SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FLUIMUCIL 600 mg effervescent tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Fluimucil 600 mg effervescent tablets

Each tablet contains:

Active ingredient

Acetylcysteine	mg	600

Excipients: sodium, aspartame

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Effervescent tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of respiratory tract diseases characterized by a thick and viscous hypersecretion: acute bronchitis, chronic bronchitis and its exacerbations, pulmonary emphysema, mucoviscidosis and bronchiectasis.

Antidotal treatment

Accidental or voluntary acetaminophen poisoning.

Iso- and cyclophosphamide uropathy.

4.2 Posology and method of administration

Treatment of respiratory tract diseases

1 tablet (preferably in the evening). The dosage should not exceed the maximum daily dose of 600 mg. The duration of therapy ranges from 5 to 10 days in acute diseases, whilst in chronic diseases the treatment should be prosecuted, according to the doctor's advice, for some months.

Accidental or voluntary acetaminophen poisoning

Initial oral dose of 140 mg/kg body weight to be administered as soon as possible, within 10 hours of toxic agent ingestion, followed by single doses of 70 mg/kg body weight every 4 hours and for 1-3 days.

Iso- and cyclophosphamide uropathy

In a standard cycle of chemotherapy with iso- and cyclophosphamide at the dose of 1200 mg/m^2 body surface area daily for 5 days every 28 days, N-acetylcysteine can be administered by oral route at the dose of 4 g/day in the days of chemotherapy administration, divided into 4 doses of 1 g.

Instructions for use

Dissolve one tablet into a glass of water, by mixing with a spoon, as needed.

In order to make easier the tablet release, strip away the blister along the lateral cuts.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients.

The product is generally contraindicated during pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Patients suffering from bronchial asthma should be closely monitored during therapy; if bronchospasm occurs, the medication should be immediately discontinued.

Special caution is required if the product is used in patients with peptic ulcer or history of peptic ulcer, especially in case of concomitant administration of other medicines known to cause gastric injury.

Acetylcysteine administration, especially at treatment start, can fluidify bronchial secretions and increase concomitantly their volume. If the patient is unable to expectorate properly, it is necessary to proceed with postural drainage and bronchoaspiration, in order to avoid secreta retention.

Important information about some of the ingredients

Tablets contain a source of phenylalanine, that can be harmful for patients suffering from phenylketonuria.

Tablets contain 156.9 mg sodium per dose and this should be taken into account in case of patients with reduced renal function or on low-sodium diets.

The possible presence of a sulfurous odour is not indicative of a product alteration, but pertains to the specific nature of the active ingredient contained in this preparation.

4.5 Interaction with other medicinal products and other forms of interaction

Drug-drug interaction

Drug-drug interaction studies have only been performed in adult patients.

Antitussive medicines and N-acetylcysteine should not be administered concomitantly, as cough reflex reduction may lead to an accumulation of bronchial secretions.

Activated charcoal may reduce N-acetylcysteine effect.

It is recommended not to mix other medicines with Fluimucil solution.

The available information concerning antibiotics-N-acetylcysteine interaction refers to in vitro tests, that evidenced a decreased antibiotic activity after mixing the two substances. Anyway, as precautionary measure, it is suggested to space the administration of oral antibiotics and N-acetylcysteine over a period of at least two hours.

It has been demonstrated that the concomitant administration of nitroglycerin and N-acetylcysteine induces a significant hypotension and causes the dilatation of the temporal artery, resulting in a possible onset of headache.

Should the concomitant administration of nitroglycerin and N-acetylcysteine be deemed necessary, the patient monitoring is required in view of hypotension onset, which may be even of severe nature, and patients should be warned of the possible onset of headache

Drug-laboratory test interactions

N-acetylcysteine may cause interferences with the colorimetric method for total salicylate assay.

N-acetylcysteine may interfere with the test for the determination of ketones in urine

4.6 Pregnancy and lactation

Although teratology studies carried out in animals with Fluimucil evidenced no teratogenic effects, as with other drugs, the administration during pregnancy and lactation should be performed only when strictly necessary and always under direct medical surveillance.

4.7 Effects on ability to drive and use machines

There are no assumptions nor evidences that the drug may affect the attention capacity and reaction times.

4.8 Undesirable effects

Here below is reported a table relating to the frequency of undesirable effects occurred after administration of N-acetylcysteine by oral route.

System-organ class	Undesirable effects			
	Uncommon (≥1/1,000; <1/100)	**Rare (≥1/10,000;<1/1,000)**	**Very rare (<1/10,000)**	**Not known**
Immune system disorders	Hypersensitivity		Anaphylactic shock, anaphylactic/ anaphylactoid reaction	
Nervous system disorders	Headache			
Ear and labyrinth disorders	Tinnitus			
Cardiac disorders	Tachycardia			
Vascular disorders			Haemorrhage	
Respiratory, thoracic and mediastinal disorders		Bronchospasm, dyspnoea		
Gastrointestinal disorders	Vomiting, diarrhoea, stomatitis, abdominal pain, nausea	Dyspepsia		
Skin and subcutaneous tissue disorders	Urticaria, rash, angioedema, itching			
General disorders and administration site conditions	Pyrexia			Face oedema
Investigations	Reduced arterial pressure			

In very rare cases the onset of severe skin reactions, such as Stevens-Johnson syndrome and Lyell syndrome, was reported to have a temporal relationship with N-acetylcysteine administration.

Although in most cases at least another suspect drug probably most involved in the genesis of the above mentioned mucocutaneous syndromes has been identified, in case of mucocutaneous alterations it is appropriate to contact one's doctor, and the administration of N-acetylcysteine should be immediately discontinued.

Some studies confirmed a reduction of platelet aggregation during N-acetylcysteine administration. The clinical significance of these findings has not been defined yet.

4.9 Overdose

No cases of overdose have been reported with oral administration of N-acetylcysteine.

The administration of a daily dose of 11.6 g N-acetylcysteine for three months in healthy volunteers, did not induce any serious adverse reactions. Doses up to 500 mg NAC / kg body weight administered by oral route were well tolerated, without any sign of intoxication.

Symptoms

Overdose may cause gastrointestinal symptoms such as nausea, vomiting and diarrhoea.

Treatment

No specific antidotal treatments are available; overdose therapy is based on a symptomatic treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Mucolytics - *ATC Code*: R05CB01

Antidotes - *ATC Code*: V03AB23

N-acetyl-L-cysteine (NAC), the active ingredient of Fluimucil, exerts an intense mucolytic-fluidifying action on mucous and mucopurulent secretions by depolimerizing mucoproteic complexes and nucleic acids that give viscosity to the vitreous and purulent component of sputum and other secreta.

In addition, NAC, as such, exerts a direct antioxidant action, being endowed with a nucleophilic free thiol (-SH) group able to interact directly with the electrophilic groups of oxidant radicals. Of particular interest is the recent finding that NAC protects α1-antitrypsin, an elastase-inhibiting enzyme, from the inactivation by hypochlorous acid (HOCl), a potent oxidant agent produced by the myeloperoxidase enzyme of the activated phagocytes. Moreover, its molecular structure allows NAC to easily cross cell membranes. Inside the cell, NAC is deacetylated, thus forming L-cysteine, an amino acid indispensable for glutathione (GSH) synthesis.

GSH is a highly reactive tripeptide, ubiquitously spread in the various tissues of animal organisms, which is essential for the maintenance of the cell functional capacity as well as morphological integrity. In fact, it represents the most important intracellular defence mechanism against oxidant radicals, both exogenous and endogenous, and several cytotoxic substances.

These properties make Fluimucil particularly appropriate for the treatment of acute and chronic respiratory tract diseases characterized by thick and viscous, mucous and mucopurulent secretions.

NAC plays a role of primary importance in the maintenance of adequate GSH levels, thus contributing to the cellular protection against noxious agents that, through a progressive GSH depletion, would be able to fully exert their cytotoxic action, as in the case of acetaminophen poisoning.

Thanks to this mechanism of action, NAC is also indicated as a specific antidote for acetaminophen poisoning and in the course of a cyclophosphamide treatment as well as in haemorrhagic cystitis, since

it provides the -SH groups necessary to inactivate acrolein, the cyclophosphamide metabolite, which is attributed the onset of uropathy in the course of treatment. Due to its antioxidant properties and as a precursor of intracellular glutathione, acetylcysteine exerts also a protective action on respiratory airways, by withstanding oxidant agent injuries.

5.2 Pharmacokinetic properties

Studies performed in humans with labelled acetylcysteine demonstrated a good drug absorption after oral administration. In terms of radioactivity, peak plasma levels are reached after 2-3 hours. The assessments performed on lung tissues, carried out 5 hours after administration, evidence the presence of significant acetylcysteine concentrations.

5.3 Preclinical safety data

Acetylcysteine is characterized by a particularly reduced toxicity. The LD_{50} is higher than 10 g/kg by oral route both in mice and rats, whilst by intravenous route it amounts to 2.8 g/kg in rats and 4.6 g/kg in mice. In long-term treatments, the 1 g/kg/day oral dose has been well tolerated in rats for 12 weeks. The oral administration of 300 mg/kg/day in dogs for a period of one year, induced no toxic reactions. The high-dose treatment in pregnant rats and rabbits during the organogenesis period, did not cause the birth of dysmorphic offspring.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium bicarbonate; Anhydrous citric acid; Lemon flavour; Aspartame

6.2 Incompatibilities

It is recommended not to mix other drugs with Fluimucil.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

Aluminium-polyethylene blisters. Box containing 10 tablets

6.6 Special precautions for disposal and handling

No special requirements.

7. MARKETING AUTHORIZATION HOLDER

ZAMBON S.p.A. - Via Lillo del Duca 10 - 20091 Bresso (MI)

8. MARKETING AUTHORIZATION NUMBER(S)

Fluimucil 600 mg effervescent tablets – 10 tablets

Nafdac Reg. No. B4 -- 2557

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Fluimucil 600 mg effervescent tablets

First authorization: 05/June/2014

10. DATE OF REVISION OF THE TEXT

GG/MM/YYYY