



## COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

### THIAMYLAL

#### SUMMARY REPORT

1. Thiamylal sodium (dihydro-5-(1-methylbutyl)-5-(2-propenyl)-2-thioxo-4,6(1H,5H) pyrimidine-dione; 5-allyl-5-(1-methylbutyl)-2-thiobarbituric acid; CAS No 337-47-3) is an intravenous ultrashort-acting thiobarbiturate which is often used to produce anaesthesia for minor surgical procedures or for induction of general anaesthesia. Its chemical structure is very similar to that of thiopental, with an allyl group instead of the ethyl group at the 5-position of the ring. Thiamylal is slightly more potent than thiopental. Thiamylal is administered intravenously to horses, cattle, pigs, goats and sheep as a 4% aqueous solution. The recommended doses in the target species ranges from 3 to 32 mg/kg bw. Thiamylal may be administered alone (to induce anaesthesia) or in conjunction with other anaesthetic agents (for extension of anaesthesia).

In human medicine, thiamylal is used by the intravenous route as a 2.5% solution at an average dose ranging from 1 to 10 mg/kg bw.

2. The onset of anaesthesia induced by thiamylal occurs within 30 to 60 seconds, and recovery may be expected within 1 to 3 hours. The duration of anaesthesia is approximately 10 to 25 minutes. The major action of thiamylal is depression of the central nervous system. Thiamylal can also act on the autonomic nervous system (depressed ganglionic neuronal synaptic transmission), cardiovascular system (negative inotropic and chronotropic effects) and on respiration (respiratory depressive effects on the medullary respiratory centre). Alterations of physical membrane properties, calcium transport in excitable tissues, changes on synaptic transmission and interactions with macromolecules are related to the mechanism of action of thiamylal. Electrophysiological data suggest that barbiturates activate inhibitory  $\gamma$ -aminobutyric acid<sub>A</sub> (GABA<sub>A</sub>) receptors and enlarge the chloride currents by prolonging periods during which bursts of channel opening occur. Other secondary pharmacodynamic effects of thiamylal at high doses on the digestive and renal tracts include transient reduced tone and motility of the gastrointestinal muscle fibres, decreased glomerular filtration and tubular reabsorption of sodium. At therapeutic doses thiobarbiturates depress uterine motility.

In dogs and cats excessive salivation is noted following intravenous administration. In dogs, cardiac arrhythmia (ventricular bigeminy), increase in the arterial blood pressure and long periods of respiratory depression may also appear after induction of anaesthesia with thiamylal.

However, no comprehensive data on pharmacodynamic effects of thiamylal were provided and therefore it is not possible to derive a NOEL.

3. A metabolism study of thiamylal was conducted in rabbits and pharmacokinetic studies were carried out in dogs, cats and sheep following intravenous administration. Thiamylal is a highly lipid soluble and rapidly crosses blood-brain and other blood-tissue barriers. Thiamylal undergoes a rapid, flow-limited uptake into the most vascular areas of the brain, going first into the grey matter. Maximal uptake occurs within 30 seconds, and sleep may be induced within a few circulation times. Within 30 minutes there is then a redistribution into the less vascularised areas of the brain and to other tissues; as little as 10% of the peak amount remains in the grey matter.

The ultrashort duration of action is the result of this rapid distribution phase. For thiamylal, there is no correlation between duration of action and elimination half-life. As with other barbiturates, thiamylal rapidly disappears from plasma because of its metabolism and secondary distribution in poorly vascularized tissues.

In mixed-breed dogs given thiamylal intravenously (15 mg/kg bw), the plasma concentration-time curve indicated a biphasic decrease. Disposition of thiamylal was characterised by a distribution phase ( $t_{1/2\alpha}$ : 38.9 minutes) and an elimination phase ( $t_{1/2\beta}$ : 666 minutes). Total body clearance and volume of distribution at steady state were 3.21 ml/min/kg and 3000 ml/kg, respectively. The mean residence time was 930 minutes. Plasma thiamylal concentration declined from 19.4 µg/ml at 1 minute to 3.13 µg/ml at 480 minutes after drug administration. In Greyhound dogs, concentration of thiamylal at 480 minutes was significantly higher than in mixed-breed dogs. In dogs (strain not stated), which were sacrificed three hours after thiamylal administration (40 mg/kg bw), the tissue to plasma ratio was 8 for fat, 0.7 for brain, 1.6 for liver, 0.9 for kidney, 1.3 for muscle, 0.9 for lung and 0.7 for spleen.

In cats (a species with limited quantity of glucuronyl transferase), a pharmacokinetic study was carried out with thiamylal after intravenous administration of 13.2 mg/kg bw. The disposition of thiamylal was characterized by a 3-compartment open pharmacokinetic model, with an initial first rapid distribution half-life of 1.91 minutes, a second distribution half-life of 26.51 minutes and a elimination half-life of 14.34 hours. The apparent volume of distribution was 3.61 l/kg, whereas the apparent volume of distribution of the central compartment was 0.46 l/kg, and the total body clearance was 0.135 l/kg·h.

Six sheep received thiamylal intravenously at a dose of 13.2 mg/kg bw. The mean kinetic parameters for thiamylal were: apparent volume of the central compartment: 0.34 l/kg; apparent volume of distribution calculated by the area method: 1.04 l/kg; apparent volume of distribution at steady state: 0.93 l/kg; distribution half-life: 5.86 minutes; elimination half-life: 112 minutes and total body clearance: 6.38 ml/min.kg. The percentage of protein binding of thiamylal ranged from 89.6 to 91.9%.

Six ponies were administered a single intravenous dose of 11 mg/kg bw thiamylal. The total and non-protein bound concentrations of thiamylal in plasma were determined using HPLC with UV detection. The pharmacokinetics were best described by a 3-compartment model. The mean kinetic parameters were: apparent volume of the central compartment 0.36 l/kg, apparent volume of distribution calculated by the area method: 0.31 l/kg; terminal elimination half-life: 312 minutes and total body clearance: 5.90 ml/min.kg. The percentage of protein binding of thiamylal ranged from 91.0 to 94.6%.

In dogs and humans, barbiturates undergo biotransformation to inactive metabolites via several metabolic pathways such as oxidation, carboxylation, N-demethylation, and glucuronide conjugation. Thiamylal is metabolised primarily by the liver and to a lesser extent by the kidney and brain. The metabolic fate of thiamylal was studied both *in vitro* and *in vivo*. The metabolic pathways were: (1)  $\omega$ -oxidation of side chain, (2) desulfuration reaction (3) ( $\omega$ -1)-oxidation of side chain, and (4) ring rupture. Following *in vitro* incubation of thiamylal with minced rat liver a metabolite was produced which was isolated and identified as secobarbital. In rabbits treated with thiamylal (total dose of 30.6 g, administration route not stated), 5 metabolites were isolated and characterised from urine. The major metabolites were thiamylal  $\omega$ -carboxylic acid and ( $\omega$ -1)-hydroxythiamylal. Two other minor metabolites were secobarbital  $\omega$ -carboxylic acid, and ( $\omega$ -1)-hydroxysecobarbital.

No pharmacokinetic data on absorption, distribution and excretion in humans are available.

4. Acute toxicity studies were performed in mice, rats, rabbits and dogs. The acute oral LD<sub>50</sub> values for dogs and mice were 134 and 180 mg/kg bw, respectively. The subcutaneous LD<sub>50</sub> values for rats, mice and rabbits were 52, 112 and 225 mg/kg bw, respectively. The intravenous LD<sub>50</sub> values for rabbits, dogs, rats and mice were 24, 32, 51 and 78 mg/kg bw, respectively. The intraperitoneal LD<sub>50</sub> value for mice was 109 mg/kg bw.
5. Repeated-dose toxicity studies conforming to current standards were not provided. Only a non-standard repeated dose toxicity study was carried in 2 dogs dosed intravenously with 16.6 mg/kg bw for 11 consecutive days. The dogs showed nervous symptoms after the 7th day but recovered quickly and completely. However, no conclusion can be reached from this study.
6. Groups of around 20 pregnant female dd (strain) mice were given a single intraperitoneal injection of 0, 20, 40, 60, 80, 100, 120 or 140 mg/kg bw thiamylal, on day 10 of gestation. Further groups were given a single intraperitoneal dose of 0 or 60 mg/kg bw on day 7, 8, 9, 10, 11, 12, 13 or 14 of gestation. Further groups were given one or two intraperitoneal doses of 0, 40, 60 or 80 mg/kg bw on days 10 or 11 or 10 and 11 of gestation. Doses of 40 mg/kg bw and above caused signs of toxicity in the dams. Doses of 60 mg/kg bw and above caused a significant increase in the numbers of malformations such as club foot, polydactyly and oligodactyly. At the lowest dose level of 20 mg/kg bw, there were no adverse effects on the dams and no evidence of teratogenicity, however foetal body weights were significantly reduced.
7. There were no data on mutagenicity or carcinogenicity and therefore no conclusion on genotoxic and carcinogenic potential for thiamylal can be drawn. However, in view of the rapid elimination of the substance, and its limited use, these data were not considered necessary.
8. Immunotoxicity studies and other specific toxicity studies (i.e. neurotoxicity, cardiotoxicity, hepatotoxicity studies) were not provided. Thiamylal causes a marked increase in the activity of cytochrome P<sub>450</sub>-dependent monooxygenases, protein and lipid content of the hepatic smooth endoplasmic reticulum and may also exhibit some hepatotoxicity (i.e. hepatitis). Cardiotoxic effects have also been described for thiobarbiturates in man.
9. The reported side effects following intravenous administration in humans were related to the anaesthetic action (restlessness can be observed in the recovery period) and limited to immediate and major cardiovascular collapse and/or severe and prolonged respiratory depression in some individuals. Hypersusceptibility can be noted in patients with asthma or urticaria.
10. Two cases of alleged allergic reactions with thiamylal were reported in the literature. The first report involves a case of intravenous administration of 250 mg thiamylal sodium in a 44-year old patient. The second report concerns a 6-year old child, who was administered intravenously with 75 mg of sodium thiamylal. Both developed symptoms such as bronchial spasma and skin rash but made a full recovery after withdrawal of treatment. Subsequent skin tests were positive in the adult but negative in the child.
11. From the limited data available, neither a pharmacological nor a toxicological NOEL could be established; therefore it is not possible to set an ADI for thiamylal. Despite this, it was considered that there would be no undue risk to consumers from residues in edible tissues, due to the rapid elimination of the substance in the pharmacokinetic studies.
12. No residue depletion studies in target species after recommended thiamylal doses were provided. However, a non-GLP compliant residue depletion study in the horse was available. This study only included the analytical part (the method was not validated) and does not specify data about the animals used (i.e. age, weight), the mode of application and the interval between treatment and sampling. Thiamylal residues were determined in the diaphragm (muscle), liver, kidney and fatty tissues of 3 horses and analysed by HPLC with UV-detection. Low thiamylal concentrations were found in muscle (average concentration of 3 samples was 5.8 µg/kg), in comparison with fat and liver where the concentrations were higher (24.6 µg/kg and 21.4 µg/kg respectively). No conclusion could be drawn due to inadequacies of the study.

## 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:

- thiamylal is used in a small number of individual animals, for infrequent or non-regular treatments only,
- the substance is rapidly eliminated from the target species after intravenous administration;

the Committee for Veterinary Medicinal Products concludes that there is no need to establish an MRL for thiamylal 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
Thiamylal	All mammalian food producing species	For intravenous administration only