FLUIMUCIL
100mg/5ml

Oral solution
N-Acetylcysteine

QUALITATIVE AND QUANTITATIVE COMPOSITION
100 ml oral solution contains:
Active principle
N-acetylcysteine 2.00 g
Excipients with known effects: sodium, sodium benzoate, methyl parahydroxybenzoate, ethanol, propylene glycol.
For the full list of excipients, see List of Excipient.
PHARMACEUTICAL FORM
Oral Solution.
PRODUCT DESCRIPTION
Clear or slightly opalescent, colourless solution with a characteristics odour of raspberry.
CLINICAL PARTICULARS
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.
Posology and method of administration
Usual posology for acute diseases
Adults: 600 mg daily, divided into one or more administrations. (e.g., 10 ml 3 times daily or 30 ml daily).
Adolescents over 12 years of age: 600 mg daily, divided into one or more administration (e.g., 10 ml 3 times daily or 30 ml daily).
Children from 2 to 12 years of age: 300 mg (e.g., half measuring cup (5 ml) 3 times daily) or 400 mg (e.g., one 10 ml measuring cup twice times 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.
Method of administration
For Oral use.
No interactions with food have been reported; there are no indications concerning administration of the medicinal product before or after meals.
Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in List of Excipients
Infants (under 2 years of age).
Special warnings and precautions for use
A productive cough must not be suppressed since this is a fundamental part of the bronchopulmonary defence mechanism.
The combination of a mucolytic with a cough suppressant medicine and/or a substance that dries out secretions (atropinic drug) is not rational.
Mucolytic agents can cause excessive bronchial congestion in infants. This is because their bronchial mucus drainage capacities are limited by the specific physiological characteristics of their airways. These agents must not be used in infants therefore (see Contraindications).
Caution is advised when the product is used in patients with a peptic ulcer or a history of peptic ulcer disease, especially when used concomitantly with other medicinal products known to irritate the mucous membrane of the gastrointestinal tract.
Patients with bronchial asthma must be closely monitored during treatment. In the event of bronchospasm, acetylcysteine must be stopped immediately and appropriate treatment initiated.
Bronchial secretions may become more fluid and increase in volume, particularly at the start of treatment with acetylcysteine. If a patient is unable to cough up the secretions effectively, postural drainage and bronchoaspiration should be performed.
Acetylcysteine may have a moderate effect on histamine metabolism; consequently, caution is required if this medicinal product is given as long-term treatment in patients with histamine intolerance due to the potential development of intolerance symptoms (headaches, vasomotor rhinitis, pruritus).
A mild sulfur odour does not indicate a change in the medicinal product, but is a property of the active substance itself.
This medicinal product contains methyl parahydroxybenzoate (E218) and may cause allergic reactions (possibly delayed).
This medicinal product contains 38.21 mg sodium per 10-mL measuring cup, equivalent to 1.9% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
This medicinal product contains 15 mg of sodium benzoate per 10-mL measuring cup.
This medicinal product contains 4.88 mg of alcohol (ethanol) per 10-mL measuring cup. The quantity per 10-mL measuring cup of this medicinal product is equivalent to at least 1 mL of beer or 1 mL of wine. The small quantity of alcohol in this medicinal product is not likely to cause any noteworthy effects.
This medicinal product contains 23.4 mg of propylene glycol per 10-mL measuring cup.
Treatment must be re-assessed if the symptoms or condition persist or worsen

Interaction with other medicinal products and other forms of interaction
Mucolytics such as acetylcysteine should not be administered concomitantly with antitussive medicinal products, because a reduction in the cough reflex could cause an accumulation of bronchial secretions.
Activated charcoal can decrease the effect of acetylcysteine.
Simultaneous dissolution of acetylcysteine formulations with other medicinal products is not recommended.
To date, the inactivation of antibiotics by acetylcysteine has been reported only in *in vitro* tests, whereby the relevant substances were mixed directly with each other. However, if oral antibiotics or other medicinal products are required, it is advised that these should be taken 2 hours before or after acetylcysteine. This does not apply to loracarbef.
It has been shown that the concomitant use of nitrate derivatives and acetylcysteine can cause severe hypotension and an increase in vasodilation of the temporal artery. If concomitant administration of a nitrate derivative and acetylcysteine is necessary, patients must be monitored to detect any hypotension, which could potentially be severe. They must also be warned that they may develop headaches.
The concomitant use of acetylcysteine and carbamazepine can result in sub-therapeutic carbamazepine concentrations.
Paediatric population
Interaction studies have only been conducted in adults.
Laboratory test changes
N-acetylcysteine may interfere with the colorimetric analysis method used to assay salicylates.
N-acetylcysteine may interfere with assay of ketonuria.
Fertility, pregnancy and lactation
Pregnancy
There are limited data about the use of acetylcysteine in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.
As a precautionary measure, it is preferable to avoid the use of Fluimucil Syrup during pregnancy.
The benefit-risk balance should be assessed before using the product during pregnancy.
Breast-feeding
It is not known whether acetylcysteine and its metabolites are excreted in breast milk.
A risk to the breastfed infant cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Fluimucil Syrup therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.
Fertility
There are no data available concerning the effect of acetylcysteine in human fertility. Animal studies do not indicate any harmful effects with respect to human fertility at the recommended dose.
Effects on ability to drive and use machines
N-acetylcysteine has no effect on the ability to drive vehicles or use machines.
Undesirable effects
Summary of the safety profile
The adverse effects most commonly associated with the oral administration of N-acetylcysteine are gastrointestinal. Hypersensitivity reactions including anaphylactic shock, anaphylactic/anaphylactoid reactions, bronchospasm, angioedema, rash and pruritus have been reported less frequently.
Summary table of undersiarble effects
The table below lists the undersirable effects recorded according to system/ organ class and frequency: very common (≥ 1/10), common (≥ 1/100 - < 1/10), uncommon (≥ 1/1,000 - < 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 group, undesirable effects are presented in order of decreasing seriousness.

Zambon 1906 Property of Zambon S.p.A Via Lillo del Duca 10 20091 Bresso / Milano			PRODOTTO / BRAND: **IS FLUIMUCIL 2% SCR - MALESIA**
			REV MOCKUP APPROVATO - DATA: **N/A** / ARTWORK REV: **REV3**
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DIMENSIONI / SIZE: **150x432/216**		FORM./TECH.CODE/MASTER LAYOUT: **IS040 AV-A**	COLORI / COLORS NO: **2** / BRAILLE: **NO**
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CHANGE DESCRIPTION: **NUOVA ISTRUZIONE / NEW LEAFLET**			

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System organ class	Adverse reactions			
	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <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			Haemorrhages	
Respiratory, thoracic and mediastinal disorders		Bronchospasm, dyspnea		
Gastrointestinal disorders	Vomiting, diarrhoea stomatitis, abdominal pain, nausea	Dyspepsia		
Skin and subcutaneous tissue disorders	Urticaria, rash, angioedema, pruritus			
General disorders and administration site conditions	Fever			Facial oedema
Investigations	Low blood pressure			

There is also a risk of worsening of bronchial congestion, especially in infants and in certain patients incapable of effective expectoration.

Description of some adverse reactions

Severe skin reactions such as Stevens-Johnson syndrome and Lyell's syndrome have been reported in very rare cases with a chronological connection with the use of acetylcysteine. In most cases, at least one other suspect medicinal product that was more likely to have been the cause of the mucocutaneous syndrome could be identified. In the event of the recent onset of cutaneous or mucosal reactions, medical advice should be sought and the treatment with acetylcysteine should be discontinued immediately.

A decrease in platelet aggregation in the presence of acetylcysteine has been confirmed in various studies. The clinical significance of this has not yet been determined.

Overdose

Healthy volunteers were treated for three months with an oral dose of 11.2 g of acetylcysteine per day without any serious undesirable effects being observed. Oral doses of up to 500 mg acetylcysteine per kg body weight have been tolerated without any signs of toxicity.

Symptoms

Overdose may lead to gastrointestinal effects such as nausea, vomiting and diarrhoea.

Treatment

There are no antidotes to acetylcysteine and treatments are symptomatic.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: mucolytics, ATC: R05CB01

N-acetyl-L-cysteine (NAC), the active substance of Fluimucil, has an intense mucolytic-fluidifying action on mucous and mucopurulent secretions. It depolymerises the mucoprotein complexes and the nucleic acids that confer viscosity to the glassy and purulent elements of the sputum and other secretions.

NAC, as such, also has a direct antioxidant action because it has a free nucleophilic thiol group ((SH) that can interact directly with the electrophilic groups of oxidising radicals. The recent evidence showing that NAC protects α1-antitrypsin (an elastase-inhibiting enzyme) from inactivation by hypochlorous acid (HOCl), a powerful oxidising agent produced by the myeloperoxidase enzyme of activated phagocytes, is particularly interesting. The molecule's structure allows it to easily cross cellular membranes. Inside the cell, NAC is de-acetylated and L-cysteine becomes available - this amino acid is essential for glutathione synthesis (GSH).

GSH is a highly reactive tripeptide that is ubiquitously present in the various tissues of animals. It is essential for maintaining the cell's capacity to function and its morphological integrity, because it is the most important intra-cellular defence mechanism against oxidising radicals (endogenous or exogenous) and against many cytotoxic substances.

These activities make Fluimucil particularly suitable for treating acute and chronic infections of the airways characterised by thick, viscous mucous and mucopurulent secretions.

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 acetylcysteine taken orally is very low (approx. 10%). No differences were reported for the various pharmaceutical forms. In patients with various respiratory or cardiac diseases, the maximum plasma concentration (C_{max}) is obtained between 2 to 3 hours after administration and the levels remained high over a period of 24 hours.

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.

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.

Acetylcysteine crosses the placenta.

Biotransformation

Acetylcysteine undergoes rapid and extensive metabolism in the gut wall and liver following oral administration.

The resulting compound, cysteine, is considered to be an active metabolite. Following this stage of transformation, acetylcysteine and cysteine share the same metabolic route.

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 to 10.6) hours.

Linearity/non-linearity

The pharmacokinetics of acetylcysteine is proportional to the administered dose in the dose range between 200-3200 mg/m2 for area under the plasma concentration time curve (AUC) and $C_{max.}$

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, the oral LD50 values were determined as 8 g/kg and > 10 g/kg in mice and rats, respectively.

In prolonged administration for 12 weeks, a dose of 1 g/kg/day by the oral route was well tolerated in rats. In dogs, the oral administration of 300 mg/kg/day for a period of one year did not result in toxic reactions.

Acetylcysteine was considered to be non-genotoxic on the basis of *in vitro* and *in vivo* studies.

Reproductive studies were conducted in rats at oral doses of up to 2,000 mg/kg per day and in rabbits at oral doses of up to 1,000 mg/kg per day; they did not demonstrate any impairment in female fertility or harmful effects on the foetus due to acetylcysteine. In addition, the treatment of male rats with acetylcysteine at an oral dose of 250 mg/kg per day for 15 weeks did not affect the fertility or general reproductive performance of the animals

PHARMACEUTICAL PARTICULARS

List of excipients

Methyl para-hydroxybenzoate, sodium benzoate, disodium edetate, sucralose, carmellose sodium, saccharin sodium, raspberry flavour (containing Propylene glycol , ethyl alcohol and flavouring substances), sodium cyclamate, sodium hydroxide, purified water.

Incompatibilities

Not applicable.

Shelf life

2 years.

Special precautions for storage

Store below 25 °C.

After opening: Do not store for more than 15 days.

Nature and contents of container

Glass bottle containing 100 ml and 200 ml of syrup.

Box with 1 bottle, supplied with measuring cup

Special precautions for disposal and other handling

Rinse the measuring cup after use

Recap the bottle after use.

Name and Address of Manufacturer

Zambon S.p.A. - Via Della Chimica, 9 - 36100 Vicenza - Italy

DATE OF REVISION

29 December 2022

Zambon 1906
Property of
Zambon S.p.A
Via Lillo del Duca 10
20091 Bresso / Milano

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