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

EMEA/MRL/488/98-FINAL
July 1998

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

DIETHYLENE GLYCOL MONOETHYL ETHER

SUMMARY REPORT

1. Diethylene glycol monoethyl ether is a solubilising agent and an absorption enhancer used in veterinary medicine. It is an excipient to be used in an injectable product (containing a non-steroidal anti-inflammatory agent) for cattle and pigs at a concentration of 30%. The compound is used in cattle at a single intravenous dose of 30 mg/kg bw or in cattle and pigs at intramuscular doses of 15 mg/kg bw given twice at a 48 hour interval.

   Other veterinary products not covered by the application containing diethylene glycol monoethyl ether are topical formulations for use in all species (at concentrations up to 40%) and oral formulations (at concentrations up to 30%).

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

   This compound belongs to the well-known family of glycol ethers. The following impurities are present: diethylene glycol, ethylene glycol and ethylene monoethyl ether. In addition, three other impurities may be found: 2-ethoxy 2-ethanol, 1,4 dioxane and ethylene oxide. Relating to the determination of the impurities, the actual quality is in compliance with the ICH Standards. The toxicity of these impurities are known, but at the concentrations found, a total of 0.3%, there is no toxic potential either to the treated animals or to the human consumers.

2. Pharmacodynamic tests showed that diethylene glycol monoethyl ether had the following secondary pharmacodynamic effects: decreased heart frequency (5 to 10%) and lowered blood pressure (5%) with intravenous administration in anesthetised rats, cats and dogs at the lowest doses (46.4 mg/kg bw in rats and cats and 10 mg/kg bw in dogs), neuroleptic effects (climbing test and rod balance test in intraperitoneally treated mice, ED_{50} was 3100 to 5000 mg/kg bw, the highest dose without effect was 1300 mg/kg bw), increase of hexobarbital sleeping time after oral administration in mice (for 2-fold potentiation the ED_{05} was 70 mg/kg bw and the ED_{50} 700 mg/kg bw), and the EC_{50} values for the spasmolytic effect measured on the isolated guinea-pig ileum were between 4600 and more than 10 000 mg/kg. With the exception of the statistically significant cardiovascular effects observed by intravenous route, all the pharmacological effects are induced at enormous doses or concentrations (of the order of at least 1 g per kg). However, the pharmacological effects observed after intravenous administration at doses similar to therapeutic doses were considered of no biological significance. A NOEL for these effects could not be derived on the available data.

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Switchboard: (+44-171) 418 8400 Fax: (+44-171) 418 8447
E_Mail: mail@emea.eudra.org http://www.eudra.org/emea.html

3. According to available literature reviews, diethylene glycol monoethyl ether is absorbed by the airways, digestive tract and skin. The main metabolic pathway involves oxidation of the hydroxyl group to the corresponding acid, under the effect of hepatic alcohol/aldehyde deydrogenases, and a less important pathway to complete biotransformation to carbon dioxide. Excretion occurs mainly by the kidneys. In man, 69% of the administered dose was reported to be eliminated in the urine within 12 hours, mainly in the form of (2-ethoxyethoxy) acetic acid. Diethylene glycol monoethyl ether is used solely as an excipient which fully accounts for the lack of kinetic data on this compound, and it is soluble both in water and in organic solvents, this would lead to think that it should have a oral bioavailability in man of about 100%, therefore, considering the overall risk assessment of the molecule, the lack of kinetic information could be considered negligible.

4. Publications on acute toxicity (LD_{50}) of diethylene glycol monoethyl ether were provided. In mice the intraperitoneal LD_{50} was determined as 2 300 mg/kg bw in one study. Another study determined the value of 6020 mg/kg bw (5.39 ml/kg bw) for the intraperitoneal LD_{50} in mice and rats and 8030 mg/kg bw (7.95 ml/kg bw) for the oral LD_{50} in these species.

   Reviews based on these and further publications mentioned oral LD_{50} values in rats and mice, subcutaneous and dermal LD_{50} in mice and dermal LD_{50} values in rats higher than 5000 mg/kg bw, oral LD_{50} values in guinea-pigs were 3700 to 5000 mg/kg bw, intravenous and intraperitoneal LD_{50} in mice and intravenous LD_{50} in rabbits were in the range 900 to 6400 mg/kg bw. The intravenous LD_{50} in dogs was 3000 mg/kg bw and in cats 5000 mg/kg bw.

5. Short-term oral repeated dose toxicity of daily doses of diethylene glycol monoethyl ether of 0, 167, 500, and 1500 mg/kg bw was studied in pigs (3 male and 3 female animals per group). Three pigs administered 1500 mg/kg bw/day over 14 to 21 days died, with signs of uraemia (kidneys enlarged, petechiae in the renal cortex, urine casts, considerable increase in urea, among others) or were sacrificed *in extremis*. In the 3 pigs that survived in this group, the daily dose was reduced to 1000 mg/kg bw/day. The pigs, which received 500 and 167 mg/kg bw/day survived in the entire study period. In the high dose group the haemoglobin level was lowered, relative kidney weights were increased, and on histological examination hydropic degeneration of the proximal tubuli was observed. This also occurred in the 500 mg/kg bw/day dose group. Liver changes were also observed in the 500 mg/kg bw/day group. No toxic effects for pigs were seen at 167 mg/kg bw/day.

   A publication on 90-day repeated oral dose toxicity studies in rats (15 animals per sex and group) at dietary concentrations of 0, 0.5 and 5%, and mice (20 animals per sex and group) at dietary concentrations of 0, 0.2, 0.6, 1.8 and 5.4% was provided. Growth was retarded in the rats and mice in the highest dose groups, with reduced food consumption also observed in the rats. In the highest dose groups in both species the haemoglobin level was lowered, oxaluria was observed, and relative kidney weights were increased (in male mice also in the 1.8% group). On histological examination, hydropic degeneration of the proximal tubuli was observed in both species at the highest dose. Liver changes were observed in mice given 1.8% and 5.4% in food. No toxic effects in rats were seen at 0.5% in food (approximately 250 mg/kg bw/day) and in mice at 0.6% in food (approximately 850 to 1000 mg/kg bw/day).

   Another publication on a 90-day study in rats was provided. Groups of 12 male and 12 female rats were given dietary concentrations of 0, 0.25, 1 or 5% of diethylene glycol monoethyl ether. There were no changes in general behaviour or state of health. In the 5% group, weight gain was retarded and food consumption was reduced. Increased aspartate aminotransferase values were found in the urine, and relative kidney weights in male and female rats, and the testes weights were higher. Histological examination revealed hydropic degeneration of the kidneys in 2 males and 1 female, as well as fatty deposits in the liver. The increased testes weight was due to interstitial testicular oedema. No toxic effects were observed in animals, which had been given dietary concentrations of 0.25% and 1% of diethylene glycol monoethyl ether, corresponding to 125 and 500 mg/kg bw/day.

The above studies do not comply with the current norms and the reporting is not comparable. A satisfactory NOEL for the purpose of establishing an ADI could not be identified, however, it is evident that the oral repeated dose toxicity of the substance is low.

Several other existing reports of subacute and sub-chronic toxicity studies including other routes of administration were mentioned in available reviews, without providing the underlying publications. The main toxic effects found include renal, hepatic and testicular toxicity. It is possible that part of the effects were related to the presence of ethylene glycol in certain tested batches. The studies could not be assessed, and no NOEL for repeated dose oral toxicity could be established.

6. In an insufficiently conducted and reported 2-year study, 12 male and 8 female rats were given 2.16% diethylene glycol monoethyl ether in the diet (approximately 1100 mg/kg bw/day). After one year weight gain and food consumption were not impaired relative to the controls; no details were given of any developments in the 2nd year of the study, or of survival times. All animals were killed after 24 months. Histopathological examinations were conducted in a number of animals (no exact details) which survived 24 months, as well as in 10/40 controls. There was some testicular swelling (interstitial oedema), livers exhibited slight diffuse centrilobular atrophy, bile duct proliferation and fatty deposits. Oxalate crystals were found in the kidney of 1 animal, but no kidney lesions were reported. Lungs, heart, spleen, lymph nodes, pancreas, stomach, intestine and adrenals were histologically no different to the controls.

   In a second insufficiently reported 2-year study running over 3 generations (F0, F1, F2), groups of 8 weaned male and 8 weaned female rats received diethylene glycol monoethyl ether at concentrations of 0.01, 0.04, 0.2 and 1% in drinking water (equivalent to 10, 40, 200 and 950 mg/kg bw/day). The F1 and F2 generations were given the same doses as the parent generation. Animals, which survived the entire study, were killed after 718 days. In the group which received 950 mg/kg bw/day severe kidney lesions and bladder calculi were observed as well as opaque swelling in the liver, pigmented deposition in the spleen and degeneration of the intestinal vili. No testicular lesions were observed. Weight gain was retarded in the groups, which received 950 and 200 mg/kg bw/day. Haematological investigations (erythrocytes, leukocytes, differential blood count) were conducted 4 times per year in 2 male and 2 female rats per group over 3 generations, but produced no notable results. There were no changes in the clinical-chemical parameters (blood urea, serum protein, blood sugar). Increased protein was observed in the urine of the high dose groups, but there was no increase in oxalic acid values. Urinary calculi were found in some male rats of the F1 and F2 generations at doses of 950 mg/kg bw/day.

   Neither study design nor reporting complies with current requirements and no NOELs can be identified, however no health risk at the doses used in veterinary medicine has become apparent from these studies.

7. Dairy cows (group of 6) received successive intravenous doses of 30, 60 and 90 mg/kg bw/day of diethylene glycol monoethyl ether for 3 consecutive days, with wash-out intervals of 7 days between successive treatments. Usual clinical parameters were investigated, including heart rate. The determination times were 4 to 5 hours after dosing on days 0, 1, 2, 3, and 4 after treatment. Administration consisted of a bolus-type intravenous administration. No significant change or alteration in heart rate was detected, even at the high dose in any animals or at any examination time. However the study design was considered insufficient to detect effects during the first 4 hours after treatment and the parameter blood pressure was not studied.

   Sows (groups of 5) weighing about 30 kg received intramuscular injections of 15, 30 or 75 mg/kg bw/day of diethylene glycol monoethyl ether. Usual clinical parameters, including heart rate**,** were measured on days 0, 1, 2, 3 and 4 within the 4 to 5 hours following dosing. The animals were slaughtered and any organs exhibiting macroscopic lesions were subjected to microscopic examination. No significant change or alteration in heart rate was detected, even at high dose, in any of the treated animals or at any examination time. No macroscopic or microscopic lesion was

detected. However the study design was considered insufficient to detect effects during the first 4 hours after treatment and the parameter blood pressure was not studied.

8. In an oral 2-generation study in mice doses up to 6200 mg/kg bw/day had no effect on numbers, body weights and sex ratio of produced offspring. Related compounds (including several glycol ethers) gave adverse effects in this study design. However, because study design was deficient (e.g. no histopathology or autopsy) and the complete report was not provided, no NOEL could be based on this study. Several other reproduction studies mentioned in available reviews could not be assessed because the complete reports were not provided. An existing multigeneration study in rats was not provided and therefore could not be assessed.

9. A publication on a study in 50 pregnant CD1 mice was provided, which were given 5500 mg/kg bw/day of diethylene glycol monoethyl ether by gavage on days 7 to 14 of pregnancy. Seven out of 50 dams (14%) died. The surviving litters, number of surviving foetuses/litter, number of dead foetuses/litter, the survival times of the foetuses after birth (observation for 2.5 days and the increase in weight of the foetuses after birth were not different from the controls. Only the weight of the foetuses at birth was significantly reduced ($p < 0.05$), but reached that of the controls after 1 to 3 days.

   Further publications on embryotoxicity, foetotoxicity and teratogenicity of diethylene glycol monoethyl ether were provided. No embryotoxic, foetotoxic or teratogenic effects were observed in mice and rats. However, as the underlying study reports were not available and the design did not comply with current requirements, a NOEL could not be established. Compounds structurally related to diethylene glycol monoethyl ether have been shown to cause developmental toxicity (including teratogenicity), however the available information does not indicate similar effects of diethylene glycol monoethyl ether.

10. In an Ames test (*Salmonella thyphimurium* strains TA 97, 100, 102, 1535, 1537 and 1538 with and without metabolic activation, not independently repeated, tested doses: 0.01, 0.1 and 1 ml/plate) dose related positive effects (increase in revertants: up to factor 2) were found with (TA 1537 and 1538) and without (TA 1535 and 1538) metabolic activation. In a non-repeated *Saccharomyces cerevisae* mutagenicity test without metabolic activation, two concentrations of diethylene glycol monoethyl ether (1 and 10%, the highest dose being cytotoxic with 30.8% survival), gave slight increases of convertants and revertants at the highest dose, but no effect on percentage of crossing-over or aberrations. A dose of 2000 mg/kg bw was negative in an *in vivo* mouse bone marrow micronucleus test. An *in vivo* unscheduled DNA synthesis (UDS) test in the liver of rats at an oral dose of 2000 mg/kg bw was negative.

11. No carcinogenicity data were provided. In view of the results of the mutagenicity tests and notably of the unscheduled DNA synthesis test, carcinogenicity tests of the compound are not necessary. In addition, there have been few carcinogenic studies with other glycol ethers and they have not demonstrated any carcinogenic potential. No increase in tumour incidence was observed in the long-term toxicity studies.

12. Some of the existing reports of skin irritation and sensitisation studies in human volunteers were not provided. Therefore this subject could not be assessed. However, the substance is widely used in human cosmetic products and this use has not given rise to concern.

13. No ADI could be calculated, since no NOEL was established. However, overall the available information allows the conclusion that there is no toxicological concern connected to the use of the substance in veterinary medicine.

14. No data are available on residue depletion of diethylene glycol monoethyl ether in food producing animals. The available information indicated rapid elimination and excretion of the compound; thus no further information will be requested.

15. No analytical method was described but is not 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:

- diethylene glycol monoethyl ether has some statistically significant pharmacological activity in laboratory animals at the at the levels administered in the dosage of the product in which the substance is contained, which is not considered of biological relevance in respect of consumer safety,
- diethylene glycol monoethyl ether is used only for infrequent treatment of individual animals,
- 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;

the Committee considers that there is no need to establish an MRL for diethylene glycol monoethyl ether 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
Diethylene glycol monoethyl ether	Bovine, porcine	