The European Agency for the Evaluation of Medicinal Products

EMEA/MRL/034/95

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

POLYETHYLENE GLYCOLS

(Includes polyethylene glycol 200, polyethylene glycol 300, polyethylene glycol 400, polyethylene glycol 600, polyethylene glycol 1000, polyethylene glycol 1500, polyethylene glycol 1540, polyethylene glycol 4000, polyethylene glycol 6000, polyethylene glycol 9000, and polyethylene glycol 10 000)

SUMMARY REPORT

1. Polyethylene glycols ($HO[CH_2CH_2]_xOH$) result from the polycondensation of ethylene with water. PEGs (molecular weight ranging from 200 to 10000) are extensively used as vehicle or cosolvent in many pharmaceutical preparations.

2. PEG 4000 and 6000 showed no absorption from the rat intestine over a five hour period, while PEG 1000 and 1540 showed a slight absorption amounting to less than 2% of the total dose during the same period.

3. Many data of Pharmacokinetic studies are available in humans. After intravenous administration of 1 g doses of PEG 1000 and PEG 6000 to six human subjects, 85% of PEG l000 and 96% of PEG 6000 were excreted in the urine within 12 hours.

   When PEG 400 was given intravenously to three human subjects, 77% recovery of this material were recovered in the urine within 12 hours. However, after oral administration, this percentage decreases to 40-50% within 24 hours.

4. Acute toxicity was tested in rat, rabbit and guinea pig after oral and intraperitoneal administrations. The LD50s determined were higher than 15 g/kg b.w.

   Clinical signs were : jumpings, tremors, convulsions, piloerection and dyspnoea. Post mortem examination revealed pulmonary hyperaemia and oedema.

5. Many three-month toxicity studies have been carried out.

   PEG 200 was administered orally to monkeys and rats for a 13-week period at dosage levels of 2 to 4 ml/kg b.w. (monkeys) and 2.5 to 5.0 ml/kg b.w. (rats) per day. Pathological lesions (intratubular deposition of small numbers of oxalate crystals in the renal cortex) were encountered only in monkeys. These lesions were not associated with other clinical or pathological findings.

   Groups of 5 rats/sex received 0, 2, 4, 8, 16 and 24% of PEGs in their diet. Some effects like an increase of the liver or the kidney weight or a decrease of the body weight were reported at dose levels higher or equivalent to 8% or 16%. The NOELs were determined at 4% for PEG 300, PEG 1500, PEG 1540, PEG 4000 and at 8% for PEG 200, PEG 400, PEG 600 and PEG 1000.

6. PEGs 400, 1540 and 4000 cause no adverse effect in dogs when fed 2% in the diet for one year.

7. For the reproduction studies, groups of 35 female and 35 male rats were given orally 2.8 g/kg b.w./day PEG 400. Administration to the females began 14 days prior to mating and continued until gestation day 13 or lactation day 21. Administration to the males began 64 days prior to mating. The female and male mating index was 100%, the female fertility index was 85.7%, copulatory interval and gestation length was normal. The number of viable embryos per dam (16) and postimplantation loss dam (0.6) were inside the biological variations. Weight gain of the pups through lactation was normal. No other adverse effects were observed.

8. Mutagenicity has only been tested for PEG 200 in the Ames test. It was not mutagenic in this test.

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9. Three carcinogenicity studies were performed in rats.

   Groups of 20 male and 20 female rats were fed 0, 0.5, 1.0, 2.0 and 4.0% of PEG 200 in their diet for two years. The results indicated that, at 4.0% dose level, PEG 200 produced no significant deviations from the control rats during the two-year feeding study.

   Dosages of 60 mg/kg b.w./day of PEG 1500 or of 20 mg/kg b.w./day of PEG 4000 did not cause any significant adverse effects (mortality, frequency of infection, life-span, fluid consumption, body weight gain, kidney and liver weights, frequency of size of litters, blood cytology, urinary albumen and sugars, occurrence of neoplasm, and micropathology) in albino rats when administered in the drinking water over a two-year period.

   Four groups received PEG 1500 via drinking water at doses approximately equal to 15, 590, 2700 and 16900 mg/kg b.w./day. Four other groups received PEG 4000 at doses of 0.85, 3.6, 17 and 620 mg/kg b.w./day. The percentage of deaths at the end of the 2 years period was within normal limits (55%). No significant clinical symptoms or (histo-) pathology lesions were found. Neoplasms and degenerative changes in the kidneys were reported, but these were distributed equally in treated and untreated animals.

10. Although early reports in 1950 indicated that skin sensitisation was observed in guinea pigs tested with certain polyethylene glycols, later studies, in 1971, showed that currently produced materials were without irritating or sensitising properties.

    Irritation studies with PEGs in the rabbit showed that 0.5 ml of undiluted PEGs 200, 300, 400, 600, 1500 and 4000 caused no visible lesions or internal congestion of the iris.

11. Many data are available in humans and some recent studies demonstrated that in 1556 treated patients only four showed allergic reactions to lower molecular weight liquid polyethylene glycols in topical medications : two cases of immediate urticarial reactions with PEG 400 and two cases of allergic eczematous reactions (one with PEG 200 and one with PEG 300) were reported.

    The PEGs appeared not to be primary irritants. Routine test in 92 dermatological patients with contact allergies gave 4% positive reactions with PEG 300.

12. The JECFA established in 1980 :

- a NOEL for rat at 2% in the diet equivalent to 1000 mg/kg b.w.,
- an Acceptable Daily Intake of 10 mg/kg b.w./day (i.e 600 mg/day for a person of 60 kg).

    The Working Group followed this proposal.

CONCLUSION AND RECOMMENDATION

Having considered the criteria laid down by the Committee for inclusion of substances into Annex II of the Council Regulation (EEC) No 2377/90 and that:

- the ADI is 10 mg/kg b.w./day (i.e 600 mg/day/person),
- PEGs are not or slight absorbed and they are rapidly excreted,
- humans are frequently exposed to PEG via for instance toothpaste, oral medicines, suppositories, topical medicines, shampoos, etc...,

The Committee for Veterinary Medicinal Products concluded that maximum residue limits for tissues are not necessary to ensure consumer safety and recommends the inclusion of polyethylene glycols in Annex II of Council Regulation (EEC) No 2377/90.

Pharmacological active substance(s)	Animal species	Other provisions
Polyethylene glycols (molecular weight ranging from 200 to 10.000)	All food producing species	