ZAMBON

FLUIMUCIL/FLUIMUCIL A

CONTENTS: Acetylcysteine.
PRESENTATION: Fluimucil: Granules 100 mg x 30's, 900's. 200 mg x 60's, 1800's. Amp 300 mg x 3 mL x 5's.
Fluimucil A: Tab 600 mg (effervescent) x 10's. Granules 200 mg x 30's.
DESCRIPTION: Fluimucil A also contains aspartame as sweetener.
Acetylcysteine is the N-acetyl derivative of the naturally occurring amino acid L-cysteine.
N-Acetylcysteine (NAC) is L-α-acetamido-β-mercaptopropionic acid. Empirical Formula: $C_5H_9NO_3S$. Molecular Weight: 163.2. Appearance: White or faintly ivory crystals or crystalline powder, with light sulfur odour and slightly saline taste. The solubility of NAC is higher than that of cysteine both in water and in buffered solutions at different pH values. The acetyl substituted amino group renders the molecule less easily oxidized than cysteine. NAC incubated up to 6 hrs in simulated gastric fluid at a concentration of 2 g/100 mL showed good stability. In simulated intestinal fluid, only 16% of NAC was oxidized while the oxidation of other thiols (eg, cysteine) ranged from 75-100%.
ACTIONS: Pharmacology: N-Acetyl-L-cysteine (NAC) exerts an intense mucolytic action on mucous and mucopurulent secretions, by depolymerizing the mucoproteic complexes and the nucleic acids which confer viscosity to the vitreous and purulent component of the sputum and of other secretions.
The mucolytic action of NAC is thought to be due to the sulfhydryl group cleaving certain disulfide bonds in the glycoprotein macromolecules of mucus through a sulfhydryl-disulfide exchange reaction (Sheffner, 1964). Thus, lower molecular weight mixed disulfides of NAC and glycoprotein subunits are formed and result in decreased viscosity of mucus (Sheffner, 1964).
The antidotal action of NAC against liver cell necrosis from acetaminophen (paracetamol) poisoning is due to NAC's being an effective precursor of intracellular cysteine. This promotes the synthesis of intracellular GSH which conjugates the toxic metabolite of acetaminophen (Flanagan, 1991).
By a similar mechanism, prolonged NAC intake might protect bronchopulmonary cells against airborne noxious agents. Intracellular cysteine is essential for both sulfation and GSH conjugation, the only 2 mechanisms available to peripheral human lung for detoxifying such substrates as phenols and arene oxides. Both thiols can also complex directly with such reactive toxins as the aldehydes (eg, acrolein and acetaldehyde, 2 components of the ciliotoxic and phagocytotoxic phase of cigarette smoke). In addition, the system of enzymes related to GSH is essential for cellular defense against peroxides and free radical chain reactions provoked by excess oxygen or other oxidants.
The effects of NAC *in vitro* on the viscosity of tracheobronchial secretions from patients with various pulmonary diseases have been assessed using various techniques (Sheffner, 1963; Lieberman, 1968; Hirsch, 1969; Grassi, 1977). After incubation of sputum with different NAC concentrations, a dose-related activity was observed and NAC showed similar effects both on nonpurulent and purulent mucus. The mucolytic activity increased with a pH over the range of 5.5-8 and was unaffected by nebulization with oxygen, thus indicating that the molecule does not undergo oxidation. *In vivo*, after nebulization for 10 min of 20% NAC solution, a significant increase of sputum volume and decrease of viscosity, measured with the consistoviscosimeter, were observed in patients with chronic bronchitis.
The beneficial effects of mucolytic drugs, also, appear to be due to an increase in bronchial secretion of the respiratory tract fluid. The influence of NAC treatment on mice lung mucus secretion was estimated measuring the concentration of extracted fluorescein from the tracheobronchial tract isolated 30 min after fluorescein injection. Since fluorescein is known to be excreted via lung secretions, the pulmonary fluorescein concentration can be considered as an index of bronchosecretogogue activity. Fluorescein (4 mg/kg/sec) given 30 min after NAC administration was extracted following 3 consecutive washings of the tracheobronchial tract. NAC administered at a dosage of 300 mg/kg/orally induced a significant increase in lung mucus secretion in mice (Graziani, 1980).
Other studies have been performed *in vitro* using rat and rabbit tracheae incubated in oxygen-equilibrated Krebs solution at 37°C. After the addition of 10^{-10} g/mL of NAC, a significant increase of mucus production (from 6.8-13.4 microlitre/hr) was observed; moreover, electron microscopy showed release of mucus from goblet cells after administration of NAC, which induced synthesis of Golgi apparatus and granulated endoplasmic reticulum in goblet cells, thus indicating increased secretory activity (Iravani, 1978).
With regards to the effects of NAC on mucociliary clearance, controversial results have been obtained by different authors. In healthy subjects with a slow mucociliary clearance rate as measured with the radioaerosol method, after treatment with 600 mg oral NAC daily for 60 days, an increase of about 35% in the parameter was observed in comparison to baseline, with return to pre-treatment values after a washout period and no response to placebo (Todisco, 1985). Also, in smokers with hypersecretory bronchitis and reduction of mucociliary transport, the administration of NAC 600 mg daily for 10 days induced a significant increase, as compared to placebo, in the rate of displacement of Teflon disks in the trachea (Olivieri, 1985).
The direct effects of NAC on cilia have been studied using human nasal epithelium and a microphoto-oscillographic method combined with microperfusion technique (Stafanger, 1987). NAC caused a dose- and time-related decrease in ciliary beating frequency that reached significant levels at a concentration of 20 mg/mL, far more than the concentrations found *in vivo* in bronchial secretions following oral administration of NAC (Rodenstein, 1978). However, NAC had no effect on the beating pattern of cilia and the inhibitory effect on the beating frequency was fully reversible (Stafanger, 1987). Using the same method, no effects of oral NAC 200 mg thrice daily or 400 mg twice daily for 3 months were observed on ciliary beating frequency and ciliary motility pattern in patients with cystic fibrosis or primary ciliary dyskinesia (Stafanger, 1988).
Furthermore, NAC exerts a direct antioxidant action, being provided with a free thiol (-SH nucleophilic) group, which is able to interact directly with the electrophilic groups of the oxidant radicals. Of particular interest is the recent demonstration that NAC protects the α_1-antitrypsin, enzyme inhibitor of elastase, from the inactivation due to the action of hypochlorous acid (HOCl), a powerful oxidant agent produced by the myeloperoxidase enzyme of activated phagocytes.
These features make Fluimucil A particularly suitable for the treatment of acute and chronic affections of the respiratory system, characterized by thick and viscous mucous and mucopurulent secretions. Furthermore, the molecular structure permits the molecule to cross cellular membranes easily. Inside the cell, NAC is deacetylized, forming L-cysteine, an amino acid indispensable for the glutathione synthesis (GSH).

GSH is a highly reactive tripeptide, found ubiquitously in the various tissues of animals and is essential for the maintenance of functional capacity as well as cellular morphological integrity, as it represents the most important protective, endocellular mechanism against oxidant radicals, either of external or internal nature, as well as towards numerous cytotoxic substances.

NAC plays a role of primary importance in the maintenance of adequate GSH levels thus, contributing to the cellular protection from harmful agents which, through progressive GSH depletion, would be able to express their cytotoxic action, as in the care of acetaminophen poisoning.

Microbiology: A bacteriostatic effect of NAC has been observed, mainly against *Pseudomonas aeruginosa* (Alfredsson, 1987; Parry, 1977), and an *in vitro* assay of *P. aeruginosa, S. pneumoniae* and *H. influenzae* (Andersson, 1991) adherence to epithelial cells obtained from human tracheal, buccal and nasal sites has shown reduced bacterial adherence at all sites after adding NAC. These findings have been recently confirmed in a clinical-microbiological study, indicating that the NAC effect on reduction of exacerbations in patients with chronic bronchitis is at least in part connected to an effect on the bacterial flora (Riise, 1994).

Pharmacokinetics: Absorption: Acetylcysteine is stable in stimulated gastric and intestinal fluid. NAC is rapidly absorbed by the oral route and after a 400-mg dose, the C_{max} of the reduced form is 3.47 mg/L with a t_{max} of 30 min. Bioavailability of NAC administered orally is about 10%, indicating that NAC is rapidly oxidised before reaching the general circulation, at the gastrointestinal level (gut wall and liver). The rate of absorption is quite similar for the 2 different forms of the drug (tablets and granules) with no significant differences in t_{max}. It has been shown that the 600-mg dose is 2.6- to 5-fold higher (C_{max}), and AUC on average 2.8- to 4.9-fold larger than with a single 200-mg dose.

However, after comparing a single oral 600-mg dose with 200 mg thrice daily of NAC, no statistically significant differences were observed in terms of C_{max} and AUC, demonstrating a substantial bioequivalence (De Caro, 1989).

Distribution: Distribution is extensive and rapid with a volume of distribution at steady state (Vd_{ss}) ranging from 0.33-0.57 L/kg for total NAC. After an oral dose of 100 mg ^{35}S-NAC in 5 patients undergoing pneumonectomy or lobectomy, the tissue distribution is high with a ratio of lung tissue/plasma concentration of about 0.9:1 (Rodenstein, 1978).

Metabolism: NAC administered orally is quickly absorbed and undergoes rapid and extensive metabolism in the gut wall and liver, resulting in a bioavailability of approximately 10% of the drug itself. From 1 hr after administration, 50% of plasma total NAC is present in a covalently protein-bound form. Analysis of lung tissue samples by the thin-layer chromatography and autoradiography shows the presence at 5 hrs of unchanged drug and metabolites, mainly inorganic sulfate. In patient with respiratory disorders, after an oral dose of ^{35}S-NAC, total plasma radioactivity reaches the peak into 2-3 hrs and remains at high levels for 24 hrs; 14.38% of the dose is excreted in the urine.

Elimination: NAC is timely excreted and approximately 70% of total clearance is nonrenal. Renal clearance is 0.19-0.21 L/hr/kg (Borgstrom, 1986; Olsson, 1988), meanwhile total body clearance is 0.84 L/hr/kg. Following oral administration of 400 mg NAC, the elimination half-life ($t_{½\beta}$), calculating measuring total NAC in non-deproteinized plasma after reductive cleavage of disulfide bonds was 6.25 hrs (Olsson, 1988). In patients with respiratory disorders, after a single oral dose of 100 mg ^{35}S-NAC, the urinary concentration of radioactivity, expressed in terms of total amount of drug and/or percentage of the dose, shows that about 22% of the dose is excreted in the urine after 24 hrs.

Levels of Sulfhydryl Groups (-SH groups): Studies in healthy volunteers showed a significant rise in -SH levels after a single oral dose of 400 mg, and a more sustained rise after 10 days of treatment with 600 mg NAC, compared with placebo (Maddock, 1980).

Toxicology: Toxicological studies have been conducted in rats, mice, dogs and rabbits. NAC was well tolerated at high doses (up to 2000 mg/kg/day) and after prolonged treatment (up to 1 year). In rats and dogs, NAC did not reveal any signs of general toxicity.

Since thiol compounds modify the chemical structure of disulfide-containing peptides and since immunoglobulins are made of heavy and light chains bound by disulfide linkages, a specific question could arise about the effects of NAC on antibody synthesis and immunoglobulins. In mice immunized by sheep red blood cells, after 500 mg/kg/day of NAC for 4 days, there were no effects on antibody synthesis or serum immunoglobulins (Bonanomi, 1980).

Teratogenicity: In doses of 250-1000 mg/kg/day in rats, the fertility in NAC males was altered because of a reduction in the fertilization and fertility index, while the female reproduction potential remained unaffected.

Neither teratogenic activity was observed in rats with doses at 500-2000 mg/kg/day and 250-750 mg/kg/day, respectively, nor were there any effects on the development at newborns where mothers received the drug during pregnancy and suckling.

Clinical Efficacy: The efficacy of NAC has been evaluated in several comparative and non-comparative clinical trials carried out in patients suffering from acute and/or chronic respiratory diseases eg, bronchitis, COPD, cystic fibrosis, atelectasis, with doses ranging between 400 and 600 mg/day (in same cases up to 1800 mg).

Over 4500 patients entered in these clinical trials with NAC. The age of the patients ranged from 4 months to 12 years in children and 19-85 years in adults. The duration of therapy was from 6-21 days in patients with acute respiratory infections (mainly bronchitis) to 10-117 months in those with chronic respiratory conditions.

Tolerability and Safety: The safety profile of Fluimucil A has been widely documented by voluntary reports, post-marketing surveillance studies and by clinical trials carried out during >30 years from the first introduction on the market. All these data show that Fluimucil A is a drug with a high degree of safety.

The clinical experience with high-dose/long-term NAC given systemically for special indications (eg, acetaminophen poisoning or meconium ileus) shows that also in these conditions NAC is well tolerated. NAC has been used up to 12 g daily for several months without gastrointestinal disturbances (Hodson, 1976). In respiratory patients, side effects leading to withdrawal of treatment were no more frequent with NAC than with placebo (Lodola, 1995). A controlled endoscopic and histological study showed that oral NAC administered to patients with full or empty stomach did not cause any lesions.

INDICATIONS: As adjuvant treatment in certain clinical conditions characterized by the presence of thick and viscous mucoid or mucopurulent secretions eg, chronic bronchopulmonary disease (chronic obstructive pulmonary disease, emphysema with bronchitis, chronic asthmatic bronchitis, bronchiectasis).

Acute bronchopulmonary disease (asthma with bronchial mucous plugging, bronchitis, bronchopneumonia, bronchiolitis, pulmonary complications associated with surgery).

Topical Use: Catarrhal otitis, tubal catarrh; mucocrustal and mucopurulent rhinitis, sinusitis, rhinopharyngitis, pharyngo-laryngitis, laryngotracheitis.

NAC is also indicated as a specific antidote in acetaminophen poisoning, in the course of a cyclophosphamide treatment and in hemorrhagic cystitis (in the latter case, it provides SH-groups necessary to inactivate acrolein, a toxic metabolite that affects the urinary mucosae, whilst not interfering with chemotherapy).

DOSAGE & ADMINISTRATION: *Fluimucil: Oral Use:* Dissolve the granules in about ½ glass of water, avoiding the addition of drugs to the solution and taking it before or after meals.

Adults:

Acute Treatment: 1 sachet (200 mg) or 2 sachets (100 mg) 3 times daily for 5-10 days.

Chronic Treatment: 1 sachet (200 mg) 2 times daily or 1 effervescent tab daily for a period of 6 months to obtain the maximum benefit eg, in the prevention of chronic bronchitis excubation. But substantial symptomatic improvement is usually already noticeable in 1-2 months.

Children:

Acute Treatment: ***Up to 2 years:*** ½ sachet (200 mg) or 1 sachet (100 mg); from 2-6 years: 1 sachet (200 mg) or 2 sachets (100 mg) 2 times daily for 5-10 days.

Mucoviscidosis: ***Up to 2 years:*** 50 mg 3 times daily; ***from 2-6 years:*** 100 mg 3 times.

Topical Use: (1 dose = 1 amp). Adults and Children:

Aerosol: 1 dose/day or 2 times a day for 5-10 days or more.

Instillation (Endobronchially): 1 or 2 doses or more per day, according to clinical requirements.

Instillation or Lavage of the Ear, Bladder, Pleura or Other Cavities: ½-1 dose per application.

Systemic Use: 1 amp in deep IM injection daily or 2 times a day according to clinical requirements. For small children, these doses must be halved. Do not use previously opened ampoules for injections. The tolerability of Fluimucil is very good. In topical applications, there are practically no side effects. By the IM route, a slight and transient burning sensation at the site of injection has been reported.

Fluimucil A: ***Adults:*** 1 sachet of Fluimucil A 200 mg or 2 sachets of Fluimucil A 100 mg, 2-3 times a day; 1 effervescent tab a day (preferably in the evening).

Children: 1 sachet Fluimucil A 100 mg 2-4 times a day, according to age.

The duration of treatment should be 5-10 days in the acute treatment, whereas it may be continued in the chronic states for several months, according to the advice of the physician.

Dissolve the tablets as well as the contents of the sachets in a glass containing a small quantity of water, mixing it, if necessary, with a spoon.

A palatable solution is thus obtained, which can be drunk directly from the glass or, in the case of infants, be given with a teaspoon or in a feeding bottle.

Antidote: *Oral* 140 mg/kg followed by 17 times of 70 mg/kg. *IV* 150 mg/kg in 200 mL D5W for 15 min; then a 2nd dose of 50 mg/kg in 500 mL D5W for 4 hrs; then a 3rd of dose 100 mg/kg in 1 L D5W for 16 hrs.

CONTRAINDICATIONS: Hypersensitivity to acetylcysteine.

As Fluimucil A contains aspartame, it is contraindicated in patients suffering from phenylketonuria.

PRECAUTIONS: Patients suffering from bronchial asthma must be strictly controlled during the therapy. Should bronchospasm occur, the treatment must immediately be suspended.

The possible presence of a sulfurous odor does not indicate an alteration of the product but is a characteristic of the active ingredient contained in Fluimucil/Fluimucil A. GSH levels thus contributes to the cellular protection from harmful agents which, through progressive GSH depletion would be able to express their cytotoxic action, as in the case of acetaminophen poisoning. Due to this mechanism of action, NAC is also indicated as a specific antidote in acetaminophen poisoning, in the course of a cyclophosphamide treatment and in haemorrhagic cystitis. (In the latter case, it provides SH-groups necessary to inactivate acrolein, a toxic metabolite that affects the urinary mucosa while not interfering with chemotherapy.)

Impairment of Fertility: In doses of 250-1000 mg/kg/day in rats, the fertility in NAC males was altered because of a reduction in the fertilization and fertility index, while the female reproduction potential remained unaffected.

Fluimucil: Each Fluimucil sachet of 100 mg contains the equivalent of 4.3 g of sucrose and each Fluimucil sachet of 200 mg contains the equivalent of 2.7 g of sucrose; this should be taken into account eg, in diabetic patients.

Fluimucil can be administered concurrently with such antibiotics as amoxycillin, doxycillin, erythromycin and thiamphenicol. When other oral antibiotics or drugs are required, they should be administered 1-2 hrs apart from Fluimucil in order to avoid possible interaction with the thiol group.

ADVERSE REACTIONS: Fluimucil: Unusual type of toxicity has been reported from the prescription experience of oral Fluimucil; slight gastrointestinal disturbance (nausea, dyspepsia, pyrosis) have occurred occasionally.

Fluimucil A: The oral intake of Fluimucil A may occasionally be followed by nausea and vomiting, and in rare cases, by hypersensitivity reactions eg, urticaria and bronchospasm.

The most common side effects involved gastrointestinal disturbances eg, nausea, dyspepsia, diarrhea, stypsis and vomiting.

INTERACTIONS: Possible interaction with thiol group.

Additive effects of oral NAC in combination with inhaled terbutaline have been shown in patients with chronic obstructive pulmonary disease. In another study, no differences were observed between patients receiving oral NAC and NAC plus β_2-agonist aerosols (Minette, 1982).

Interaction studies between oral NAC and antibiotics have demonstrated no effect on the bioavailability of amoxicillin and doxycycline, whereas a slightly reduced absorption of cefalexin was observed (Lualdi, 1979). NAC also failed to affect the bioavailability of ampicillin. A slight but insignificant increase in erythromycin serum levels was seen with NAC co-administration. Absorption of NAC is slightly reduced by bacampicillin but increased by erythromycin (Paulsen, 1988).

CAUTIONS FOR USAGE: Fluimucil: The ampoule containing Fluimucil should be opened immediately before use. Open ampoules must be kept in the refrigerator and used within 24 hrs.

Fluimucil may be administered with common bronchodilators, vasoconstrictors, etc. When local mucolytic and antibiotic treatment is required, it is advisable to administer the 2 drugs separately, or preferably use Fluimucil and thiamphenicol.

The aerosol apparatus used should be made of glass or plastic material. When the apparatus has parts of metal or rubber, these have to be washed with water after use.

Oral Use: Dissolve the granules in about ½ glass of water, avoiding the addition of drugs to the solution and take it before or after meals.

STORAGE: Fluimucil: The storage of the sachets needs no special conditions.

Fluimucil A: Protect from heat and humidity.

Shelf-Life: Tablet: 3 years.

Sachet: 4 years.