



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

POLYETHYLENE GLYCOL STEARATES and POLYETHYLENE GLYCOL 15 HYDROXYSTEARATE

SUMMARY REPORT

1. Polyethylene glycol stearates (synonyms: macrogol stearates, polyoxylstearates, polyoxyethylene stearates, ethoxylated stearates; CAS-No. 9004-99-3, 9005-08-7) are mixtures of mono- and distearate esters of mixed macrogols (polyoxyethylene polymers) and corresponding free glycols. The general formula for the compounds is $C_{17}H_{35}COO.(O.CH_2CH_2)_nH$ or $C_{17}H_{35}COO.(O.CH_2CH_2)_n.COOC_{17}H_{35}$. The average length or the molecular weight of the polymer chain is often indicated in the name of the specific substance, e.g. macrogol stearate 400/polyoxyl 8 stearate, macrogol stearate 2000/polyoxyl 40 stearate or polyethylene glycol 30 dipolyhydroxystearate. The compounds are anionic or nonionic surfactants. Water solubility increases with chain length of the polymer. They are used as emulsifying and solubilising agents in pharmaceutical preparations and cosmetics. They appear in liquid veterinary medicinal products intended for topical, oral and parenteral administration.

Polyethylene glycol 15 hydroxystearate (synonym: polyoxyl-15-hydroxystearate) is a reaction product of 12-hydroxystearic acid with 15 moles of ethylene oxide. This non-ionic surfactant belongs to the family of polyethylene glycol fatty esters or polyethylene glycol esters of fatty acids. It is also called Macrogol-660- or polyoxyethylene-660-hydroxystearate. The application is restricted to its use as excipient in a new anthelmintic product for cattle and non-lactating dairy animals. When used as excipient, the concentration in the formulation is around 20%, resulting in a dose of approximately 4 mg/kg bw administered by subcutaneous route, 1 to a maximum of 4 times per year.

2. The pharmacological studies carried out for polyethylene glycol 15 hydroxystearate in order to follow the histamine release were limited to *in vitro* models (mast cells from human material, from guinea pig lungs or from rat peritoneum) and *in vivo* studies carried out in dogs after intravenous administrations in a range of 25 to 200 mg/kg bw. For intravenous doses higher than 25 mg/kg bw, clinical effects such as apathy, transient restlessness, urticaria were reported. No side-effects were reported after 19 intravenous administrations of 25 mg/kg bw in dogs. However, the pharmacological tests were too limited to state that this substance is not pharmacologically active at the doses at which it is administered to the target species by the means of the veterinary medicinal product in which it is included.
3. No data on metabolism and pharmacokinetics of polyethylene glycol 15 hydroxystearate and polyethylene glycol stearates were provided. However, it is known that polyoxyethylene compounds are poorly absorbed from the gastrointestinal tract.
4. For the polyethylene glycol stearates only very few data were provided. The oral LD₅₀ of polyethylene glycol 8 stearate in rats is 250 mg/kg bw. No data have been presented concerning the toxic effects following repeated exposure. The same applies to data concerning reproductive effects of exposure, and data concerning the mutagenic/carcinogenic potential of the substances.

¹ Revised on 18 June 2003 to include polyethylene glycol 30 dipolyhydroxystearate (Paragraph 1)

5. No death occurred after single oral administration of doses up to 20 g/kg bw of polyethylene glycol 15 hydroxystearate in mice and in rats. The intravenous LD₅₀ values were in the magnitude of 1300 mg/kg bw in rats and in rabbits and ranged from 3160 to 5000 mg/kg bw in mice. In Beagle dogs the compound caused no deaths up to 3160 mg/kg bw administered by intravenous route.
6. No oral toxicity studies were carried out with polyethylene glycol 15 hydroxystearate in laboratory species. However, three intravenous repeated dose toxicity studies were conducted in rats and one in dogs. In 2-week and 4-week toxicity studies, rats received daily doses of 25, 75 and 200 mg/kg bw of polyethylene glycol 15 hydroxystearate by intravenous route. Lipid deposit was reported in the two highest dose groups. After a 4-week recovery period, this effect could only be seen in the 200 mg/kg dose group. A NOEL of 25 mg/kg bw was derived from these two studies.

In a 3-month toxicity study with polyethylene glycol 15 hydroxystearate, rats received intravenous administrations of 0, 250, 500 and 750 mg/kg bw/day. Deaths occurred at the two highest doses. Slight reversible haematological and biochemical changes were noted (increase in serum haemoglobin derivatives and in mean corpuscular, decrease in mean platelet, in serum cholesterol concentrations and in the mean total protein values). For all dosages, a dose-dependent lipid deposit in reticulo-endothelial systems of the spleen and in the liver was noted. No NOEL (less than 250 mg/kg bw/day) could be retained from this study.

In a 4-week toxicity study, dogs received daily doses of 0, 5, 25, 50 and 100 mg/kg bw of polyethylene glycol 15 hydroxystearate by intravenous route. Transient dose-related pseudo-anaphylactic reactions (pruritus, erythema) were noted at 100 and 50 mg/kg bw/day. No adverse effects were reported at 25 and 5 mg/kg bw/day. A toxicological NOEL of 25 mg/kg bw/day could be retained.

7. In a tolerance study carried out in cattle, polyethylene glycol 15 hydroxystearate was well tolerated when administered by subcutaneous route at dosages corresponding to 3, 5 and 10 times the recommended dosage.
8. No data on reproductive toxicity nor on mutagenicity were provided.
9. Polyethylene glycol 40 stearate, being an individual substance of the group of polyethylene glycol stearates has been approved as a food additive, implying that the substance is already in Annex II. In addition, all the compounds covered by the applications are closely related to the polyethylene glycols which are already included in Annex II. (Council Regulation (EEC) No. 1147/96; polyethylene glycols with molecular weights 200 to 10000).

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) established in 1973 a ADI of 25 mg/kg for the compounds polyethylene glycol-8-stearate and polyethylene glycol-40-stearate.

Although only limited toxicity data were provided, taking also into account all the information available for close-related compounds, it can be assumed that polyethylene glycol 15 hydroxy stearate and polyethylene glycol stearates will not present a risk for human health and consequently, no additional information on the toxicity of these compounds are requested.

10. No residue depletion studies were carried out with polyethylene glycol 15 stearate and polyethylene glycol stearates. However, taking into account the poor gastro-intestinal absorption of polyethylene glycol stearates and polyethylene glycol 15 hydroxy stearate and their low oral toxicity, it may be concluded that the incorporation of polyethylene glycol stearates and the polyethylene glycol 15 hydroxy stearate in medicinal products intended for use in food producing species is unlikely to result in residues in food products of animal origin at concentrations of toxicological relevance to the consumer.

Conclusions and recommendations

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

- the substances are poorly absorbed following oral application,
- the substances are of low oral toxicity,
- a group of closely related compounds (i.e. the polyethylene glycols) is already included in Annex II to Council Regulation (EEC) No 2377/90,
- one of the members of the group (i.e. polyethylene glycol 40 stearate) is permitted as a food additive,
- the incorporation of polyethylene glycol stearates and the polyethylene glycol 15 hydroxystearate in medicinal products intended for use in food producing species is unlikely to result in residues in food products of animal origin at concentrations of toxicological relevance to the consumer,
- the treated animals are unlikely to be sent to slaughter during or immediately after treatment;

the Committee concludes that there is no need to establish an MRL for polyethylene glycol stearates and polyethylene glycol 15 hydroxystearate and recommends their inclusion in Annex II to Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Polyethylene glycol 15 hydroxystearate	All food producing species	For use as excipient
Polyethylene glycol stearates with 8-40 oxyethylene units	All food producing species	For use as excipient