UNILAB

Acetylcysteine

Exflem®

200 mg Powder for Oral Solution

MUCOLYTIC

Rx

FORMULATION

Each sachet contains:

Acetylcysteine ....200 mg

PHARMACEUTICAL FORM

Powder for oral solution.

CLINICAL PARTICULARS

Therapeutic Indications

Secretolytic therapy in acute and chronic bronchopulmonary diseases accompanied by impaired formation and transport of mucus.

DOSAGE AND METHOD OF ADMINISTRATION

If not otherwise prescribed, the following dosage is recommended for acetylcysteine:

Adults and adolescents from 14 years of age
1 powder sachet 2-3 times daily (equivalent to 400 - 600 mg acetylcysteine/day)

Children and adolescents 6-14 years of age
1 powder sachet twice daily (equivalent to 400 mg acetylcysteine/day)

Method of administration
Acetylcysteine is to be taken dissolved in a glass of water after meals.

Duration of use
Acetylcysteine should not be taken for more than 4-5 days without medical advice.

In case of chronic bronchitis and mucoviscidosis, longer-term treatment should be performed in order to achieve infection prophylaxis.

CONTRAINDICATIONS

- Hypersensitivity to acetylcysteine or to any of the excipients
- Active peptic ulceration
- Children below 2 years of age

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Patients with bronchial asthma must be closely monitored during therapy. If bronchospasm occurs, the use of acetylcysteine must be stopped immediately and appropriate treatment initiated.

Caution is advised when using this product in patients with a history of ulcers, particularly if additional drugs are being taken that are known to irritate the mucous membranes of the gastrointestinal tract.

The use of acetylcysteine, especially in early treatment can lead to liquefaction and thus to an increase in volume of bronchial secretions. If the patient is unable to expectorate (sufficiently expectorate), appropriate measures (such as drainage and aspiration) should be performed.

The occurrence of severe skin reactions such as Stevens-Johnson syndrome and Lyell's syndrome has very rarely been reported in temporal connection with the use of acetylcysteine. If cutaneous and mucosal changes newly occur, medical advice should be sought without delay and use of acetylcysteine be terminated (see also Undesirable effects).

Caution is advised in patients with histamine intolerance. Treatment with acetylcysteine for longer periods should be avoided in such patients, as acetylcysteine affects histamine metabolism and can result in symptoms of intolerance (e.g. headache, runny nose, itching).

Children and adolescents
Mucolytics can result in blockage of the respiratory tract in children under 2 years of age, due to the characteristics of their respiratory tract and their limited ability to cough up mucus. Therefore, mucolytics must not be used in children under 2 years of age (see Contraindications).

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Combined administration of acetylcysteine with antitussives may cause a dangerous secretory congestion due to the reduced cough reflex, so that an especially careful diagnosis is required for this combination treatment.

Reports to date on an inactivation of antibiotics due to acetylcysteine exclusively refer to *in vitro* experiments in which the relevant substances were mixed directly. Nevertheless for safety reasons, oral antibiotics should be administered separately and at an interval of at least 2 hours. This does not apply to cefixime and loracarbef.

Acetylcysteine/glyceryl trinitrate
The concomitant administration of acetylcysteine can potentially result in an intensification of the vasodilatory and inhibition of platelet aggregation effects of glyceryl trinitrate (nitroglycerine).

If concomitant treatment with glyceryl trinitrate and acetylcysteine is considered necessary, patients should be monitored for the possible development of hypotension, which can be serious, and advised of the possibility of headaches.

Activated carbon in high doses (as an antidote) can reduce the effectiveness of acetylcysteine.

Changes in the determination of laboratory parameters
Acetylcysteine can affect the colorimetric determination of salicylates.

In urine tests, acetylcysteine can affect the results of determinations of ketone bodies.
The dissolution of acetylcysteine formulations together with other medicinal products is not recommended.

Pregnancy and lactation

Pregnancy
No sufficient data on exposed pregnant women are available for acetylcysteine. Experimental animal studies do not suggest direct or indirect harmful effects on pregnancy, embryonal/foetal development, birth or postnatal development (see also Preclinical safety data). Acetylcysteine should be used during pregnancy after strict assessment of the benefit-risk ratio.

Lactation
No information is available regarding excretion into breast milk. Acetylcysteine should be used during lactation only after strict assessment of the benefit-risk ratio.

Fertility
No data are available on the effect of acetylcysteine on human fertility. In animal studies, no adverse effects on fertility were observed at therapeutic doses of acetylcysteine (see Preclinical safety data).

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

UNDESIRABLE EFFECTS

The evaluation of adverse reactions is based on the following information on frequencies:

Very common:	(≥ 1/10)
Common:	(≥ 1/100 up to < 1/10)
Uncommon:	(≥ 1/1,000 up to < 1/100)
Rare:	(≥ 1/10,000 up to < 1/1,000)
Very rare:	(< 1/10,000)
Not known:	(cannot be estimated from the available data)

Immune system disorders

Uncommon:	Hypersensitivity reactions

Very rare: Anaphylactic shock, anaphylactic/anaphylactoid reactions

Nervous system disorders
Uncommon: Headache

Ear and labyrinth disorders
Uncommon: Tinnitus

Cardiac disorders
Uncommon: Tachycardia

Vascular disorders
Very rare: Hemorrhage

Respiratory, thoracic and mediastinal disorders
Rare: Dyspnoea, bronchospasm

Gastrointestinal disorders
Uncommon: Nausea, vomiting, diarrhoea, abdominal pain, stomatitis
Rare: Dyspepsia

Skin and subcutaneous tissue disorders
Uncommon: Urticaria, rash, angioedema, itching, exanthema

General disorders and administration site conditions
Uncommon: Fever
Not known: Facial edema

Investigations
Uncommon: Hypotension

In very rare cases, severe skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in temporal association with the use of acetylcysteine. In most of these reported cases, at least one additional drug that could potentially have intensified the described mucocutaneous effects was being taken at the same time.

If skin or mucous membrane abnormalities develop, medical advice should therefore immediately be sought and the use of acetylcysteine discontinued.

A decreased blood platelet aggregation in the presence of acetylcysteine has been confirmed by different studies. The clinical relevance has not yet been clarified to date.

Overdose

No case of toxic overdose has been observed to date in association with oral pharmaceutical forms of acetylcysteine. Volunteers were treated with a dose of 11.6 g acetylcysteine/day over 3 months without observing any severe side effects. Oral doses up to 500 mg acetylcysteine/kg BW were tolerated without any symptoms of intoxication.

Symptoms of intoxication
Overdoses may lead to gastrointestinal symptoms, such as nausea, vomiting and diarrhoea. Infants are at risk of hypersecretion.

Therapy of intoxication
If necessary, according to the symptoms.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: mucolytics
ATC Code: R05CB01

Acetylcysteine is a derivative of the amino acid cysteine. The efficacy of acetylcysteine is secretolytic and secretomotoric in the area of the respiratory tract. It is discussed that it splits off the interconnecting disulphide bonds between the mycopolysaccharide chains and that it has a depolymerizing effect on DNA-chains (in purulent mucus). Due to these mechanisms, the viscosity of mucus should be reduced.

An alternative mechanism of acetylcysteine is meant to be based on the capacity of its reactive SH group to bind chemical radicals and to detoxify them in this way.

Furthermore, acetylcysteine contributes to an increase in glutathione synthesis, which is important for the detoxification of noxae. This provides the explanation for its antidotal effect in paracetamol intoxication.

Pharmacokinetic properties

Absorption

Following oral administration, acetylcysteine is rapidly and almost completely absorbed and metabolized in the liver to cysteine, the pharmacologically active metabolite, as well as to diacetylcystine, cystine and further mixed disulphides.

Distribution

Due to the high first-pass effect, the bioavailability of orally administered acetylcysteine is very low (approx. 10%). In humans, maximum plasma concentrations are achieved after 1-3 hours with the maximum plasma concentration of the metabolite cysteine in the range of approx. 2 µmol/L. The protein binding of acetylcysteine was determined to be about 50%.

Biotransformation

Acetylcysteine and its metabolites occur in three different forms in the organism: partially in free form, partially bound to proteins via labile disulphide bonds and partially as incorporated amino acid. Acetylcysteine is excreted almost exclusively in the form of inactive metabolites (inorganic sulphates, diacetylcystine) via the kidneys. The plasma half-life of acetylcysteine is approximately 1 hour and is mainly determined by the rapid hepatic biotransformation. Impaired hepatic function therefore leads to prolonged plasma half-lives of up to 8 hours.

Elimination

Pharmacokinetic studies with intravenous administration of acetylcysteine revealed a distribution volume of 0.47 L/kg (in total) or 0.59 L/kg (reduced); the plasma clearance was determined to be 0.11 L/h/kg (in total) and 0.84 L/h/kg (reduced), respectively.

No knowledge is available concerning the behaviour of acetylcysteine at the blood-brain barrier in humans.

Preclinical safety data

Acute toxicity

The acute toxicity in animal experiments is low. For the treatment of overdoses, see Overdose.

Chronic toxicity

Studies in various animal species (rat, dog) with a duration of up to one year did not show any pathological alterations.

Tumorigenic and mutagenic potential

No mutagenic effects of acetylcysteine are to be expected. An *in vitro* test was negative.

No studies of a tumorigenic potential of acetylcysteine have been carried out.

Reproductive toxicology

No malformations were detected in embryotoxicity studies in rabbits and rats. Studies of fertility and perinatal or postnatal toxicity were negative.

Acetylcysteine passes the placenta in rats and was detected in amniotic fluid. The concentration of the metabolite L-cysteine is above the maternal plasma concentration in placenta and foetus for up to 8 hours after oral administration.

PHARMACEUTICAL PARTICULARS

Incompatibilities

Not applicable

ADVERSE DRUG REACTION REPORTING STATEMENT

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at +632-8-**UNILAB-**1 (+632-8-**864522**-1) for Metro Manila or toll-free +1-800-10-UNILAB-1 for provinces, or e-mail productsafety@unilab.com.ph.

By reporting undesirable effects, you can help provide more information on the safety of this medicine.

CAUTION

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without a prescription.

STORAGE CONDITION

Store at temperatures not exceeding 30°C.

AVAILABILITY

Thermo-sealed Triple-layer Polyethylene Aluminum paper sachet x 2's (Box of 30's)

Date of First Authorization: May 2018
Date of Revision: May 2020, CDSv05
DRP-7843-01

The elimination half-life after intravenous administration is 30-40 minutes while excretion follows three-phase kinetics (alpha, beta, and terminal gamma phase).

Acetylcysteine crosses the placenta and is detected in cord blood. No information is available regarding excretion into breast milk.

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