

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

MERCAPTAMINE HYDROCHLORIDE

SUMMARY REPORT

1. Mercaptamine hydrochloride (synonym: cysteamine hydrochloride) is recommended for use only in combination with other compounds, in particular dexamethasone and ascorbic acid. Indications for the combined formulations are a range of metabolic diseases, for instance ketosis, and inappetence in cattle and horses and mastitis-metritis-agalactia complex in pigs (in formulations for pigs other active compounds like carbachol may also be present).

For cattle and horses, maximal recommended doses of mercaptamine administered with the combined products are 0.75 g mercaptamine hydrochloride (equivalent to 0.51 g mercaptamine base)/animal (intravenous route, 1 to 3 doses at intervals of 24 to 36 hours) and for pigs (sows and gilts) 0.38 g mercaptamine hydrochloride (equivalent to 0.20 g mercaptamine base)/animal (intramuscular route, each injection is divided over two sites, 2 to 3 doses at intervals of 24 hours). The dose ranges per kg bw for cattle or horses weighing 200 to 700 kg or pigs weighing 100 kg are approximately 1 to 3.8 mg mercaptamine hydrochloride (equivalent to 0.7 to 2.5 mg mercaptamine base)/kg bw. However, mercaptamine is known also to be used in younger pigs (bodyweight 20 to 50 kg) at doses of 3.6 to 9 mg (as the hydrochloride)/kg bw.

In human patients, mercaptamine has been used to protect against hepatotoxic compounds and it is used orally to reduce cystine levels in cystinosis patients. Therapeutic doses in humans are 50 mg/kg bw/day and higher.

Mercaptamine is present in the normal diet as it occurs naturally in animal tissues and vegetable foods.

2. Mercaptamine is an endogenous compound, formed by decarboxylation of cysteine and by the enzymatic cleavage of pantetheine. The reactivity of the compound is due to the SH and the NH₂ group in the molecule. In particular the SH group interacts with various substances in the body by various mechanisms. The mechanisms includes the formation of disulfide groups, reducing activity resulting in inhibition of oxidoreductases, production of H₂O₂, formation of complexes with heavy metals (cadmium, mercury, selenium), nucleophilic properties causing inactivation of electrophilic metabolites (e.g. from acetaminophen), radical scavenging and antioxidant action resulting in protection against cellular damage caused by e.g. oxidative stress caused by e.g. UV irradiation).

Mercaptamine may be present as free base, as oxidised form or as protein bound form (e.g. as component of pantetheine). In 5 male and 3 female healthy subjects of 21 to 38 years of age normal total plasma concentrations were in the range 0.09 to 0.30 µg/ml. Total human body content of free mercaptamine may be estimated to be about 7 mg (based on plasma concentrations of total mercaptamine in humans). No data on endogenous production were available.

3. The intended pharmacodynamic action in target animals is the reversible effect of mercaptamine on the endocrine system resulting in metabolic effects. It reduces somatostatin concentration (produced in hypothalamus, pancreas, intestinal tract) and affects (directly or indirectly) a number of pituitary (growth hormone, prolactin, vasopressin, oxytocin) and pancreatic hormones (insulin), resulting in various endocrine and metabolic effects (increased plasma growth hormone, plasma insulin and glucose levels, effects on heat production).

The endocrine effects may last from several hours to a few days and are reversible. In the available experimental literature (on laboratory animals and ruminants) these effects were found at high doses (30 mg/kg bw and higher), but the order of magnitude of a low recommended (parenteral) dose in target animals is about 1 mg/kg. A NOEL for these effects was not available.

Other pharmacodynamic effects mentioned in literature were: protection against radioactivity dilation of blood vessels (at intravenous doses of 5 to 30 mg/kg bw in mice), decrease of body temperature in cold exposed rats, stimulation of gastric juice production and effects on gastric emptying and gastric blood flow (probably secondary to the effect on somatostatin), interaction with amino acids (cystine storage in cystinosis patients), stimulation of adrenaline production by the adrenal medulla, effects on biogenous amines and catecholamines in the central nervous system, effects on histamine production in liver and duodenum, interaction with biotransformation and toxicity of drugs and chemicals (e.g. acetaminophen, anthracycline, adriamycin, heavy metals), depigmentation (in laboratory animals). No data to establish NOELs for these effects were available.

4. Mercaptamine is quickly absorbed from the intestinal tract. It is incorporated in endogenous compounds and excreted by the renal route. In humans, mercaptamine is quickly metabolised to excretable sulfur-containing compounds. In a patient orally dosed with 26.1 mg/kg bw mercaptamine hydrochloride (equivalent to 17.7 mg/kg expressed as base) a plasma C_{max} of 4.32 mg/l mercaptamine (base) was reached after 1 hour. Plasma half-lives of 20 minutes to 3 hours have been reported. Less than 2% of an oral dose of 508 to 1217 mg/day was excreted intact in the urine. Part of the compound may also be excreted by breath as dimethylsulfide. Other metabolites are cystamine, cysteine, homocysteine, glutathione.
5. After intravenous treatment of rats with 200 mg/kg bw mercaptamine hydrochloride, the highest concentrations (expressed in mercaptamine base) were found in kidney, duodenum, jejunum, pancreas, liver and heart (995, 262, 231, 224, 177 and 272 mg/kg, respectively; concentrations in negative controls were: 162, 20, 7.7, 21, 21, and 2.3 mg/kg, respectively) at 2 minutes after dosing. At 30 minutes post dose concentrations of 617 (kidney), 116 (duodenum), 62 (jejunum), 85 (pancreas) and 46 (heart) mg/kg were found (at this time point the concentration in liver was not available, at 10 minutes post dose the liver concentration was 216 mg/kg). However, the concentrations in control tissues in this study were high compared to those reported in more recent publications, possibly as a consequence of the analytical method used. Therefore, the reliability of these data is uncertain.

Mercaptamine concentrations in animal tissues reported in literature vary widely, probably because of *post mortem* production and unreliability of analytical methods. Published concentrations (expressed as mercaptamine base) in mouse tissues are: 4.15 mg/kg in liver (18% as reduced mercaptamine, 68% as oxidised free forms, 14% as protein bound compound), 8.23 mg/kg in kidney (66% as reduced mercaptamine, 28% as oxidised free forms, 6% as protein bound compound) 0.74 mg/kg in muscle (17% as reduced mercaptamine, 47% as oxidised free forms, 37% as protein bound compound).

6. Oral LD_{50} values in mice of 625mg/kg bw to 1352 mg/kg bw were reported. Reported subcutaneous and intraperitoneal LD_{50} values were in the range 157 to 250 mg/kg bw in mice and rats and the intravenous LD_{50} in rabbits was 102 mg/kg bw.
7. No repeated dose toxicity studies were available. However, experimental literature contains extensive documentation about many different pharmacodynamic and toxic effects of the compound. In many cases, mercaptamine may have opposite effects on the same parameters, dependent on the conditions. For instance, mercaptamine acts as a gastric ulcerogenic (at doses of 100 to 300 mg/kg bw and higher, route of the low dose unknown, route of the high dose: stomach tube), but also protects against ulcerogenic effects of other compounds. It may act as a radical scavenger and an antioxidant. Most of the effects of the compound have been found at relatively high doses (at the level used in human therapy and higher) and NOELs are not available. Because mercaptamine is an endogenous compound, it may be expected to play a role in normal physiological processes at concentrations present in the body and to cause disturbance of physiological processes at abnormally high concentrations.

8. Mercaptamine is an *in vivo* mutagen but also has some antimutagenic properties. The effects depend on the test conditions (concentration of the compound, oxygen concentration, pH, presence of metal ions and others). Mercaptamine hydrochloride was positive in a bone marrow micronucleus test (animal species and route: not mentioned) at a dose of 200 mg/kg bw. At concentrations of 7.7 to 770 mg mercaptamine/l, sister chromatid exchange were induced in hamster ovary cells. The clastogenic effect of bleomycin in G₀ human lymphocytes was potentiated by mercaptamine in concentrations of 385 to 1540 mg/l. However, evidence was found that under hypoxic conditions mercaptamine protected against the effects of bleomycin. In combination with irradiation, mercaptamine in a concentration of 38.5 mg/l induced single-strand DNA breaks in mammalian cells. In high concentrations (over 385 mg/l) mercaptamine protected against radiation-induced single strand breaks and double-strand cuts and inhibited DNA synthesis and rejoining of radiation induced single-strand breaks. In a study in mice it was found that a large proportion of orally or intratesticularly administered ³⁵S-mercaptamine found back in the cell nucleus was bound to DNA. Mercaptamine in a dose above 7.7 mg/l reduced colony formation of baker's yeast, which was probably due to interaction with cell division. Mercaptamine may protect against carcinogenic effects of certain compounds (e.g. at an intraperitoneal dose of 150 mg/kg bw it reduced the number of mammary tumors induced by 7,12-dimethylbenzo(α)anthracene in rats).
9. In human medicine mercaptamine is used for the treatment of cystinosis and sialic acid storage disease, two inborn disorders of carrier-mediated transport of respectively cystine and sialic acid across the lysosomal membrane, resulting in abnormal intracellular accumulation of these compounds, causing damage to various organs. It is also known for its radioprotecting effect, but high (toxic) doses are needed for this effect. Furthermore, it may be used against toxicity of heavy metals, overdose of acetaminophen, and other chemicals. In human therapy oral mercaptamine (dose 50 to 60 mg/kg bw) can cause gastro-intestinal side-effects. Side effects reported after parenteral use are nausea, vomiting, anorexia, abdominal cramps, flushing, irritability, meningism, leucopenia, ventricular tachycardia, lethargy and seizures. In nephropathic cystinosis patients receiving daily oral doses of 53 to 75 mg/kg bodyweight, reversible fever, maculopapular eruption, leucopenia and headache were found. These patients tolerated daily doses of 10 mg/kg.
10. Mercaptamine and some of its precursors are normal constituents of the daily diet in appreciable amounts, and because mercaptamine is also produced endogenously a purely toxicological approach was not considered to be justified in this case.
11. Published data indicate that concentrations (expressed as mercaptamine base) in untreated bovines were: liver 1.5 to 4.0 mg/kg. Concentrations (expressed as mercaptamine base) in untreated pigs were: liver 0.08 to 0.35 mg/kg, kidney 0.77 to 2.3 mg/kg and heart 0.12 mg/kg. In untreated sheep a concentration of 0.93 mg (as base)/kg was found in liver. Based on these data, the estimated daily intake from tissues of untreated animals is about 1 mg/day.
12. No residue data in target animals treated in accordance with the recommendations were available. Considering the available data, it is unlikely that residues in mercaptamine treated animals would represent a significant risk for human health, provided that they do not increase the normal total daily intake by more than 1 mg.

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:

- mercaptamine is a compound of the normal diet,
- mercaptamine hydrochloride is intended for treatment of individual animals,
- mercaptamine is rapidly and extensively metabolised and excreted,
- mercaptamine is produced endogenously in the human body and in animals;

the Committee for Veterinary Medicinal Products concludes that there is no need to establish an MRL for mercaptamine hydrochloride 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
Mercaptamine hydrochloride	All mammalian food producing species	