SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NACOSEL 300 mg / 3 mL ampoule containing solution

Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Each 3 mL ampoule contains 300 mg acetylcysteine as active substance.

Excipients:

Disodium EDTA……...3.00 mg

Sodium hydroxide…….73.00 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ampoule containing solution

Amber color glass ampoule containing clear, colorless, sulfur-odor solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

NACOSEL is indicated for bronchopulmonary diseases in cases where intense viscous sputum should be eliminated, reduced and expectoration should be facilitated.

It is also used to prevent liver failure due to high dose paracetamol intake.

4.2. Posology and method of administration

Posology /administration frequency and duration

Unless otherwise recommended, the prescribed dosage for the ampoule containing NACOSEL 300 mg / 3 mL solution is as follows:

Mucolytic use

• Parenteral administration:

NACOSEL can be administered intramuscularly or intravenously.

In adults, 1 ampoule 1 or 2 times a day, and in children, 2 equal doses of a total of 15-30 mg / kg / day is recommended (See “Method of Administration”).

The duration of treatment should be adjusted according to clinical development.

• Administration by inhalation:

NACOSEL can be nebulized with compressed air or oxygen, ultrasonic nebulizer and intermittent positive pressure breathing apparatus.

In adults, 1 ampoule 1 or 2 times a day is nebulized for 5-10 days. The dose range and dose amount may be rearranged by the physician according to the clinical response.

In children, the recommended indications should be used at a dose of 150 mg twice a day. In cystic fibrosis, the daily dose can be increased up to several grams.

• Intrathecal administration:

In the routine care of patients with tracheostomy, NACOSEL can be administered into 1-2 mL tracheostomy every 1-4 hours. In cases of thoracic trauma or surgery, NACOSEL with a percutaneous intrathecal catheter can be administered 2-4 mL every 1-4 hours.

Use in paracetamol poisoning

1- The recommended posology of intravenous N-acetylcysteine treatment for overdose of paracetamol is 3 consecutive infusions.

a) Initial infusion: initial loading dose 150 mg / kg in 1 hour

b) Second infusion: 50 mg / kg over the next 4 hours

c) Third infusion: 100 mg / kg over the next 16 hours

2- It is recommended that the patient be given a total of 300 mg / kg within 21 hours. When calculating the dose for obese patients, it is recommended that the patient weight be taken as 110 kg.

3- For the third infusion dose; Clinical evaluation of each patient is required prior to surgery.

Administration frequency and duration:

The duration of treatment should not be longer than 4-5 days unless otherwise recommended.

Method of administration:

Only for parenteral administration, inhalation and intrathecal administration. In parenteral administration, the infusion should be administered very slowly to prevent any anaphylactic reactions. For this purpose, should be diluted with 5% glucose or 0.9% NaCl initially.

Plenty of fluid intake supports the mucolytic effect of NACOSEL.

Additional information for special populations:

Renal failure:

The safety and efficacy of acetylcysteine in patients with renal failure has not been investigated.

Hepatic failure:

In patients with advanced hepatic failure (Child-Pugh Class C), the average elimination half-life of acetylcysteine is prolonged and clearance decreases (see Sections 4.4 and 5.2).

Pediatric population:

Acetylcysteine should be used under the supervision of a physician in children under 2 years.

NACOSEL ampoule form should be used in doses appropriate to the pediatric age group (see "Posology /administration frequency and duration").

Geriatric population:

The safety and efficacy of acetylcysteine in elderly patients has not been investigated.

4.3. Contraindications

NACOSEL is contraindicated in the following cases;

Patients having sensitivity to acetylcysteine or to any substance in the composition of the drug product.

4.4. Special warnings and special precautions for use

There may be a significant increase in bronchial secretions after acetylcysteine administration. In this case, care should be taken to keep the airway open if the cough reflex or cough is not enough. It should be used with caution in patients with asthma or bronchospasm.

• When prepared for use, care should be taken not to inhale NACOSEL, especially by atopic persons and asthmatic patients.

• The occurrence of severe skin reactions such as Stevens-Johnson syndrome and Lyells syndrome in connection with the use of acetylcysteine has rarely been reported. If cutaneous or mucosal changes occur, its relevance to acetylcysteine should be investigated immediately and NACOSEL should be discontinued if necessary.

• Rarely, it may cause irritation in the gastrointestinal tract (See Section 4.8.). Therefore, caution should be exercised in patients with ulcers.

• In patients with gastrointestinal bleeding (risk of peptic bleeding and risk of paracetamol-induced hepatotoxicity), it should be decided because it may cause vomiting or exacerbate vomiting due to overdose of paracetamol.

• In patients with severe hepatic insufficiency and cirrhosis (Child-Pugh Class C), the elimination of acetylcysteine can slow down, increasing blood concentration and increasing side effects.

• NACOSEL should be used with caution in patients with renal and hepatic failure to avoid supply of more nitrogenous substances.

• Acetylcysteine may cause tonic-clonic convulsions in epileptic patients receiving chronic carbamazepine treatment.

• When ampoule is opened, it may smell of sulfur, which is characteristic of the product

and it does not indicate deterioration.

• Acetylcysteine solution can be stored in an opened ampoule or transferred in an aerosol device. In this case, it may turn pink. This does not mean that there is any change in the effectiveness and tolerability of the drug product.

NACOSEL contains disodium EDTA and sodium hydroxide. This drug product contains 42.34 mg sodium per ampoule. This should be considered for patients on a controlled sodium diet.

4.5. Interaction with other medicinal products and other forms of interaction

Antitussives:

If acetylcysteine and antitussives are used together, there may be a significant increase in respiratory secretion due to reduced cough reflex. Therefore, such combination therapy should be performed upon a definitive diagnosis.

Antibiotics:

Due to the free sulfhydryl group, acetylcysteine may interact with various penicillins, tetracyclines, cephalosporins, aminoglycosides, macrolides and amphotericin B. These drugs should not be used concurrently with acetylcysteine, if necessary, the interval of administration should be at least 2 hours.

No incompatibility with amoxicillin, doxycycline, erythromycin, or thiamphenicol and cefuroxime has been reported.

Other medicines:

It has been reported that there may be an increase in the effect of nitroglycerine when used in combination with acetylcysteine, inhibiting vasodilator and platelet aggregation.

It has been reported that acetylcysteine causes tonic-clonic convulsion by decreasing carbamazepine blood level in an epileptic patient receiving chronic carbamazepine treatment.

If acetylcysteine is to be administered in admixture with bronchodilators or other drugs, it should be administered immediately and should not be stored.

In combination with nitrates, it may cause headache and hypotension.

Since activated charcoal may affect the absorption of acetylcysteine, concomitant use is not recommended.

Additional information for special populations:

No interaction studies have been performed for special populations.

Pediatric population:

No interaction studies have been performed for pediatric population.

4.6. Pregnancy and lactation

General advice

Pregnancy category is B.

Women with child-bearing potential / Contraception

There are no studies showing that NACOSEL has an effect on women with childbearing potential or contraception. Animal studies have shown no reproductive toxicity (see Section 5.3). There are no data on women who became pregnant during use of acetylcysteine. The interaction of acetylcysteine with birth control pills has not been reported.

Pregnancy

Studies on animals have not shown direct or indirect harmful effects on pregnancy, embryonal/fetal development, birth or postnatal development (see Section 5.3). However, since there is not enough data about use of acetylcysteine in human beings during pregnancy, it should be decided after assessment of benefit/risk. Care should be taken when administering to pregnant women.

Lactation

It is not known whether acetylcysteine passes into breast milk. Therefore, NACOSEL should not be used in lactation unless the expected benefits for the patient outweighes the risks to the baby.

Fertility

There is no evidence that acetylcysteine may adversely affect fertility (see section 5.3).

4.7. Effects on ability to drive and use machines

NACOSEL ampoule has no known negative effect on the ability to drive and use machines.

4.8. Undesirable effects

Undesirable effects because of use of acetylcysteine are listed below according to frequency.

Frequencies are defined as: 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), unknown (cannot be estimated from the available data).

Immune system disorders

Uncommon: Allergic reactions (pruritus, urticaria, exanthema, rash, bronchospasm, angioedema, tachycardia and hypotension).

Very rare: Anaphylactic reactions that can go up to shock.

Respiratory disorders, chest diseases and mediastinal diseases

Rare: Dyspnea, bronchospasm (especially in patients with hyperreactive bronchial system diseases with bronchial asthma).

Gastrointestinal disorders

Rare: Stomatitis, pyrosis, nausea, vomiting and diarrhea.

General disorders and application site diseases

Very rare: Fever.

In addition, hemorrhage due to acetylcysteine use has rarely been reported in the context of hypersensitivity reactions. Platelet aggregation may be reduced.

Reporting of suspected adverse reactions

If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9. Overdose and treatment

Toxic overdose has not been reported to date with systemic overdose of acetylcysteine. There may be an increase in secretion in the use of very high doses of acetylcysteine topically. Therefore, patients with insufficient cough reflex may require mechanical bronchial aspiration.

No serious side effects were observed when volunteers were treated with 11.6 g acetylcysteine per day for 3 months. 500 mg/kg acetylcysteine oral dose per day is tolerated without any toxic effects.

Symptoms of Poisoning:

In case of overdose gastrointestinal symptoms such as nausea, vomiting and diarrhea may occur.

There is a danger of hypersecretion in breastfed infants.

Treatment of overdose and precautions to be taken:

If necessary, symptomatic treatment is applied.

Through to intravenous acetylcysteine treatment in paracetamol poisoning, maximum dose

information about acetylcysteine is available up to 30 grams per day.
Very high concentrations of acetylcysteine were given in i.v. administration, in particular when administered quickly, has partly led to anaphylactic reactions.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Mucolytic
ATC Code: R05CB01
Acetylcysteine is an amino acid cysteine derivative. Acetylcysteine is a mucolytic agent. Acetylcysteine breaks disulfide bonds with the sulfhydryl group in the mucus glycoprotein and has a mucolytic effect on mucoid and mucopurulant secretions. It reduces the density and viscosity of the phlegm in the airways and makes it fluid like water. It helps to regulate lung function by facilitating excretion and respiration of bronchial secretions.
Acetylcysteine is an antioxidant. It participates in the synthesis of glutathione in lung and liver as a cysteine donor and increases glutathione synthesis. Acetylcysteine and glutathione bind free oxygen radicals produced by inhalation of neutrophils, cigarette smoke and other harmful substances, especially during lung infections, and have a protective effect by preventing possible cell damage.
Acetylcysteine has the effect of reducing liver damage in paracetamol poisoning. Normally, paracetamol is metabolised in the liver, with a small proportion of which is reactive with the cytochrome P450 enzyme system. In this intermediate metabolite, it is conjugated with glutathione and excreted in urine. If paracetamol is taken at high doses, the formation of reactive intermediate metabolite increases and inactivation of intermediate metabolite decreases as glutathione decreases. In this case, acetylcysteine administered to normal levels of glutathione in liver cells and reactive metabolite to prevent possible liver damage by binding.
Acetylcysteine is administered locally to the intestines especially in patients with cystic fibrosis, meconium ileus in newborns and meconium ileus in adults.

5.2 Pharmacokinetic properties

Absorption:
After oral inhalation or intrathecal administration, most of administered acetylcysteine reacts with disulfide bonds in the structure of the mucus to exhibit a sulfhydryl-disulfide reaction. The remaining drug is absorbed by the pulmonary epithelium and can be detected as cysteine in the liver.

Distribution:

Volume of distribution (Vd) is between 0.33-0.47 L/kg and passes primarily to the lung, kidney and liver. 48% of the amount passed into the blood after oral administration was detected in the lungs. Acetylcysteine is present in the plasma and lungs, both free and disulfide bridges are recycled to the protein. The binding rate to plasma proteins is about 50%.

Acetylcysteine was found to pass through the placenta and was found in amniotic fluid. The concentration of L-cysteine metabolite of 100 mg / kg acetylcysteine at 0.5, 1, 2 and 8 hours after oral administration is higher than the maternal plasma concentration in the placenta and fetus. N-acetylcysteine crosses the placenta and can be detected in umbilical cord blood. There is no information that it passes into breast milk.

There is no information as to whether acetylcysteine crosses to human blood-brain barrier.

The 600 mg acetylcysteine reached C_{max} 300 nmol / L after intravenous administration and plasma distribution volume was 0.34 L / kg. The binding rate to plasma proteins is 50%. It has good distribution to liver and kidneys, mainly lung tissue and bronchial secretions.

Biotransformation:

It is metabolized in the liver to cysteine, a pharmacologically active metabolite, as well as diacetylcysteine and other mixed disulfides.

Elimination:

Acetylcysteine is mostly excreted through the kidneys as inactive metabolites. The plasma half-life of acetylcysteine is approximately 2.27 hours. A defect in liver function leads to an increase in plasma half-life of up to 8 hours.

Linearity / non-linearity:

There are not enough studies on the linearity / non-linearity acetylcysteine status.

Characteristics of patients

In patients with hepatic failure:

In patients with advanced hepatic failure (Child-Pugh Class C), the average elimination half-life ($T_{1/2}$) of acetylcysteine is prolonged by 80% and clearance is reduced by 30%.

In patients with renal failure:

There is no information on the pharmacokinetics of acetylcysteine in patients with impaired renal function.

In pediatric patients:

The elimination half-life ($T_{1/2}$) of N-acetylcysteine is longer in neonates (11 hours) than in adults (5, 6 hours). There is no pharmacokinetic information for other age groups.

5.3 Preclinical safety data

Acute toxicity:

Acute toxicity was low in animal experiments. See section 4.9 for overdose treatment.

Chronic toxicity:

Approximately one year of research with different animal species (rats, dogs) shows that there are no pathological changes.

Tumor formation and mutagenic potential:

Acetylcysteine is not expected to have a mutagenic effect. The *in-vitro* test was negative.

The tumor-forming potential of acetylcysteine has not been investigated.

Reproductive toxicology:

Embryotoxicological studies with rabbits and rats showed no abnormality. Fertility, perinatal and postnatal toxicity studies were negative.

N-acetylcysteine was detected in amniotic fluid through the placenta in rats. The concentration of L-cysteine metabolite is above the mother's plasma concentration in the placenta and fetus until 8 hours after oral administration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium EDTA

Sodium hydroxide

Water for injection

6.2 Incompatibilities

It does not have any known incompatibilities.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at room temperature below 30 ° C.

Ampoule should be opened by opening just before parenteral administration. An opened ampoule can be stored in the refrigerator for 24 hours, but should not be administered parenterally.

For parenteral administration, it should be diluted with 5% glucose or 0.9% NaCl to slow the infusion.

6.5 Nature and contents of container

5 or 10 pcs in a 3 mL amber colored type I glass ampoule, separated by a transparent PVC separator in a box.

6.6 Instructions for use and handling and disposal

Unused products or waste materials must be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulation".

Since acetylcysteine administered as nebulization and lavage may chemically interact with various metals such as iron, copper, the aerosol device must be made of non-interacting material such as glass, plastic or stainless steel.

7. MARKETING AUTHORISATION HOLDER

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Akbaba Mah. Maraş Cad. No:52/2/1 34820
Beykoz/İstanbul

8. MARKETING AUTHORISATION NUMBER

2015 / 60

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization: 02.02.2015
Date of latest renewal: -

10. DATE OF REVISION OF THE TEXT