



## COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

### ACETYL CYSTEINE

### SUMMARY REPORT

1. N-Acetyl-L-cysteine (NAC) is an acetylated derivative of the amino acids-L-cysteine. The compound possesses mucolytic activity and is intended for oral use in horses suffering from respiratory tract diseases involving increased mucus production. The suggested dose in horses is 10 mg per kg bw b.i.d.
2. The pharmacokinetics and biotransformation appears quite similar in all animal species investigated as well as in humans. Orally administered NAC is rapidly and almost completely absorbed. During the absorption phase the compound is subject to an extensive first pass metabolism, resulting in a rather low bioavailability of unchanged NAC, in humans probably not exceeding 10%.
3. Labelled studies in laboratory animals indicate a rapid and wide distribution to all organs/tissues examined, irrespective of route of administration. Peak values are usually attained within 1-4 hours post dose. Highest total activities are observed in kidney, liver and duodenum with the lowest values in muscle and brain tissue. The serum protein binding of radioactive compound(s) is 70 to 90 pct. the major part of the nonprotein-bound activity is attached to "free thiols" (unchanged NAC plus metabolites possessing free  $^{35}\text{SH}$ -groups, mainly cysteine) or "free disulfides", i.e. compounds containing  $^{35}\text{S}=\text{S}$  bonds (e.g. cysteine, N, N'-diacetyl-cysteine and N-acetyl-cysteine). Protein-bound activity can be separated into two parts, i.e. activity attached to compounds binds to protein by disulfide linkage, and activity attached to compounds incorporated in the protein structure by peptide bonds. Upon repeated administration no accumulation of free or protein-bound thiols is observed.
4. Irrespective of route of administration the radioactivity is mainly excreted via the kidneys. The major urinary excretion product is inorganic sulfate while the amount of unchanged drug is insignificant. Since NAC is a normally occurring intermediate, small amounts of NAC of endogenous origin will probably always be present in urine.
5. The initial step in the metabolism of NAC is deacetylation to cysteine. The transformation takes place in the gastro-intestinal (GI) tract, in the intestinal mucosa and, to a lesser extent, in the liver. Cysteine is further metabolized by incorporation into GSH, mixed disulfides and proteins as well as by degradation to inorganic sulfate, i.e. the metabolite profile of NAC consists purely of endogenous substances.
6. The acute oral toxicity of NAC is low, eg. LD<sub>50</sub> being > 10.000 mg/kg bw in adult non-fasted rats, while rats fasted for 16 hours are somewhat more sensitive (LD<sub>50</sub> about 6.600 mg/kg). Almost all symptoms of acute toxicity stem from the irritative effects of NAC on the mucosal membranes of the GI tract. In normally fed rats 2000 mg/kg caused virtually no GI-lesions. NAC-related effects observed in repeated-dose studies on rats and dogs are also dominated by gastro-intestinal lesions accompanied by secondary changes in haematologic parameters. In rats, administered 250 mg NAC/kg bw per day for 28 weeks, all NAC-related effects observed were marginal.

7. NAC does not affect the fertility of female rats at daily oral doses < 1000 mg/kg bw. Neither do doses in the same range produce any adverse effects on the offspring during the peri- and postnatal period. In male rats dosed with 250/500/1000 mg NAC/kg bw per day the sperm counts were decreased at > 500 mg/kg, and there was a dose-related decrease in mating performance (copulation rate). There was no significant difference in pregnancy rates, but an increase of preimplantation losses (not dose-related) was observed among females mated to NAC-treated males. Studies in rats and rabbits did not produce evidence of teratogenic potential.
8. The results of an Ames test did not indicate mutagenic potential. Therefore it was not regarded necessary to carry out carcinogenicity studies.
9. NAC has been and still is used - on a wide scale in humans, especially as an adjunct in the treatment of chronic respiratory diseases. The dose employed in adult humans for long-term therapy is 200 mg per person t.i.d. In addition, NAC exerts a protective effect against organ toxicity caused by various chemical substances. An important indication in humans is the treatment of paracetamol poisoning at doses of 50-150 mg per kg bw. Maximum doses of 400, or 600 mg NAC per day in two or three daily oral administrations have been given for up to 180 days with only a few adverse reactions. Apart from rare skin affections all effects can be ascribed to the local GI-toxicity of NAC. Symptoms of anaphylatic reactions, e.g. rash, bronchospasm, hypotension, nausea, and vomiting, have been reported in a few cases after NAC administration, but only at doses > 3000 mg/person/day as used in paracetamol poisoning.
10. NAC is of low toxicity in both animals and humans. NAC is a naturally occurring compound in the animal body. When administered orally to experimental animals and to humans NAC undergoes extensive first-pass metabolism to cysteine and other endogenous substances without toxicological relevance. It seems justified to assume that the same is the case in the horse. After oral administration to experimental animals NAC has not been detected in "edible tissues" and the metabolites are found in increased concentrations only for a few hours. NAC has been used for decades in the human therapy. NAC is intended for use in the horse only. In horses NAC will be used for treatment of individual animals only.

The toxicological data gathered for acetyl cysteine allow to conclude that an MRL is not needed for acetyl cysteine since its residues do not present a hazard for the health of the consumer. The Committee for Veterinary Medicinal Products considers that these conclusions can apply to all food-producing species and recommends that acetyl cysteine be inserted in Annex II of Regulation 2377/90.