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

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

PREGNANT MARE SERUM GONADOTROPHIN (PMSG)

SUMMARY REPORT

Safety File

1. Pregnant Mare Serum Gonadotrophin (PMSG) is a natural glycoprotein consisting of two subunits (alpha and beta). For use in veterinary medicine it is extracted from serum of pregnant mares.

2. PMSG has follicle stimulating (FSH-like) and luteinizing (LH-like) activities. In veterinary medicine, it is recommended for the stimulation of ovarian function and activity, improvement of fertility in estrus-synchronized animals and the induction of superovulation. Formulations are available as lyophilized preparations in combination with a solvent for single i.m. and s.c. use. For food producing animal species the following doses/animal are recommended: cattle 300 - 3000 I.U., goats and sheep 400 - 750 I.U., rabbits 40 I.U., and deer 200 I.U. A fixed combination product containing PMSG and human chorionic gonadotrophin (hCG) for treatment of pigs is available (400 I.U. PMSG plus 200 I.U. hCG/animal).

3. The biological activity of PMSG was demonstrated in a rat ovarian weight bioassay following repeated s.c. administrations totalling dose levels in the range of 10.32 I.U. to 20.64 I.U. per rat.

   The clinical efficacy of PMSG in inducing estrus, improving fertility rate and inducing multiple ovulations was demonstrated in sheep, goats, and cattle. No data is available for pigs, rabbits and deer.

4. A rat ovarian weight bioassay with repeated intragastric administrations of PMSG at a total dose of 145.8 I.U./animal (2916 I.U./kg bw), was negative. Since only one dose level was tested in a limited number of animals a NOEL could not be derived.

   Oral administration high doses (400 I.U. PMSG plus 200 I.U. hCG/animal/day or of 4000 I.U. PMSG plus 2000 I.U. hCG/animal/day) to young hypophysectomized rats for 2 weeks resulted in distinct stimulating effects on the reproductive organs of both males and females (increase in weight of reproductive organs, signs of spermatogenesis, hyperstimulation of ovaries and uterus). The effects were more pronounced in the high dose group. In serum samples obtained from high dosed females at necropsy, PMSG concentrations of up to 177 mU/ml were measured while only trace amounts of the compound were detected in samples from the low dose group. hCG could not be detected in any of the samples. In males, all hormone measurements were negative. A NOEL was not established in this study.

5. Pharmacokinetics of PMSG were studied in various animal species including rat, dog, sheep, cow, pig, and pony using bioassays, haemagglutination inhibition tests as well as RIA and ELISA techniques. In plasma, PMSG declined biphasically with species specific terminal half-lives of 6 hr, 22-64 hr, 118-220 hr, and 35 hr as measured in rats (i.v.), sheep (i.v., i.m.), cows (i.v., i.m.), and pigs (i.v., i.m.), respectively.

   A published distribution study in rats (i.v.) revealed considerable amounts of PMSG in liver and kidney. In vitro incubation of PMSG with blood plasma or extracts obtained from liver or kidney for 16 hr resulted in a destruction in the biological activity by 58%, 64%, or 96%, respectively, as measured by the rat testis Leydig cell assay.

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According to cited literature, urine and milk from pregnant ponies (gestational day 63 - 128) contains endogenous chorionic gonadotrophin at concentrations of approximately 1/100 and 1/500, respectively, of that in plasma.

Although the site of metabolism was not investigated under in vivo conditions it is suggested that PMSG is mainly degraded in liver and kidney. The identity of the degradation products and their residual biological activity is not known.

No pharmacokinetic data is submitted for goats, rabbits, and deer.

6. In pigs, PMSG was shown to be well tolerated after a single s.c. administration of a dose corresponding to 25times the recommended clinical dose, or following 5 s.c. injections of the recommended clinical dose in 3 week intervals.

   In heifers, no toxic or adverse effects were observed following a single i.m. administration of PMSG at a dose corresponding to 25times the recommended maximum clinical dose. The relevance of this study is limited by the fact that the animals were i.v. injected with neutralizing PMSG antibodies 4 days after PMSG treatment.

   No data on the tolerance of PMSG in sheep, goats, deer, and rabbits is available.

7. According to cited literature formation of antibodies against PMSG is elicited in sheep and goats but not in cows following repeated PMSG treatments. A concurrent reduction in the clinical response was only reported for goats. No data on antibody formation in pigs, rabbits, and deer is available.

8. No data on single and repeat dose toxicity, reproduction toxicity including teratogenicity, mutagenicity, and carcinogenicity of PMSG is available.

9. The applicant proposes to insert PMSG into Annex II. Reference is made to the negative results of a rat study in which a total oral dose of 2916 I.U. PMSG/kg bw has been administered within 3 days.

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 PMSG in edible tissues and milk was not provided, because the applicant and the expert consider the residues as orally inactive.

Conclusion

Pregnant mare serum gonadotrophin (PMSG), like other exogenous gonadotrophins is a peptide which is destroyed in the gastrointestinal tract. As a consequence, such substances are inactive in humans by the oral route. It is only used in single treatments in animals which are unlikely to be sent to slaughter immediately after drug use as they will, by nature of the drug, be involved in breeding programmes. Thus, PMSG offers no risk to the consumer and it is recommended for inclusion into Annex II.