1. NAME OF THE MEDICINAL PRODUCT

Fluimucil effervescent tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One (pharmaceutical form) contains 600 mg Acetylcysteine

Excipient(s):
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Effervescent tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mucolytic agent for the treatment of respiratory system such as bronchitis, emphysema, mucoviscidosis and bronchictasia [1, 2, 3, 4, 5, 6].

4.2 Posology and method of administration

Posology

Adults [8, 9, 10, 11]

600 mg daily.

Method of administration
No interaction with food has been reported; there is no indication regarding product administration before or after the meals.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Children under 18 years of age.
Active peptic ulcer.
Phenylketonuria.
Fluimucil should not be used during breastfeeding.

With caution - Gastric ulcer and duodenal ulcer, esophageal varices, hemoptysis, pulmonary hemorrhage, bronchial asthma, diseases of the adrenal glands, liver and / or renal failure, hypertension.

4.4 Special warnings and precautions for use

Mucolytic agents can induce respiratory obstruction in children under 2 years of age. Due to the physiological characteristics of the airways in this age group, the ability to expectorate may be limited. Therefore mucolytic agents should not be used in children under 2 years of age (see paragraph 4.3 Contraindications).

Caution is recommended when using the product in patients with peptic ulcer or history of it, especially in case of concomitant administration of other medicines with a known irritating effect on the gastric mucosa.

Patients suffering from bronchial asthma must be closely monitored during therapy. Should bronchospasm occur, acetylcysteine must be stopped immediately and appropriate treatment must be initiated.

The administration of acetylcysteine, mainly at treatment start, might fluidify bronchial secretion and increase their volume. If the patient is not able to effectively expectorate, postural drainage and bronchoaspiration should be performed.

Acetylcysteine may moderately affect histamine metabolism, therefore caution should be used when administering the product for long-term therapy in patients with histamine intolerance, since symptoms of intolerance can occur (headache, vasomotor rhinitis, itching) [17, 18].

A mild smell of sulphur does not indicate an alteration of the product but pertains to the specific nature of the active ingredient.

Fluimucil contains aspartame, a source of phenylalanine. May be harmful for people with phenylketonuria.

Subjects suffering from hypertension, who are on a strict salt-free diet, should take into account that 600 mg acetylcysteine effervescent tablet contains about 140 mg of sodium (corresponding to about 350 mg NaCl).

4.5 Interaction with other medicinal products and other forms of interaction

Drug-drug interactions
Antitussive drugs and mucolytic agents, like acetylcysteine, should not be concurrently administered, because the reduction in cough reflex could lead to accumulation of bronchial secretions.

Activated charcoal [19, 20, 21] may reduce the effect of acetylcysteine.

Dissolution of acetylcysteine formulations concomitantly with other drugs is not recommended.

Reports of an inactivation of antibiotics resulting from acetylcysteine so far only relate to in-vitro tests in which the relevant substances were mixed directly. Nevertheless, when other oral drugs or antibiotics are required, it is advisable to administer them 2 hours apart from acetylcysteine [22, 23, 24, 25, 26]. This does not relate to loracarbef [27].

Concurrent administration of nitroglycerin and acetylcysteine has been shown to cause significant hypotension and enhance temporal artery dilation [28, 29]. If concurrent nitroglycerin and acetylcysteine therapy is necessary, patients should be monitored for hypotension, which can be

severe, and warned of the possibility of headaches.

Concurrent use of acetylcysteine and carbamazepine may result in subtherapeutic carbamazepine levels [30].

Paediatric population
Interaction studies have only been performed in adults.

Drug-Lab modifications
Acetylcysteine may cause interference with colorimetric assay method for salicylate measurement [31].
Acetylcysteine may interfere with urine ketone test [32].

4.6 Fertility, pregnancy and lactation [33]

Pregnancy
There are limited clinical data from the use of acetylcysteine in pregnant women.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of Fluimucil during pregnancy. Prior to use in pregnancy, the potential risks should be balanced against the potential benefits [34]
.

Lactation
It is unknown whether acetylcysteine/metabolites are excreted in human milk.
A risk to the suckling child cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Fluimucil therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
No data are available on the effect of acetylcysteine on human fertility. Animal studies do not indicate harmful effects with respect to fertility for humans at the recommended doses (see section 5.3).

4.7 Effects on ability to drive and use machines

Acetylcysteine has no known influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most frequent adverse events associated with the oral administration of acetylcysteine are gastrointestinal in nature [25]. Hypersensitivity reactions including anaphylactic shock, anaphylactic/anaphylactoid reaction, bronchospasm, angioedema, rash and pruritus have been reported less frequently [23].
Tabulated list of adverse reactions
In the table below adverse reactions are listed by system organ class and frequency (very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

	Uncommon (>1/1,000 to <1/100)	**Rare** (≥1/10,000 to <1/1,000)	**Very rare** (<1/10,000)	**Unknown**
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, pruritus			
General disorders and administration site conditions	Pyrexia			Face oedema
Investigations	Blood pressure decreased			

Description of selected adverse reactions

In very rare cases, the occurrence of severe skin reactions such as Stevens-Johnson syndrome and Lyell's syndrome has been reported in temporal connection with the administration of acetylcysteine. In most cases at least one co-suspect drug more probably involved in triggering the reported mucocutaneous syndrome could be identified. Because of this, medical advice should be sought straight away if any new changes to the skin or mucous membranes occur, and acetylcysteine should be stopped immediately.

A decrease in platelet aggregation in the presence of acetylcysteine has been confirmed by various investigations. The clinical significance has not yet been established.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

Healthy volunteers received 11.2 g acetylcysteine daily for three months without any serious undesirable effects. Oral doses of up to 500 mg acetylcysteine / kg body weight were tolerated without any symptoms of poisoning [35, 36].

Symptoms
Overdoses may lead to gastrointestinal symptoms, such as nausea, vomiting and diarrhea.

Treatment
There is no specific antidote for acetylcysteine and treatment is symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: mucolytics ATC code R05CB01

Mechanism of action and pharmacodynamics effects

Acetylcysteine [N-acetyl-L-cysteine (NAC)] exerts marked mucolytic-fluidifying action on mucous and mucopurulent secretions by depolymerising mucoproteic complexes and nucleic acids which increase the viscosity to the vitreous and purulent component of sputum and other secreta [37, 38, 39, 40]. Additional properties are: reduction of induced hyperplasia of mucous cells [41, 42 43], increase in surfactant production by stimulation of type II pneumocytes , stimulation of mucociliary activity, leading to improved mucociliary clearance [44, 45, 46].

Acetylcysteine also exerts a direct antioxidant action, being endowed with a nucleophilic free thiol group (-SH) able to interact directly with the electrophilic groups of oxidizing radicals [47, 48]. Particularly interesting is the finding that acetylcysteine protects α1-antitripsin, an elastaseinhibiting enzyme, from the inactivation by hypochlorous acid (HOCl), a potent oxidizing agent produced by the myeloperoxidase enzyme of activated phagocytes [49, 50].

Moreover, its molecular structure enables acetylcysteine to easily cross cell membranes. Inside the cell, acetylcysteine is deacetylated, thus yielding L-cysteine, an amino acid indispensable for glutathione (GSH) synthesis [51]. Acetylcysteine exerts in addition an indirect antioxidant effect through its role as GSH precursor. 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 is the most important intracellular defence mechanism against oxidizing radicals, both exogenous and endogenous, and several cytotoxic substances, including paracetamol.
Paracetamol exerts its cytotoxic action through progressive GSH impoverishment [49]. Acetylcysteine plays its primary importance role by maintaining of adequate GSH levels, thus contributing to the cellular protection. Therefore acetylcysteine represents a specific antidote for paracetamol poisoning [52, 53].

Clinical efficacy and safety

The mucolytic effect of acetylcysteine was clinically demonstrated in several placebo-controlled clinical trials. Brocard et al. [9] evaluated the mucolytic activity of acetylcysteine in a double-blind, placebo-controlled, study involving 215 patients with following diagnoses; acute bronchitis (84), superinfections of chronic bronchitis (95), complication bronchitis in patients with severe chronic respiratory insufficiency (36). Patients received 1 sachet of 200 mg acetylcysteine three times daily or placebo for 10 days. In addition all patients received standard antibiotic therapy (amoxicillin) for 7 days. Statistical analysis comparing sputum volume and viscosity showed that acetylcysteine was very significantly more effective than placebo.
A large multicentre study was performed to assess the efficacy of acetylcysteine 200 mg b.i.d. in 495 patients (254 acetylcysteine; 241 placebo) with chronic bronchitis over 6 months [10]. The results of the study demonstrated that mean monthly scores for sputum characteristics, difficulty in expectorating and severity of cough generally kept declining from start to end of the 6th month. This general trend was also seen in the placebo group; however, treatment with acetylcysteine involved a very significantly greater decline in monthly scores for each character of sputum, effort of expectoration and cough severity. After 6 month on acetylcysteine, mean scores for sputum

volume, thickness and purulence reached value of 1 or less, implying 'least altered' and in a proportion of cases 'no sputum'. This indicated that long-term acetylcysteine on average substantially abolished the bronchial mucus hypersecretory state and its attendant symptoms in the study population. The basic course of the disease improved significantly ($p<0.001$) in the patients receiving acetylcysteine compared to the placebo group, both in overall scores and in increasingly divergent scores over successive months.

The anti-oxidant effect of acetylcysteine was suggested as possible explanation for the results obtained in the study by Stav et al. [6]. In this study, acetylcysteine 1200 mg daily for 6 weeks was compared to placebo in 24 patients with COPD. Results demonstrated that the use of acetylcysteine was significantly associated with an improvement in inspiratory capacity and in Forced expiratory Vital Capacity (FVC), probably due to a reduction in air trapping.
The use of acetylcysteine has been evaluated as oral or aerosolized treatment also in subjects with idiopathic pulmonary fibrosis. In the IFIGENIA [54] study, one year of treatment with acetylcysteine 600 mg x 3 in addition to standard treatment of IPF (prednisone and azathioprine) preserved the vital capacity and single-breath carbon monoxide diffusing capacity (DLco) in such a population. The study of Tomioka et al. [55] compared inhalation therapy with acetylcysteine and bromhexine hydrochloride as control group; treatments were administered for 12 months. Acetylcysteine demonstrated to delay disease progression as evidenced by exercise desaturation, high-resolution CT, and serum KL-6, without influencing pulmonary function and quality of life.
Two studies evaluated acetylcysteine treatment in subjects affected by cystic fibrosis [56, 57]. In both these studies, acetylcysteine was administered at a very high dosage (up to 3000 mg daily for 4 weeks), without significant toxicity. The anti-oxidant efficacy of acetylcysteine was associated with a marked decrease sputum elastase activity, the strongest predictor of pulmonary function in subjects affected by cystic fibrosis. Additionally, neutrophil burden in the airways was decreased upon treatment as was the number of airways neutrophils actively releasing elastase-rich granules [56].

Paediatric population

Within the clinical development program, several studies have examined the efficacy and the safety of oral acetylcysteine in paediatric patients.
Miranda Ribeiro et al. [12] studied the use of oral acetylcysteine in the treatment of bronchial diseases in paediatric patients using an open, non-comparative study design. Eighty patients were studied. The mean age was 2.9 years (23 days to 11 years). Acetylcysteine was administered orally at 10-50 mg/kg/day in 2 to 3 divided doses for 7 to 110 days (mean duration 26.7 days). Excellent or good clinical results were achieved in 59 patients (88% of the evaluable population) and good radiological results in 55 patients (82%). Clinical and radiological results indicated that oral acetylcysteine was very useful in the treatment of paediatric patients with respiratory diseases.
Nikolic [13] evaluated the influence of acetylcysteine on respiratory functions in a study performed in 20 patients aged 3 to 14 years suffering from various acute recurrent bronchitis. Antibiotics were used only in the acute phase of febrile bronchitis and no other drugs were given during treatment with acetylcysteine, which was administered orally for 4 days at the dose of 100 or 200 mg t.i.d. depending on age. Some patients underwent spirometry but some did not cooperate and were observed only clinically. Results obtained with acetylcysteine showed that the duration of catarrhal throat inflammation and clinical signs of bronchitis was shortened. Removal of mucus by using acetylcysteine helps to heal the catarrhal process. After 4 days of acetylcysteine treatment, values of vital capacity and pulmonary air flow returned to normal in patients with simple or recurrent catarrhal bronchitis, and remained unchanged in patients with bronchial allergy.
Rudnik et al. [14] carried out 3 uncontrolled trials to assess efficacy and safety of oral acetylcysteine (50 mg b.i.d. to 200 mg t.i.d.) for 4 weeks in 58 children with chronic lung disease. In particular the first study evaluated chest clinical findings and chest X-ray in 46 children aged 2 months to

12 years. Favourable effects were obtained in 41 children, with disappearance of clinical symptoms in 17 and improvement in 24 children. Disappearance or reduction of chest X-ray pathological findings were also reported in 15 cases. Only in 5 children no improvement was observed.
Szekely [15] treated 20 children aged 6 to 12 years with bronchoscopically ascertained chronic bronchitis with 100 mg t.i.d. acetylcysteine for 37 days. During the study no other medication was given, except in case of fever with antipyretics. Cough disappeared in all patients by the end of the first week of treatment. Regression of mucus membrane inflammation in 10 patients, cessation of hypersecretion in 2 patients, confirmed the therapeutic effectiveness of oral acetylcysteine.

5.2 Pharmacokinetic properties

Absorption
In humans, acetylcysteine is completely absorbed after oral administration. Because of the gut wall metabolism and first-pass effect, the bioavailability of acetyl cysteine taken orally is very low (approx 10%) [58, 59]. No differences were reported for the various pharmaceutical forms [60, 61]. In patients with various respiratory or cardiac diseases, the maximum plasma concentration is obtained between two and three hours after administration and the levels remained high over a period of 24 h [62].

Distribution
Acetylcysteine is distributed both in the non-metabolized (20%) and the metabolized (active) (80%) form, and can mainly be found in the liver, kidneys, lungs and bronchial secretions [63, 51]. The volume of distribution of acetylcysteine ranges from 0.33 to 0.47 L/kg. Protein binding is about 50% four hours after the dose and decreases to 20% at 12 h [58, 59, 61].

Biotransformation
Acetylcysteine undergoes rapid and extensive metabolism in the gut wall and liver following oral administration [60].
The resulting compound, cysteine, is considered to be an active metabolite. Following this stage of transformation, acetylcysteine and cysteine share the same metabolic route [64].

Elimination
Renal clearance may account for about 30% of total body clearance. Following oral administration the terminal half-life of total acetylcysteine is 6.25 (4.59 – 10.6) h [59, 23].

Linearity/non-linearity
The pharmacokinetics of acetylcysteine is proportional to the administered dose in the dose range between 200-3200 mg/m^2 for AUC and C_{max} [35].

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development. In acute toxicity studies, oral LD_{50} values were determined at 8 and > 10 g/kg bw for mice and rats, respectively [65].

In prolonged treatments a dosage of 1g/kg/day orally has been well tolerated in rats for 12 weeks [66]. In dogs the oral administration of 300 mg/kg/day for the duration of 1 year has not determined toxic reactions [67].
Acetylcysteine was considered to be not genotoxic based on results from in vitro and in vivo tests [68, 69, 70, 71].

Reproduction studies were performed in rats at oral doses up to 2000 mg/kg/day and in rabbits at oral doses up to 1000 mg/kg/day and revealed no evidence of impaired female fertility or harm to the fetus due to acetylcysteine [72, 73, 74]. Also the treatment of male rats with acetylcysteine at an oral dose of 250 mg/kg/day for 15 weeks did not affect the fertility or general reproductive performance of the animals [75].

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid 680 mg, sodium bicarbonate 500 mg, aspartame 20 mg, lemon flavor 100 mg

Composition of lemon flavouring: flavouring 2.4%, dextrose 60%, maize maltodextrin 32%, arabic gum E414 3%, modified waxy maize starch E1450 2.5%, ascorbic acid E300 0.1%

6.2 Incompatibilities

Acetylcysteine containing products must not be mixed with other medicinal products.

6.3 Shelf life

3 years

6.4 Special precautions for storage

At temperature below 25°C

6.5 Nature and contents of container

Not all pack sizes may be marketed.

600 mg effervescent tablets: 10, 20

7. MARKETING AUTHORISATION HOLDER

Zambon SpA, Italy

Via Lillo del Duca, 10 – 20091 Bresso (MI)

8. MARKETING AUTHORISATION NUMBER(S)

37561, 45179, 57279 (Swissmedic).

9. DATE OF FIRST AUTHORISATION

05/07/1993

10. DATE OF REVISION OF THE TEXT

10/20/2015

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