FLUIMUCIL® A
600mg granules

N-Acetylcysteine

For oral use

CHARACTERISTICS
N-acetyl-L-cysteine (NAC), the active ingredient of FLUIMUCIL A 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.
Furthermore, NAC, exerts a direct antioxidant action, being provided with a free thiol (-SH nucleophillic) 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 a1-antitrypsin, enzyme inhibitor of elastase, from the inactivation due to the action of hypochlorous add (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 easily cellular membranes. 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 radials, 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 a 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 a haemorrhagic 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).
Absorption
Acetylcysteine absorption after oral administration is rapid and complete.
The bioavailability of free acetylcysteine is only of 10%, due to a high first-pass metabolism.
After administration of a relatively high dose of 30 mg/kg body weight acetylcysteine, total acetylcysteine (free and bound) peak plasma concentration is about 67 nmol/ml, with a tmax of 0.75 -1 hour.
After administration of 600 mg acetylcysteine in the form of tablets, the peak plasma concentration (Cmax) of total acetylcysteine (free and bound) amounts to 3.40 µg/ml (20.83 nmol/ml) with a tmax of 0.71 h (43 minutes). The AUC (area under the curve) is 10.06 µg*h/ml. The effect of food intake on systemic bioavailability after orally administered acetylcysteine has not been tested.
Distribution
Acetylcysteine is found in the body both in unchanged form and as oxidative metabolites, either in free form or reversibly bound to plasma proteins through disulfide bonds. Acetylcysteine is mainly spread within the extracellular aqueous milieu. It is found mostly in the liver, kidneys, lungs and bronchial mucus.
Biotransformation
The metabolic process starts soon after the product administration: acetylcysteine is deacetylated in the intestinal wall through first-pass metabolism to L-cysteine, equally active, and then metabolized to inactive products.
Elimination
Approximately 30% of the administered dose is eliminated directly by renal excretion. The main metabolites are cystine and cysteine, but also small amounts of taurine and sulfates are excreted.
No studies concerning the elimination of the non-renally cleared fraction are available to date. After intravenous administration of 200 mg acetylcysteine in 6 subjects, an elimination half-life of 1.95 (0.95 - 3.57) hours for the reduced forms and of 5.58 (4.1 - 9.5) hours for total acetylcysteine was observed. After administration by oral route of a 400 mg effervescent tablet (not identical to Fluimucil formulations), the half-life of total acetylcysteine amounts to 6.25 (4.59 - 10.6) hours.

THERAPEUTIC INDICATIONS
All respiratory tract diseases leading to the formation of thick secretions difficult to be expectorated, such as acute and chronic bronchitis, laryngitis, sinusitis, tracheitis, influenza, bronchial asthma and (as complementary treatment) mucoviscidosis.

CONTRAINDICATIONS
Hypersensitivity to the active substance acetylcysteine or to any of the excipients according to the composition;
Small children under 2 years;
Active peptic ulcer;

POSOLOGY
Usual posology for acute diseases.
Adolescents over 12 years of age and adults :
One 600mg sachet daily.
Special posologies
Long-term treatment: 400–600 mg daily, divided into one or more administrations, with a maximum treatment duration of 3 - 6 months.
If the excessive mucus production and the consequent cough do not disappear after a two- week treatment, the diagnosis should be re-evaluated in order to exclude a possible malignant disease of the respiratory tract.
Mucoviscidosis: the same dosage as above, however, for children from 6 years of age, 200 mg 3 times daily or 600 mg once daily.

MODALITY OF USE
Dissolve the content of one sachet into a glass of cold or warm water. It is recommended not to dissolve other medicines concomitantly with FLUIMUCIL A.
Effects of food on drug absorption are unknown. Therefore, no recommendations on taking FLUIMUCIL A before or after meals can be made.

The slight sulphur smell emanating from sachet after opening evaporates rapidly, and has no influence on the product efficacy.

WARNING AND PRECAUTIONS
Granules containing 600 mg acetylcysteine: children under 12 years (in children with cystic fibrosis: under 6 years).
The simultaneous administration of an antitussive drug is not reasonable from a

Zambon 1906 — Property of Zambon S.p.A, Via Lillo del Duca 10, 20091 Bresso / Milano		PRODOTTO / BRAND: IS FLUIMUCIL A 600MG BST MY	LATO STAMPA BIANCA/VOLTA (SIDE PRINT FRONT/REAR): LATO BIANCA / FRONT SIDE
CODICE / ITEM: H02V605	ED. / VERSION N.: E01.0218	REV MOCKUP APPROVATO - DATA: N/A	ARTWORK REV: REV6
DATA / DATE: 25/01/2021		CONFORME AL MASTER LAYOUT - NOTE: FI 510 CC	FONT/CORPO MIN./INTERLINEA (FONT/MIN. SIZE/SPACING): HELVETICA NEUE Corpo 9 pt. - Interlinea 9 pt.
DIMENSIONI / SIZE: 135x320	FORM./TECH.CODE/MASTER LAYOUT: FI 510 CC	COLORI / COLORS NO: 2	BRAILLE: N/A
COD. CLIENTE / CUSTOMER CODE: N/A	PHARMA CODE: 1662(XIIXXXXXXX) / EDGE CODE: A-F-0	BLACK; P 390 U	ISTRUZIONI FORNITORE / SUPPLIER INSTRUCTION: N/A
STABILIMENTO / PLANT: CADEMPINO	PACKAGING LINE: N/A		
CHANGE DESCRIPTION: NUOVA GRAFICA / NEW CORPORATE BRAND			

Scale 1:1

Esecuzione impianti: GROWE srl - Vicenza

medical point of view (see «Warnings and precautions»).
Caution is recommended in patients with risk for gastrointestinal haemorrhage (for example, in latent peptic ulcer or oesophageal varices), as orally administered acetylcysteine can induce vomiting.
Due to the risk of bronchospasm, caution is also recommended in patients with bronchial asthma and a hyper-reactive bronchial system.
When hypersensitivity reactions or bronchospasm occur, the medicine should be discontinued immediately, and if necessary appropriate measures must be taken.
The use of acetylcysteine might, mainly at treatment start, fluidify bronchial secretions and promote expectoration. If the patient is not able to effectively expectorate, it can be supported with postural drainage and broncho-aspiration.
Acetylcysteine leads in vitro to an inhibition of diamine oxidase (DAO) by 20-50%. Therefore, caution should be used in patients with histamine intolerance.
The simultaneous administration of antitussive drugs may, by suppressing the cough reflex and the physiological self-cleaning of the respiratory tract, result in congestion of the mucus with risk of bronchospasm and respiratory tract infection.
Mucolytic agents may cause respiratory obstruction in children under 2 years of age. Due to the physiological characteristics of the airways in this age group, the physiological self-cleaning ability may be limited. Therefore, mucolytic agents should not be used in children under 2 years of age (see «Contraindications»).

Excipients of particular interest
Fluimucil granules contain 25 mg resp. 75 mg of aspartame. In case of patients suffering from phenylketonuria it should be considered that aspartame is a source of phenylalanine.
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product, as the pharmaceutical form granules contains glucose and lactose.
Patients with rare hereditary problems of fructose intolerance, e.g. hereditary deficiency of fructose-1,6-diphosphatase, should not take this medicinal product, as the pharmaceutical form granules contains sorbitol (that will be metabolized into fructose).

STATEMENT ON USAGE DURING PREGNANCY AND LACTATION
Pregnancy
Data from a limited number of exposed pregnant women showed no adverse effects on pregnancy or the health of the foetus or the new-born.
No experience from epidemiological studies is available.
Animal studies do not indicate direct or indirect toxicity with any effect on pregnancy, embryonic development, development of the foetus and/or postnatal development.
Caution is indicated when used in pregnancy.

Lactation
There are no studies showing whether or not acetylcysteine passes into breast milk.
Fluimucil should not be used during breastfeeding, unless absolutely necessary

SIDE EFFECTS
The following undesirable effects have been highlighted based on long-term post-marketing experience (after market launch); their frequency cannot be estimated from the available data.
Hypersensitivity, anaphylactic shock, anaphylactic/anaphylactoid reaction;
Headache;
Tinnitus;
Tachycardia;
Haemorrhage;
Bronchospasm, dyspnoea;
Vomiting, diarrhoea, stomatitis, abdominal pain, nausea, dyspepsia;
Urticaria, rash, angioedema, pruritus;
Fever, face oedema;
Blood pressure decreased.
In predisposed patients, hypersensitivity can occur in the form of skin and respiratory organs reactions, and bronchospasm can occur in patients with bronchial asthma and a hyperreactive bronchial system (see «Warnings and precautions»). The occurrence of severe skin reactions such as Stevens-Johnson syndrome and Lyell's syndrome has been very rarely reported in temporal relation to the use of acetylcysteine. In case of new manifestations of cutaneous and mucosal manifestations, a doctor should be consulted immediately, and the use of acetylcysteine should be discontinued. In most of these reported cases, at least one other drug had been used simultaneously and possibly enhanced the observed mucocutaneous effects.
Different studies confirm a decrease in platelet aggregation when using acetylcysteine. The clinical significance of this is still unknown.
The exhaled air may temporarily have an unpleasant odour, probably due to the elimination of hydrogen sulphide from the active substance.

DRUG INTERACTION
There are no *in vivo* interaction studies.
The co-administration of activated charcoal in case of intoxications may reduce the effect of acetylcysteine administered gastrointestinally.
So far, the reports mentioning an inactivation of antibiotics by acetylcysteine relate exclusively to in-vitro tests in which the substances concerned had been directly mixed.
Nevertheless, for safety reasons, the oral administration of antibiotics should be done separately within an interval of at least two hours.
In case of a simultaneous administration of glyceryl trinitrate, the vasodilatory and the inhibiting thrombocytes aggregation effects may be enhanced.
The co-administration of acetylcysteine and carbamazepine may result in subtherapeutic carbamazepine concentrations.
Simultaneous administration of an antitussive: see «Warnings and precautions».

SYMPTOMS AND TREATMENT FOR OVERDOSAGE AND ANTIDOTE(S)
Healthy volunteer subjects were treated with a dose of 11.2 g acetylcysteine/day for 3 months without any serious side effects. Oral doses of up to 500 mg acetylcysteine/kg of body weight were tolerated without symptoms of intoxication.
Overdose may lead to gastrointestinal symptoms such as nausea, vomiting and diarrhoea.
Therapeutic measures in cases of overdose are symptomatic.

STORAGE TEMPERATURE
Store below 30°C, prevent from heat and humidity.

SHELF-LIFE
3 years

PRODUCT DESCRIPTION
FLUIMUCIL A 600 mg white granules with a characteristic orange and slightly sulphureous odour.

NAME AND ADDRESS OF MANUFACTURER
Zambon Switzerland Ltd.
Via Industria, 6814 Cadempino - Switzerland

PACKAGING
- FLUIMUCIL A 20, 30, 60 sachets of 600 mg acetylcysteine.

KEEP OUT OF THE REACH OF CHILDREN

Zambon 1906 — Property of Zambon S.p.A Via Lillo del Duca 10 20091 Bresso / Milano	PRODOTTO / BRAND: **IS FLUIMUCIL A 600MG BST MY**	LATO STAMPA BIANCA/VOLTA (SIDE PRINT FRONT/REAR): **LATO VOLTA / BACK SIDE**
	REV MOCKUP APPROVATO - DATA: **N/A** / ARTWORK REV: **REV6**	
CODICE / ITEM: **H02V605** / ED. / VERSION N.: **E01.0218** / DATA / DATE: **25/01/2021**	CONFORME AL MASTER LAYOUT - NOTE: **FI 510 CC**	FONT/CORPO MIN./INTERLINEA (FONT/MIN. SIZE/SPACING): **HELVETICA NEUE** **Corpo 9 pt. - Interlinea 9 pt.**
DIMENSIONI / SIZE: **135x320** / FORM./TECH.CODE/MASTER LAYOUT: **FI 510 CC**	COLORI / COLORS NO: **2** / BRAILLE: **N/A**	ISTRUZIONI FORNITORE / SUPPLIER INSTRUCTION: **N/A**
COD. CLIENTE / CUSTOMER CODE: **N/A** / PHARMA CODE: **1662(XIIXXXXXXX)** / EDGE CODE: **A-F-0**	BLACK	
STABILIMENTO / PLANT: **CADEMPINO** / PACKAGING LINE: **N/A**	P 390 U	
CHANGE DESCRIPTION: **NUOVA GRAFICA / NEW CORPORATE BRAND**		

Scale 1:1

Esecuzione impianti: GROWE srl - Vicenza