COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

HUMAN CHORIONIC GONADOTROPHIN (HCG)

SUMMARY REPORT

Safety File

1. Human Chorionic Gonadotrophin is a natural glycoprotein consisting of two subunits (alpha and beta). For use in veterinary medicine, Human Chorionic Gonadotrophin is extracted from the urine of pregnant women.

2. Human Chorionic Gonadotrophin exerts primarily luteinizing (pituitary LH-like) activity. In veterinary medicine it is recommended for the treatment of ovarian dysfunction (anestrus, prolonged estrus associated with nymphomania), for the induction of ovulation and improvement of the conception rate, and for the treatment of cryptorchism. Formulations are available as lyophilized preparations in combination with a solvent for reconstitution. For cows/heifers and mares the recommended doses for single intravenous or intramuscular treatments are 1500 - 3000 I.U./animal. In mares, the treatment can be repeated after two days, where necessary. Fixed combination products containing Human Chorionic Gonadotrophin and progesterone or Pregnant Mare Serum Gonadotrophin (PMSG) are available for cattle (3000 I.U. Human Chorionic Gonadotrophin plus 125 mg progesterone/animal) or pigs (200 I.U. Human Chorionic Gonadotrophin plus 400 I.U. PMSG/animal), respectively.

3. The biological activity of Human Chorionic Gonadotrophin was demonstrated in a rat seminal vesicle weight bioassay following repeated subcutaneous administrations totalling dose levels of 1 to 4 I.U./animal. The clinical efficacy of Human Chorionic Gonadotrophin in inducing ovulation was shown for mares. No data on efficacy is available for cattle and pigs.

4. A rat seminal vesicle weight bioassay with repeated intragastric administrations of Human Chorionic Gonadotrophin at a total dose of 20 I.U./rat was negative. Since only one dose level was tested in a limited number of animals a NOEL could not be derived.

   Oral administration of doses of 200 I.U. Human Chorionic Gonadotrophin plus 400 I.U. PMSG/animal/day or of 2000 I.U. Human Chorionic Gonadotrophin plus 4000 I.U. PMSG per animal/day to young hypophysectomized rats for 2 weeks resulted in distinct stimulating effects on reproductive organs of both males and females (increase in weight of reproductive organs, signs of spermatogenesis and hyperstimulation of ovaries and uterus). The effects were more pronounced in the high dose group. Only PMSG, but not Human Chorionic Gonadotrophin was detected in serum samples obtained from treated animals at necropsy. A NOEL was not derived from this study.

5. Pharmacokinetics were studied in various animal species including rats, dogs, cows, pigs, and also in humans. In plasma, Human Chorionic Gonadotrophin declined biphasically with species-specific terminal half-lives of 12 h (rat, intravenous), 31.6 - 32.7 h (dog, intravenous, intramuscular, subcutaneous), 10.3 or 31.6 - 32.7 h (in one study 57 h) (cow, intravenous, intramuscular), 27.3 - 54.9 h (pig, intravenous, intramuscular), and 39.8 h (human, intravenous). The half-lives were dependent on the vehicles used and the reliability of the methods applied for anlysis.

   The bioavailability of Human Chorionic Gonadotrophin in cattle, pigs and dogs following i.m. administration was found to be 101%, 78% and 103%, respectively.

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel: (+44-171) 418 84 00 Fax: (+44-171) 418 84 16

A published distribution study in rats (intravenous) revealed the presence of Human Chorionic Gonadotrophin in the ovaries and kidneys. Following intravenous injections of the alpha or beta subunit of Human Chorionic Gonadotrophin none of the subunits was found in the ovaries. It was concluded, that these are biologically inactive.

Following intravenous administration of Human Chorionic Gonadotrophin to humans (published data), approximately 30% of the dose are excreted via the kidneys, and the remaining 70% are disposed by metabolic degradation, probably in the liver and kidney. In urine samples, only the Human Chorionic Gonadotrophin subunits were found but no intact Human Chorionic Gonadotrophin.

No data on the metabolism and excretion of Human Chorionic Gonadotrophin in the target animal species is available. In particular, the identity and residual biological activity of degradation products is not known. No pharmacokinetic data is submitted for mares.

6. In pigs, Human Chorionic Gonadotrophin was shown to be well tolerated after a single subcutaneous injection of a dose corresponding to 25 times the recommended clinical dose, or following 5 subcutaneous injections of the recommended clinical dose in 3 week intervals.

   In lactating cows, no adverse effects were observed following a single intravenous injection of Human Chorionic Gonadotrophin at a dose corresponding to 4 times the recommended maximum clinical dose.

   No adverse effects were observed in mares following a single intravenous administration of Human Chorionic Gonadotrophin at doses up to 4 times the recommended maximum clinical dose during 5 to 6 successive cycles (published data).

7. According to cited literature formation of antibodies is elicited in mares following repeated Human Chorionic Gonadotrophin treatments. Reports on concurrent reductions in the clinical response are equivocal. No data on antibody formation in pigs and cattle is available.

8. No data on single or repeated dose toxicity, reproduction toxicity including teratogenicity, mutagenicity, and carcinogenicity of Human Chorionic Gonadotrophin is available.

9. Although a clear NOEL for Human Chorionic Gonadotrophin following oral administration could not be established, the submitted data indicate that ingested Human Chorionic Gonadotrophin residues in food derived from treated animals are biologically inactive.

   Reference is made to a 5 day oral rat study in which a total dose of 400 IM Human Chorionic Gonadotrophin/kg bw revealed no effects.

10. The original source of Human Chorionic Gonadotrophin is the urine of pregnant women. The national authorities will resume responsibility for assessment of the necessary measures taken by the manufacturer against microbial contamination of the product, including the infective agents of AIDS.

Residue File

1. No residue depletion studies have been performed in food producing animals, because the applicant and the expert consider the residues as orally inactive.

2. A routine analytical method for the determination of Human Chorionic Gonadotrophin in edible tissues and milk was not provided, because the applicant and the expert consider the residues as orally inactive.

Based on the indication that ingested residues are biologically inactive, it is concluded that Maximum Residue Limits are not required to ensure consumer safety.

It is proposed to include Human Chorionic Gonadotrophin into Annex II of Council Regulation n° 2377/90 for use in all food producing species.