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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

GLYCEROL FORMAL

SUMMARY REPORT

Name of the substance

Glycerol formal

Indication for use

As a solvent in oral, dermal and injectable products administered at a dose of 10-60 mg/kg (0.008-0.048 ml/kg) bodyweight.

Pharmacological activity

Glycerol formal is a mixture of two isomers, 4-hydroxymethyl-1,3-dioxolane and 5-hydroxy-1,3-dioxane. These isomers are present in a constant ratio of 40% to 60% respectively.

In rats, intravenous dose of 0.5-0.75 ml/kg bodyweight caused incoordination or narcosis with accelerated respiration. An intravenous dose of 1 ml/kg bw slowed respiration and produced respiratory standstill after 30 minutes.

Toxicological profile

1. Glycerol formal has low toxicity when given orally or intravenously to rats and mice. LD_{50} orally in rats is 8 ml/kg. LD_{50} intravenously in mice is approximately 4 ml/kg.

   Three 90-day repeated dose toxicity studies in rats, a 3-month repeated dose study in dogs and a 4 week repeated dose study in rabbits were carried out with glycerol formal. The studies were generally old but there was evidence of testicular atrophy in the rat studies at dose levels equivalent to 122 mg/kg and above when administered orally and 293 mg/kg and above when administered subcutaneously. A recent GLP compliant oral gavage study in rats given glycerol formal for 90 days at doses up to 25 mg/kg indicated no treatment changes in physical signs of animals, bodyweight gain, haematological, biochemical or urine analysis. Furthermore there was no drug related changes in organ weights, or in macroscopic or microscopic appearance of tissues of treated rats.

2. Two rat teratology studies, both GLP compliant, gave evidence of teratogenic effects (anal atresia and tail malformations at 300 and 600 mg/kg bw) as well as anasarca at 600 mg/kg bw. A 75 mg/kg bw/day dose was not considered to be teratogenic but was foetotoxic as evidenced by an increased incidence in sites of delayed ossification compared to the concurrent control group, although an unusual lesion (absence of a small area of skin in the perineal region) was seen in 2 foetuses in this group as well as in 3 foetuses in the 300 mg group and 1 in the 600 mg group. 10 mg/kg bw/day produced no teratogenic or foetotoxic effects in rats. There was no evidence of maternal toxicity at any of the dose levels tested.

   Teratogenic effects in rats following treatment with glycerol formal are also recorded in open literature at doses of 0.25 ml/kg (300 mg/kg bw) and above. At doses of 0.5ml (600mg/kg bw) and above there was a significant increase in cardiac abnormalities in treated rats. A second species teratology study is not presented but is unlikely to reveal further useful information.

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3. Glycerol formal was administered to pregnant swine and cattle. In 16 swine, 32 mg glycerol formal/kg bw was administered at 28 day intervals during the last 10 weeks of pregnancy without adverse effect on litter size or piglet development. In cattle the compound was administered at a dose of 19 mg/kg bw on three occasions during pregnancy, 12 to 28 days apart. There was no increase in abortion rate and no decrease in birth weights among any of the 53 treated animals when compared to the controls.

4. A battery of mutagenicity studies in compliance with GLP were carried out with glycerol formal:

   i) No mutagenic potential was found in *Salmonella typhimurium* TA 1535, TA 1537, TA 1538, TA 98 and TA 100 with and without activation;

   ii) No evidence of mutagenicity in V79 Chinese hamster lung cells with and without metabolic activation;

   iii) No evidence of unscheduled DNA synthesis in human IMR - 90 embryonic lung fibroblasts with and without the presence of a liver enzyme activation system.

   iv) No evidence of clastogenic activity in a published study in the mouse micronucleus assay.

   The tests carried out do not indicate mutagenic potential for this compound which is structurally unrelated to any known carcinogen.

5. Glycerol formal does not possess antimicrobial activity.

Pharmacokinetics

The *in vitro* metabolism by rat and bovine liver homogenates has been studied. Under the incubation conditions employed, glycerol formal does not appear to be metabolised to any great extent (less than 10% in rats and 10-20% in bovines in the 30 minute study period).

Residue depletion studies were conducted in cattle and swine in non-GLP compliant studies.

1. In cattle dosed subcutaneously with 0.012 ml glycerol formal (14.4 mg/kg bw) residues were quickly depleted. At 2 days post treatment the maximum residues in treated animals were as follows : muscle 0.16 mg/kg, injection site 0.16 mg/kg, kidney 0.13 mg/kg, liver 0.07 mg/kg, fat less than 0.05 mg/kg. Residue assay was by a GLC chemical ionization MS procedure.

2. In swine dosed subcutaneously with 0.016ml glycerol formal/kg (19.2mg/kg bw) and slaughtered 1 day after dosing, no residues were detected in liver, kidney, muscle fat or injection site. The limit of detection of the method was 0.05 ppm. The assay method was as described above.

No information is available on excretion in milk of treated animals.

Risk assessment

Using the NOEL of 10 mg/kg bw from the rat teratology study and a safety factor of 1000 based on this end point, an acceptable daily intake of 600 µg per person per day for glycerol formal is calculated.

Residues are rapidly depleted in swine and are quickly depleted in cattle.

Total intake of residues in cattle slaughtered 2 days after dosing with 14.4 mg glycerol formal/kg bw (including residues at the injection site) is : 64 µg. This residue level is almost 10 times less than the ADI. While doses of up to 60 mg/kg may be administered to animals, residues in edible tissues are still likely to be well below the ADI established, the ADI itself is based on a very conservative safety factor and NOEL.

Conclusions and recommendation

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:

- glycerol formal is of low toxicity and,
- it is rapidly excreted;

the Committee considers that there is no need to establish an MRL for glycerol formal and recommends its inclusion in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table :

Phamacologically active substance(s)	Animal species	Other provisions
Glycerol formal	All food producing species	