function in both males and females (reduction of estradiol synthesis and secretion, inhibition of follicular maturation and uterine involution, and inhibition of testes function and prostate involution). The suppressive effects were shown to be reversible.

7. Studies on embryotoxic effects in rats and rabbits revealed a dose-dependent inhibition of implantation in both species following s.c. doses from 4 µg (rats) and 10µg (rabbits) per kg b.w. onwards, due to the suppressive influence of buserelin on the endocrine system. There was no evidence of teratogenic effects of buserelin.

   Fertility studies in rats revealed an inhibition of the fertility in males following repeated s.c. doses of 0.6 and 1.8µg/kg b.w. which can be explained by the inhibition of testosterone synthesis.

8. Studies on mutagenicity of buserelin (AMES test, Micronucleus test) were negative.

   A carcinogenicity study performed in rats was negative.

9. No antibody formation was observed in long term studies in rats and dogs following high buserelin doses or during long term clinical treatment in humans.

10. No data on the tolerance of buserelin in the target animal species (cows, mares, rabbits) is available.

11. Irritation studies in dogs and rabbits following intranasal or conjunctival application, or i.v., i.m. or s.c. injection were negative.

12. Like other peptide hormones, buserelin will be largely digested. In humans, buserelin was demonstrated to be orally inactive following extremely high doses. The pharmacokinetic data obtained in rats and guinea pigs show a short half life and a rapid clearance. In the pituitary gland, the liver and kidneys, buserelin is enzymatically (peptidases) degraded into smaller peptides with negligible biological activity, and is excreted through the urine.

13. In conclusion, there is no need to define an ADI and, therefore, to establish MRLs. It is recommended to insert buserelin into Annex II for use in all food-producing species.