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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

ETAMSYLATE

SUMMARY REPORT

1. Etamsylate (diethylamine 2,5-dihydroxy-benzenesulphonate) is a haemostatic agent used in human and veterinary medicine to control spontaneous and postoperative haemorrhage. The dose used in veterinary medicine is in the range 5 to 10 mg/kg bw. It may be administered orally or parenterally to all species. Treatment is normally made until the desired effect is reached; it may be for one day but could be repeated for a further 2 to 3 days in order to obtain control of the bleeding.

2. The precise mode of action of etamsylate is unknown. It is thought to act by increasing capillary wall resistance and platelet adhesiveness, in the presence of a vascular lesion, by inhibiting the biosynthesis and actions of those prostaglandins which cause platelet disaggregation, vasodilation and increased capillary permeability. It does not affect the normal coagulation mechanism and administration is without effect on prothrombin time, fibrinolysis, platelet count or function. It reduces the bleeding time in healthy human patients and in those with platelet dysfunction. In pigs, it reduced blood loss from a standard wound. It prevented intraventricular haemorrhage in neonatal dogs. In the carrageenan-induced rat paw oedema test, ethamsylate was shown to be an anti-inflammatory agent with an effect similar to that of indomethacin but with only 4% of the potency of indomethacin. Intraperitoneal doses of etamsylate were tested in the hamster cheek pouch model; 25 mg/kg bw had no effect but 50 and 100 mg/kg bw inhibited thrombus formation by 41% and 61% respectively. The substance had no adrenergic or vasoconstrictor activity.

3. Pregnant mice were given an intravenous dose of 170 mg/kg bw of ^{14}C-labelled etamsylate. The distribution of radioactivity in both the dam and foetus was investigated using autoradiography. In the dam, high concentrations of radioactivity were observed in the kidney and radio-labelled material was observed in the bladder, within 10 minutes of dosing. Radiolabelled material was present in bile from 30 minutes to 3 hours after dosing. Small amounts of radioactivity were detected in the foetus from 10 minutes after treatment. There was no evidence of accumulation and elimination of radioactivity was very rapid. 4 hours of administration, no radioactivity was detectable in tissues of the dam or foetus.

4. Rabbits were given an intravenous dose of 30 to 40 mg/kg bw ^{14}C-labelled etamsylate. Blood samples were collected and the radioactivity determined. Blood concentrations of radioactivity declined rapidly and were undetectable around 3 hours after dosing. The substance was rapidly excreted, predominantly as unmetabolised etamsylate, in the urine. Sixty six to 69% of the dose was excreted in the urine within 12 hours of dosing.

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5. The pharmacokinetics of etamsylate was investigated in healthy human volunteers. Residues of etamsylate in body fluids were determined using high pressure liquid chromatography. After oral administration of 500 mg etamsylate, peak plasma concentrations in the range 10 to 20 µg/ml were achieved 3 to 4 hours after dosing. Area under curve (AUC) values indicated that oral bioavailability was close to 100%. Following intravenous and intramuscular dosing at the same dose level, peak blood concentrations were achieved 2 to 3 minutes and one hour after dosing, respectively. The half-lives of elimination were 1.8 to 2 hours and 1.7 to 2.5 hours after intravenous and intramuscular dosing, respectively. Elimination was slower after oral administration with small quantities of etamsylate found in the urine for up to 48 hours after dosing. Etamsylate was excreted unmetabolised, chiefly in the urine. No metabolites were detected in urine.

6. The acute intravenous LD_{50} values of etamsylate in the mouse and the rat were 800 and 1350 mg/kg bw, respectively.

7. Groups of Wistar rats were given daily subcutaneous doses of 0, 10 or 100 mg/kg bw/day of etamsylate, 6 days per week, for 32 weeks. There were no overt signs of toxicity and treated rats gained weight in a similar manner to the controls. Haematology parameters were measured during week 32 and there were no treatment-related effects. At termination, there were no gross pathological changes and no effects on organ weights. The study was not conducted to modern standards. No histopathology was carried out.

8. No formal target species tolerance studies were provided. However, pharmacovigilance records revealed no evidence of adverse effects. Studies in female pigs designed to investigate the anti-haemorrhagic effect of the substance showed that an intravenous dose of etamsylate which was effective in reducing bleeding had no effect on pulse rate, blood pressure or platelet count.

9. No multigeneration studies were provided. In humans, etamsylate is used in gynaecology and obstetrics, following surgical procedures and to treat heavy menstrual bleeding and post-intra-uterine-device menorrhagia. No adverse reproductive effects in humans have been reported. It is secreted in breast milk; no resulting effects on the neonates have been reported. Etamsylate is well tolerated in human neonates when parenteral doses of 12.5 mg/kg bw are given every 6 hours for the treatment and prevention of periventricular haemorrhage. Using this dosage regime, a reduction in patent *ductus arteriosus* was observed in a multicentre trial.

10. A published account of some teratogenicity studies was provided. Groups of pregnant female Wistar rats and Swiss albino mice were given doses of 0, 100, 200 or 300 mg/kg bw/day and rabbits were given oral doses of 0, 150, 200 or 300 mg/kg bw/day, during gestation. There was no evidence of maternal toxicity or teratogenicity at any dose level. The incidence of resorptions were comparable with the controls. The studies were adequately performed in terms of group sizes and dosing periods but no raw animal data were available. Details of foetal weights were not provided.

11. Summaries of two *in vitro* studies for gene mutation using *Salmonella typhimurium* TA98, TA100, TA1535 and TA1538, both with and without metabolic activation, were provided. In the first assay, concentrations of etamsylate of 0.001 to 10% were reported to produce no evidence of mutagenicity. In the second assay, concentrations of 0.312 to 10.0 mg/plate were again reported to produce no evidence of mutagenicity. The full reports and original data from these studies were unavailable. In a published scientific paper, a formulation containing etamsylate, used in human medicine was found to cause mitotic non-disjunction in an *in vitro* study using diploid strains of *Aspergillus nidulans*.. However, this was not a recognised validated assay and so no conclusions could be drawn from the results.

12. There were no data on carcinogenicity.

13. Etamsylate has been used in human medicine for over 30 years. The usual therapeutic dose is 750 to 1000 mg which is administered by intramuscular or intravenous injection, followed by maintenance doses of 500 mg by injection or orally, every 4 to 6 hours. In clinical trials in humans, doses of 250 mg to 1500 mg per person were well tolerated. The reported adverse effects in humans are nausea, headache and skin rash; these effects usually resolve on reducing the dosage or administering the dose after food.

14. No information was provided concerning the depletion of residues in tissues of the target species. The rapid elimination of etamsylate from the body suggests that significant residues are unlikely to occur in tissues of the target species.

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:

- etamsylate is used for the treatment of individual animals only;
- the animals are unlikely to be sent for slaughter during or immediately after treatment;
- pharmacokinetic data indicated that etamsylate was rapidly eliminated from the body;

the Committee concluded that there is no need to establish an MRL for etamsylate 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
Etamsylate	All food producing species	