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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

POLYOXYL CASTOR OIL
POLYOXYL HYDROGENATED CASTOR OIL

SUMMARY REPORT

1. Polyoxyl n castor oil (n=30 to 40) (synonyms: ethoxylated castor oil, polyethylene glycol castor oil) is a mixture of triricinoleate esters of ethoxylated glycerol with small amounts of polyethyleneglycol (macrogol) ricinoleate and the corresponding free glycols. The number (n) associated with the name of the substance represents the average number of oxyethylene units in the compound. Polyoxyl n hydrogenated castor oil (n=40 to 60) is a mixture of trihydroxystearate esters of ethoxylated glycerol with small amounts of macrogol trihydroxystearate and the corresponding free glycols. The substances are generally highly dispersible in water.

2. Polyoxyl castor oil and polyoxyl hydrogenated castor oil are nonionic surfactants, which are used as emulsifying and solubilising agents in pharmaceutical preparations and cosmetics. Examples are polyoxyl 35 castor oil (Cremophor EL; CAS 61791-12-6), polyoxyl 40 castor oil (Marlowet 40, Emulgin RO 40), polyoxyl 40 hydrogenated castor oil (Cremophor RH 40) and polyoxyl 60 hydrogenated castor oil (Cremophor RH 60). The substances are included as excipients in numerous preparations intended for use in all food producing species by parenteral, oral or topical administration. The concentration in products is usually between 0.1% and 20% with a maximum of 27.5%. The doses of concentrated substances to different species is in a range of 0.01 and 2.5 ml/day (cattle and horses 0.75 to 2.5 ml, sheep and goats 0.2 to 0.5 ml, swine 0.25 to 1.20 ml, poultry 0.001 to 0.03 ml and salmon as a dip for 30 minutes in a 36% solution diluted 1/3 x 10^6 before use).

3. In rats, polyoxyl 35 castor oil, had some antidiuretic effect after oral administration of 2.5 ml/kg bw. It was shown that polyoxyl 35 castor oil could bind to membrane transport P-glycoproteins *in vitro*, thereby inhibiting the elimination of drugs out of cells and increasing bioaccumulation of drugs within cells. It was concluded that polyoxyl 35 castor oil is a pharmacological active substance. However, polyoxyl castor oil and polyoxyl 40 hydrogenated castor oil are claimed to be devoid of pharmacological activity at the concentrations at which they are employed as excipients, i.e. a maximum of 2.5 ml/animal by the intramuscular, subcutaneous, topical or oral route. Studies showing possible pharmacological activity have not been performed in the target species.

4. No data on metabolism and pharmacokinetics of polyoxyl castor oil and polyoxyl hydrogenated castor oil were provided. However, it is known that polyoxyethylene compounds are poorly absorbed from the gastrointestinal tract due to their high dispersibility in water and limited liposolubility.

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5. For polyoxyl 35 castor oil oral LD_{50} values of 640 mg/kg bw in the dog and 6500 mg/kg in the mouse have been reported in the published literature. The acute oral toxicity of polyoxyl 40 castor oil appears to be low, the LD_{50} in rats being greater than 10000 mg/kg bw. According to summary information provided In another study the acute oral toxicity of polyoxyl 40 castor oil was investigated in male Wistar rats. The LD_{50} was reported to be greater than 2000 mg/kg. The acute toxicity of polyoxyl 25 hydrogenated castor oil, polyoxyl 40 hydrogenated castor oil, polyoxyl 60 hydrogenated castor oil were reported to be very low with LD_{50} values of more than 5000 mg/kg body weight in rats.

6. Polyoxyl 35 castor oil and polyoxyl hydrogenated castor oil were judged slightly irritating when applied to skin to both humans and rabbits and non-irritating to the eye. Polyoxyl 35 castor oil did not induce sensitisation in guinea pigs.

7. In the published literature there are toxicology studies reported for polyoxyl-40 hydrogenated castor oil, polyoxyl 40 castor oil, polyoxyl 35 castor oil and polyoxyl castor oil (number of moles of ethyleneoxide was not specified).

   Studies with polyoxyl-40 hydrogenated castor oil were performed in rats for 6 months with doses up to 100 000 mg/kg/feed (theoretical calculated doses 5000 mg/kg bodyweight) and in dogs for 6 months with doses up to 5% of the diet (theoretical calculated doses 3750 mg/kg bw). No treatment related effects were observed.

   Furthermore, polyoxyl castor oil 10% (number of moles of ethyleneoxide was not specified) was tested as a vehicle control in a study with mice for 90 days in the drinking water. The absolute and relative liver and kidney weights were significantly increased and the weight of the brain was significantly less than in the control group who received de-ionised water. Some statistically significant differences in the haematological and clinical chemistry values were also recorded. The same substance was tested for 3 weeks in Sprague Dawley rats in a dose of 0.5% in drinking water. The only change that was observed was reduced weight of the brains in the treated groups compared to the controls.

   Polyoxyl 40 castor oil was tested in rats and in dogs for 90 days with doses up to 5% in the feed. No treatment related effects were observed.

   Repeated dose studies after intramuscular injection were performed in dogs, after dosing with 11 injections of 1 ml 50% polyoxyl 35 castor oil, in rabbits after dosing with 10 injections of 0.5 ml and in guinea pigs after dosing with 10 injections of 0.1 ml polyoxyl 35 castor oil, respectively. No significant effects were recorded.

8. Only summaries of published studies concerning reproductive and teratogenic effects have been provided. Polyoxyl 40 hydrogenated castor oil was tested in rats fed up to 5 g/kg bw in the feed day 0 to 20 of gestation and to mice fed up to 1.5 g/kg bw in the feed during day 6 to 15 of gestation. No maternotoxic or teratogenic effects were recorded. Furthermore, a 3-generation study was performed with 1% polyoxyl 30 castor oil given to mice in the drinking water. No significant changes in reproductive performance were observed in any of the 3 generations. Mean litter size, postnatal body weights and survival indices were unaffected. The F_{1c} and F_{2b} matings were produced to screen for dominant lethal and teratology effects. In this screening tests an increase in the ratio of dead foetuses to live foetuses was observed. In addition, polyoxyl-35 castor oil was tested as a vehicle control in a teratogenicity study in mice. The mice were given oral doses of 0.005 ml/1 g bw of an 8% polyoxyl 5 castor oil in water at day 9, 10 or 11 of gestation. No treatment related effects were observed.

9. Only summaries of published studies of mutagenicity tests have been provided. Polyoxyl-35 castor oil was tested in a dominant lethal test, micronucleus test in mice, spermatogonial test in Chinese hamsters. Polyoxyl-30 castor oil was tested in a chromosomal aberration assay using Chinese hamster ovary (CHO) cells, micronucleus and spermhead abnormality assays in mice. Furthermore, polyoxyl-60 hydrogenated castor oil was tested in *Salmonella* microsomal assay, with and without metabolic activation, in a chromosome aberration test in Chinese hamster V79 cells, with and without metabolic activation, and in a micronucleus test in mice. None of the substances showed any mutagenic effect in any of the studies performed.

10. Polyoxyl castor oil, when used as a vehicle in parenteral preparations, has been associated with severe anaphylactic reactions in humans. No reports of sensitisation after oral treatment either in humans or in animals have been reported even though the polyoxyl castor oil derivatives have been used in several cosmetic products. In the toxicity studies provided, no allergic reactions have been observed after oral treatment.

11. Polyethylene glycols with molecular weights 200 to 10000 are already included in Annex II of Council Regulation (EEC) No. 2377/90). The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has evaluated castor oil as a food additive and established an ADI of 0.7 mg/kg bw. Castor oil is approved by the FDA for use in e.g. hard candy.

Conclusions and recommendation

Having considered that:

- polyoxyl castor oil and polyoxyl hydrogenated castor oil are of low oral toxicity,
- only low doses administered to the target species,
- the incorporation of polyoxyl castor oil and polyoxyl hydrogenated castor oil 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 Committee for Veterinary Medicinal Products concludes that there is no need to establish an MRL for polyoxyl castor oil and polyoxyl 40 hydrogenated castor oil and recommends its inclusion in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table.

Pharmacologically active substance(s)	Animal species	Other provisions
Polyoxyl castor oil with 30 to 40 oxyethylene units	All food producing species	For use as excipient
Polyoxyl hydrogenated castor oil with 40 to 60 oxyethylene units	All food producing species	For use as excipient