



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

PRETHCAMIDE (Crothetamide and cropropamide)

SUMMARY REPORT

1. Prethcamide is composed by a 1:1 mixture of crothetamide (ethylbutamide) (a-(N'-crotonyl-N'-propyl)-N,N-amino-dimethylbutyramide) and cropropamide (propylbutamide) (a-(N'-crotonyl-N'-ethyl)-N,N-amino-dimethylbutyramide). It is a respiratory analeptic. In veterinary medicine, it is administered as a single dose up to 750 mg/animal (about 10 mg/kg bw) for calves and foals, and about 9 mg/kg bw for lambs and piglets. If there is no response within 30 seconds, the dose should be repeated at 30 seconds interval; the recommended dose cannot be repeated more than twice. The indications for use of prethcamide are: hypoxia neonatorum, respiratory stimulation during neuroleptic anaesthesia and stimulation of respiration following anaesthesia. In human medicine, it was indicated for the treatment of respiratory insufficiency. The recommended dose ranged from 3.5 to 30 mg/kg bw according to the route of administration (intravenous or oral) and the age of the patient.
2. Several pharmacodynamics studies performed with prethcamide in different laboratory animals (mice, rats, guinea-pigs, rabbits, dogs, cats) and large animals (horses) were provided. Pharmacodynamic effects are targeted mainly on the respiratory system. Prethcamide stimulates the respiration by increasing the respiratory rate and/or the depth of respiration. Intravenous doses of 3 to 5 mg/kg bw in rabbits lead to a 15 to 30% increase in respiratory rate lasting 5 to 10 minutes. Prethcamide was examined in 5 horses given 5 or 10 mg/kg bw by intravenous infusion over 8.5 minutes; within 1 to 2 minutes there was a 20 to 30% increase in respiration. Respiration returned to normal in 30 to 45 minutes. Prethcamide counteracts the respiratory depression induced by certain substances, notably anaesthetics. The site of action of prethcamide is in the medullary respiratory centres. However, the vagal nerve stimulation could also contribute to the respiratory stimulation.

With respect to the secondary pharmacodynamics effects, after bolus injection at doses of 30 mg/kg bw in dogs prethcamide had a minimal effect on the cardio-vascular system consisting in bradycardia, hypotension and peripheral vasodilatation. It can be concluded that cardio-vascular effects induced by prethcamide, which are dose-dependent, are very transient and last only a few minutes after dosing.

In rats, prethcamide increased the motor activity in a dose-dependent manner. This effect was seen at doses between 33 and 60 mg/kg bw and it is interpreted as a stimulation of the central nervous system.

In a large study performed in healthy adult female patients, prethcamide at the dose of 2.9 mg/kg bw by intravenous perfusion lasting approximately 1 hour, produced an increase of the tidal volume and of the alveolar ventilation without changes in the respiratory rate.

However, the data available on pharmacodynamic effects of prethcamide provided in animals and human beings are not sufficient to derive an oral NOEL.

3. Several pharmacokinetic studies were performed in laboratory animals and target species. In these species the pharmacokinetic characteristics appear very similar. Crothetamide and cropropamide are quickly absorbed and eliminated from the body.

In the rat, following the intravenous administration of prethcamide at a dose of 60 mg/kg bw peak plasma level of 52 µg/ml occurred at 5 minutes and declined to 4 µg/ml (2.6 µg/ml crotethamide + 1.4 µg/ml cropropamide) after 30 minutes. The elimination half-lives of the two components of prethcamide were 7.3 minutes (crotethamide) and 6.5 minutes (cropropamide). After 30 minutes the tissue concentrations for crotethamide and cropropamide were: heart 1.56 and 0.97 µg/g; kidney 2.86 and 1.72 µg/g; liver 1.30 and less than 0.5 µg/g; brain 0.85 and less than 0.5 µg/g, respectively (limit of quantification of the analytical method: 0.5 µg/ml). Crotethamide and cropropamide undergo biotransformation to respective single hydroxylated metabolite in the presence of rat hepatic microsome and the NADPH generating system.

In the rabbit, a pharmacokinetic study of prethcamide was performed following rapid intravenous injection and oral administration of a dose of 15 mg/kg bw. For the quantitative determination of for crotethamide and cropropamide in plasma and tissue, a gas chromatographic method (limit of detection 0.1 µg/ml) was used. The mean half-life, the body clearance and the mean absorption rate constant values were: 43.07 and 30 minutes; 0.05 and 0.096 l/min; 0.033 and 0.051 min⁻¹ for crotethamide and for cropropamide, respectively. The t_{max} was 30 minutes in both cases. The bioavailability of the compounds ranged from 24 to 32%. After the dose of 40 mg/kg bw cropropamide was detectable for up to 90 minutes, and crotethamide even further. The pharmacokinetic and bioavailability parameters for crotethamide and cropropamide after oral administration (40 mg/kg bw) were: area under curve (AUC) 673 and 263 µg·min/ml; C_{max} , 8.83 and 4.48 µg/ml; t_{max} , 30 minutes in both cases; bioavailability, 32 and 24.4%. Tissue levels of the two components of the drug were measured. Decreasing concentrations were found in liver, kidney, lung-heart and brain. In the liver, concentrations were only slightly higher than those of blood after intravenous injection. Elimination half-life was longer for crotethamide than for cropropamide. However, it was in the same range of magnitude for all tissues, ranging from 11.1 to 29.6 minutes for cropropamide, and from 31.6 to 42.6 minutes for crotethamide. These substances rapidly disappeared from all tissues, including the liver, so that after 3 hours they could rarely be detected.

In a pharmacokinetic study performed in the new-born calf, following application of 750 mg of the drug product to the tongue, absorption and elimination half-life were respectively 2 and 54 minutes (crotethamide), and 0.95 and 46.5 minutes (cropropamide). The plasma concentrations of the active constituent were assayed quantitatively by a gas chromatographic method (limit of detection 0.1 µg/ml). The mean plasma concentrations declined from a peak of 22 µg/ml (crotethamide) and 22.4 µg/ml (cropropamide) at 3 minutes to 7.6 µg/ml (crotethamide) and 7.1 µg/ml (cropropamide) at 60 minutes after dosing. The systemic clearance was 346 and 367 ml/min, respectively. It can be concluded, the prethcamide is rapidly absorbed and active constituents are eliminated by first-order kinetics with a half-life of about 50 minutes. No pharmacokinetic studies in foals, lambs and piglets were available.

4. Acute toxicity studies were performed in rats and mice. The oral LD₅₀ values for neonatal rats and mice after administration of the drug compound were 800 and 1300 mg/kg bw, respectively, thus prethcamide was considered slightly toxic. In rats, prethcamide caused non-characteristic signs of excitation at sub lethal and lethal dose levels. The two components of the drug (crotethamide and cropropamide) have very different LD₅₀ values. Crotethamide is 7 times more toxic than cropropamide. Crotethamide treated rats showed tonic-clonic convulsions shortly after injection but they generally recovered. Death occurred 18 to 48 hours later. In cropropamide treated rats the convulsions, which were violent and often fatal, appeared shortly after treatment. The intravenous LD₅₀ values for rats and mice were 250 to 500, and 573 mg/kg bw, respectively.
5. A series of repeated dose toxicity studies were conducted in rats, dogs and primates. These studies were old and non-GLP compliant.

A 26-week oral study was performed in the Sprague Dawley rat (groups of 15/sex/dose were treated at dose levels of 100, 200 and 400 mg/kg bw/day diluted in distilled water). Individual bodyweights, clinical symptoms and abnormal behaviour were recorded daily and food consumption was recorded weekly. Also haematological measurements, blood chemistry and urinalysis were fulfilled. Naturally occurring nephrosis was enhanced at a dose level of 400 mg/kg bw/day and there was evidence of mild toxicity. The compound, at the lowest dose of 100 mg/kg bw showed no evidence of toxicity. The NOEL of this study was 100 mg/kg bw/day.

A 26-week oral study was conducted in Beagles dogs of both sexes at doses of 20, 40 and 80 mg/kg bw/day (6 dogs per groups). The same parameters than those measured for rats were analysed. At all dose levels respiration was stimulated and abnormal thirst observed. A dose-related disturbance of the central nervous system was seen. Slight muscular tremors at the lowest dose level was noted in two instances. Tetanic convulsions (one animal) and severe muscular tremors occurred at the highest dose level. Evidence of hepatic disturbance appeared at the highest dose. A NOEL could not be established from this study.

A 26-week oral study was conducted in baboons (groups of 3/sex/dose) treated at dose levels of 120, 240 or 480 mg/kg bw/day in gelatine capsules. Two animals died in the 480 mg/kg bw group, one on day 2 and the other on day 81 following a convulsive episode. One animal of the 240 mg/kg bw group died on day 79 following evidence of central nervous system stimulation. Clinical signs of convulsions were seen in 4 out of 6 baboons receiving 480 mg/kg bw. Muscular tremors were observed immediately after dosing in 3 animals in the highest dose level group and 4 animals in the group receiving 240 mg/kg bw/day. Excitability was observed in animals receiving 480 mg/kg bw/day, during the first 2 weeks of dosing. Vomiting was occasionally observed. Male baboons receiving 480 mg/kg bw/day showed a loss of body weight whilst those receiving the intermediate dose showed no weight gain. No differences among groups were found for females. No clear effect of the tested drug was seen in terms of food intake. Laboratory investigations and pathological macroscopic organ or tissue examinations at the end of the study revealed no abnormalities. A tendency towards anaemia and reduction of total serum protein and albumin level was, however, noted from weeks 12 to 20 of the study in baboons receiving 480 mg/kg bw/day. An increase in liver and adrenal weight was also noted in this group. A NOEL of 120 mg/kg bw/day was established in this study.

6. No tolerance studies in the target species were available. However, there is considerable species variation in the oral dose level at which side effects are first noted. Generally, the first toxic signs are muscular tremors which occur at 20 mg/kg bw in dogs chronically dosed at 40 mg/kg bw in lambs and at doses greater than 150 mg/kg in rats and baboons.
7. No data on multigeneration reproductive studies were available.
8. Three non-formal teratogenicity studies were performed in mice, rats and rabbits. No evidence of teratogenic effects were found following oral application of prethcamide to Swiss White mice at a single dose rate of 200 mg/kg bw/day during days 1 to 18 of pregnancy. The number of new born and implantation sites were similar to those seen in untreated animals (12 treated and 4 controls). In Wistar rats, (16 treated and 17 control) no evidence of teratogenic effects were found following the oral administration of prethcamide at a single dose rate of 200 mg/kg bw/day during days 1 to 21 of pregnancy. In Yellow-silver rabbits (12 rabbits per dose in comparison with 11 control animals), no evidence of teratogenic effects were found following the oral administration of prethcamide at a dose rate of 50 and 100 mg/kg bw/day during days 7 to 16 of pregnancy. A dose related reduction of maternal body weight-gain occurred during the dosing period. In conclusion, these studies were conducted on small numbers of animals and dose range effects were not tested. However, tested doses were quite high and no clear evidence of teratogenic effect was found.

9. No data on mutagenicity of prethcamide were available.
10. No data on carcinogenicity of prethcamide were available. However, prethcamide does not possess a chemical analogy with known carcinogens.
11. No data on immunotoxicity or other effects were supplied.
12. No data on the effects of prethcamide on human gut flora or microorganisms used in food processing were presented. However, no microbiological data are needed for this type of compound.
13. Prethcamide has been used in humans since 1962. This product is no longer marketed since it has been replaced with more specific and potent drugs. In a large study healthy adult females patients undergoing breast biopsy under anaesthesia with thiopental nitrous oxide and oxygen, received also doses of 1 to 3 mg/kg of prethcamide.

It has also been reported that respiratory stimulation was characterised mainly by an increase in the depth of respiration. The main reported adverse effects were nausea, vomiting, agitation, and convulsion. They appear frequently in patients under perfusion with high doses.

14. No residue studies have been conducted with prethcamide in the target species. This information was not considered necessary due to the rapid excretion of the substance.
15. No routine analytical method for the determination of prethcamide in tissues of target animals was provided.

Conclusions and recommendation

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

- prethcamide is used occasionally for treatment of individual animals,
- the animals are unlikely to be sent for slaughter during or immediately after treatment,
- prethcamide is rapidly absorbed, extensively metabolised and completely excreted,
- prethcamide was of low toxicity;

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

Pharmacologically active substance(s)	Animal species	Other provisions
Prethcamide (crothetamide and cropropamide)	All food producing mammalian species	