European Medicines Agency
Veterinary Medicines and Inspections

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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE

PEFORELIN

SUMMARY REPORT

1. Peforelin (CAS Number: 147859-97-0) is a decapeptide analogue of the natural gonadotropin releasing hormone (GnRH). Compared to the natural GnRH, peforelin has chemical modifications in the amino acid composition at positions 5, 6, 7, and 8. It has the following amino acid sequence: pyro-glutamyl-histidyl-tryptophyl-seryl-histidyl-asparagyl-tryptophyl-lysyl-prolyl-glycine-amide. Peforelin is intended for induction of the oestrous cycle in weaned sows and induction of oestrus in sexually mature gilts following a previous inhibition of oestrous cycle. It is recommended to be used as a single intramuscular injection of 150 µg per animal, corresponding to 1.5 µg/kg bw.

2. In general, GnRH analogues control the release of pituitary gonadotrophins such as luteinising hormone (LH) and follicle stimulating hormone (FSH). This effect is assumed to be the most sensitive and relevant pharmacodynamic response for this group of compounds. Specific data for peforelin obtained in rats and cattle yielded inconsistent results in respect to the action on LH and FSH release. A primarily FSH-releasing activity of peforelin was demonstrated in some studies in rats and cattle, but it was also reported in other studies that the substance stimulates both gonadotropins.

   Investigations performed in the target species (pigs) also demonstrated a primary activity following short-term administration of peforelin on FSH secretion. The stimulatory effect of short-term administration of peforelin on the induction of oestrus has been demonstrated in weaned sows and sexually matured gilts. No adverse findings were noted in these studies.

3. In an oral bioavailability study in pigs (8 castrated boars) doses of 150 and 15000 µg/animal showed no clearly discernible increase in plasma FSH and LH-concentrations compared to basal levels over the 24 and 96 hour observation period while intramuscular administration of the lower dose (150 µg/animal) resulted in a marked increase of FSH- and a less pronounced one of LH-concentration in serum from 0.5 hours post administration up to 12 hours post administration. These data indicated that oral bioavailability of peforelin is very low. *In vitro* analysis of peforelin stability in artificial gastric and intestinal juices confirmed rapid degradation of the substance as a result of digestive processes.

   In pigs following a single intramuscular injection of 150 µg per animal, (1.5 µg/kg bw), serum concentrations of FSH peaked at 1 hour post-treatment (2.19 mIU/l) with a 2-fold increase above basal levels (about 1.02-1.21 mIU/l). At 16 hours FSH concentrations returned to pre-treatment levels. In parallel, LH levels were only slightly elevated between 3 and 12 hours post-treatment (3.37 to 3.67 mIU/l compared to 2.76 to3.01 mIU/l). These data suggested rapid absorption and elimination of the compound.

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The pharmacokinetic results for peforelin are 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%. In humans, a closely chemically related peptide 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 after administration). Similarly, oral administration of another GnRH analogue 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 by 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 peforelin 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 peforelin. Published information on oral repeated dose toxicity or oral reproductive or teratogenicity studies for other GnRH analogues is not available. Considering the chemical nature of the substance the absence of data was considered acceptable.

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

7. No carcinogenicity studies were available. Related compounds have not been reported to be carcinogenic following long-term parenteral treatment of rats. Considering the chemical nature of the substance the absence of data was considered acceptable.

8. No studies on other effects as immunotoxicity, neurotoxicity, and microbiological properties have been carried out. There is no indication of a potential of the substance in relation to such effects.

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 was no need to establish an ADI.

10. Conventional residue depletion studies in pigs were not carried out. Peak concentrations of FSH in pigs at 1 hour after administration (intramuscular injection) of peforelin and absence of hormonal effects after 16 hours suggested rapid release from injection sites and effective inactivation or elimination of the substance.

    A worst case exposure estimate illustrated that, in the case of consumption of meat from treated animals immediately after administration, the mean tissue residue concentration in the pig after absorption of the full parenteral dose (150µg per 100 kg bw) could amount to about 1.5 µg/kg bw (the substance is assumed to be well and homogeneously distributed within the animal). This corresponds to an intake of 0.75 µg peforelin/person in the 500 g standard meat portion or 0.0125 µg/kg bw in the 60 kg person, a dose which is about 12 000 times below the oral peforelin dose of 15 mg per animal that was shown to be virtually inactive in pigs. Even residues from an injection site containing the full dose would be far below the orally inactive dose (margin of exposure of about 60). A large margin of exposure therefore exists even for pig meat immediately after treatment.

Conclusions and recommendation

Having considered that:

- peforelin is a peptidic substance closely related to the natural occurring GnRH, which has been previously assessed and included in Annex II for all food producing species,
- peforelin is expected to be rapidly metabolised and quickly degraded/eliminated in the target animal,
- oral bioavailability of tissue residues in humans is negligible due to low absorption and inactivation in the gastrointestinal tract;

the Committee for Medicinal Products for Veterinary Use concludes that there is no need to establish an MRL for peforelin for use in pigs 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
Peforelin	Porcine	