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

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

ETAMIPHYLLINE CAMSYLATE

SUMMARY REPORT

1. Etamiphylline is a methylxanthine. It is the 7-(2-diethylamino ethyl) derivative of theophylline. It is used in both human and veterinary medicine, usually as the camsylate salt. The salt is very water-soluble and is much less irritant than theophylline to the gastro-intestinal tract.

2. In veterinary medicine, etamiphylline camsylate is used in the treatment of cardiac and respiratory distress in neonatal lambs, calves, pigs, foals and deer. It is administered orally at doses of 140 mg to 280 mg per animal depending on the size of the animal. A second dose may be given 3-4 hours later. Larger animals (over 2.5 kg) require a dose of 280 mg. It is also administered orally (300 mg/100 kgbw) or by intramuscular injection (1400 mg/animal) to older horses for the treatment of respiratory distress or cardiac conditions.

3. Etamiphylline camsylate has pharmacodynamic properties similar to those of theophylline. It is a smooth muscle relaxant and stimulates the heart and respiration. In contrast to theophylline, it has only a weak diuretic effect. The pharmacodynamic effects were transient in most studies and lasted at most only 1-2 hours.

4. Etamiphylline camsylate was rapidly absorbed following oral and intramuscular administration to dogs (14 and 28 mg/kgbw), horses (7 and 14 mg/kgbw) and intramuscular administration to calves (14 and 28 mg/kgbw). C_{max} was directly proportional to the dose administered.

   Etamiphylline camsylate was rapidly eliminated; the half-life for plasma elimination was around 100 minutes in horses and around 60 minutes in dogs and calves. Absorption following oral administration of 28 mg/kgbw to calves was very low and plasma concentrations never exceeded 1 µg/ml. In Wistar rats, the bioavailability following oral dosing with 150 mg/kg bw etamiphylline hydrochloride was estimated to be 84%. Only trace amounts were excreted in rat faeces. Around 20% of the dose recovered from rat urine was unchanged etamiphylline; residues of 2 unidentified metabolites were also found. The half-life for elimination of etamiphylline hydrochloride in rats was estimated to be 1.6 hours.

5. Etamiphylline was less acutely toxic than theophylline. In mice, the acute oral and intraperitoneal LD_{50} values were 1237 and 254 mg/kgbw respectively (the values for theophylline were 332 and 217 mg/kgbw respectively). All deaths occurred within 24 hours of dosing. Convulsions were the most notable sign of toxicity. In rats, the acute subcutaneous LD_{50} values for etamiphylline camsylate and theophylline were 330 and 180 mg/kgbw respectively; the rats given theophylline, but not those given etamiphylline, experienced pain. Oral doses of etamiphylline induced emesis in cats (ED_{50} = 210 mg/kgbw) and dogs (ED_{50} = 300 mg/kgbw).

6. No classical repeated-dose toxicity studies were carried out in laboratory animals. However the effects of repeated dosing were evaluated in the target species. Horses tolerated daily oral doses of 0.4-4.0 mg/kgbw per day of etamiphylline camsylate for up to 85 days. Dogs tolerated daily oral doses of 3-50 mg/kgbw for periods of up to 84 months. No adverse effects were recorded following the use of etamiphylline camsylate in lambs given up to 5 times the indicated dose.

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7. After a single slow intravenous dose of 40 mg/kgbw, the main effects in dogs were an increase in urine volume with a increase in both Na^+ and K^+ excretion; serum Na^+ and K^+ values were not significantly affected and there was no change in the glomerular filtration rate or the renal plasma flow. In contrast, urine volumes, glomerular filtration and renal plasma volume were depressed in normal humans given an intravenous dose of 0.5 g which was administered over a period of 20 minutes. There was an increase in Na^+ excretion in normal humans but the majority of patients in cardiac failure showed a reduction in Na^+ excretion.

8. There were no reproductive toxicity data for etamiphylline camsylate. Teratogenicity studies were carried out with the related substance, theophylline. Theophylline was not teratogenic in the rat. However theophylline induced cleft palate and limb and digit defects in mice - the oral doses needed to produce these effects were 16-times the human therapeutic dose. In humans, theophylline readily crosses the placenta. A large collaborative study found no association between the human therapeutic use of theophylline and congenital malformations. Human neonates tolerated therapeutic theophylline concentrations (administered for treatment of neonatal respiratory distress syndrome) without serious side effects.

9. No mutagenicity or carcinogenicity studies were carried out with etamiphylline camsylate. However some information concerning other methylxanthines, notably caffeine, has been published. Caffeine gave negative results in an *in vitro* bacterial assay for gene mutation, an *in vitro* DNA-cell-binding assay, and in carcinogenicity studies in laboratory animals. As a group, the methylxanthines are not considered to be genotoxic. Etamiphylline is not structurally-related to any known carcinogen. Therefore, carcinogenicity data are not required.

10. Etamiphylline camsylate has been used in human medicine for the treatment of asthma. It may be given by slow intravenous injection in doses of 350 mg, once or twice daily, orally in doses of 100-300 mg, 3 or 4 times daily, or by intramuscular injection in doses of 700 mg, 3 or 4 times daily. In humans the bronchodilator effect of etamiphylline camsylate was estimated to be not more than 20% that of theophylline; this was attributed to unfavourable pharmacokinetics, particularly the short half-life of the substance. Etamiphylline camsylate caused no adverse effects in human clinical trials. Around 12 g of the substance was ingested in an attempted suicide case, the main effects were tachycardia, elevated blood pressure, tremor and generalised seizure with a blood plasma concentration of 43 µg/ml etamiphylline; 15 hours after gastric lavage, the patient was normotensive with a heart rate of 72 beats/minute.

11. Two ruminating calves were given an intramuscular injection of 28 mg/kgbw etamiphylline camsylate and killed 48 hours later. Residues in samples of muscle, kidney, liver, heart and fat were below the limit of detection (LOD) of the GLC analytical method employed (<10 µg/kg).

Conclusions and recommendation

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

- etamiphylline camsylate is used infrequently, in individual animals;
- pharmacokinetic data indicate that the substance is rapidly eliminated;
- etamiphylline camsylate is of low toxicity;
- the substance has a record of safe use in human medicine,

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

Pharmacologically active substance(s)	Animal species	Other provisions
Etamiphylline camsylate	All food producing species	