European Medicines Agency
Veterinary Medicines and Inspections

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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE

DIETHYLENE GLYCOL MONOETHYL ETHER
(Extension to all ruminats)

SUMMARY REPORT (2)

1. Diethylene glycol monoethyl ether belongs to a well-known family of glycol ethers and is used as a solubilising agent and an absorption enhancer in veterinary medicinal products. The substance is used as an excipient in an injectable product (containing a non-steroidal anti-inflammatory agent) for cattle and pigs at a concentration of 30%. The substance is also known to be used in topical formulations (at concentrations up to 40%) and oral formulations (at concentrations up to 30%) in all species.

   It has been used in human therapeutics, in cosmetics and other topical formulations (such as adhesives) and in oral and sublingual preparations.

   Currently, diethylene glycol monoethyl ether is included in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Diethylene glycol monoethyl ether	Bovine, porcine	

2. A request was submitted to the EMEA for the extension of the existing entry in Annex II of Council Regulation (EEC) No. 2377/90 to ovine species. The scientific justification for this extension was assessed taking into account the Note for Guidance on Risk Analysis Approach for Residues of Veterinary Medicinal Products in Food of Animal Origin (EMEA/CVMP/187/00-FINAL).

3. The original safety assessment of diethylene glycol monoethyl ether achieved in 1998 was mainly based on public bibliographic data. The main outcome of this original assessment is reported in the paragraphs below.

   Pharmacological effects (cardiovascular effects) were reported after intravenous administration in rats, cats and dogs at doses similar to therapeutic doses, however the Committee considered that such effects were of no biological significance.

   The substance was considered of low acute toxicity (oral LD_{50} of 5.54 g/kg in rats, 6.58 g/kg in mice and 3.87 g/kg in guinea-pigs).

   Publications on repeated-dose toxicity and reproductive toxicity were reviewed but on the basis of the information available no NOEL could be identified for the purpose of establishing an ADI. The substance was however considered to have low oral repeated dose toxicity.

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The mutagenic potential of of diethylene glycol monoethyl ether was assessed in an Ames test with and without metabolic activation. Dose related positive effects (increase in revertants: up to factor 2) were found with and without metabolic activation. A non-repeated *Saccaromyces cerevisiae* mutagenicity test without metabolic activation, was provided and showed slight increases of convertants and revertants at the highest dose, but no effect on percentage of crossing-over or aberrations was observed. In an *in vivo* mouse bone marrow micronucleus test diethylene glycol monoethyl ether was negative at the dose 2000 mg/kg bw. In *in vivo* unscheduled DNA synthesis (UDS) test in the liver of rats at an oral dose of 2000 mg/kg bw was negative.

No carcinogenicity data were provided but considering the negative results of the unscheduled DNA synthesis test, that no increase in tumour incidence was observed in the long-term toxicity studies and the fact that in carcinogenic studies with other glycol ethers no carcinogenic potential has been demonstrated, carcinogenicity tests of the compound were not considered necessary.

Although no ADI could be established for the substance since no NOELs could be identified from the data available on the relevant toxicity endpoints, the overall available information allowed to conclude that there is no toxicological concerned linked to the use of the substance in veterinary medicine.

4. Residue depletion studies in target species were not provided. Pharmacokinetic information available indicated a rapid elimination and excretion of the substance. In view of the overall safety evaluation of the substance and its use in veterinary medicine no further data were considered necessary.

Conclusions and recommendation

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

- While some statistically significant pharmacological activity was observed in laboratory animals at corresponding doses to those administered to target animals, these effects were not considered of biological relevance in respect of consumer safety,
- diethylene glycol monoethyl ether is of low oral toxicity,
- the available information indicates that diethylene glycol monoethyl ether is rapidly absorbed and excreted after intravenous and intramuscular injection,
- diethylene glycol monoethyl ether is already included in Annex II for bovine and porcine species,

the Committee recommends the extension of the existing entry in Annex II of Council Regulation (EEC) No 2377/90 to include all ruminants in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Diethylene glycol monoethyl ether	All ruminants and porcine	