ACETYLCYSTEINE SANDOZ EFFERVESCENT TABLET

1. NAME OF THE MEDICINAL PRODUCT
Acetylcysteine Sandoz Effervescent Tablet 200mg
Acetylcysteine Sandoz Effervescent Tablet 600mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Acetylcysteine Sandoz Effervescent Tablet 200 mg
Each effervescent tablet contains 200 mg acetylcysteine.

Acetylcysteine Sandoz Effervescent Tablet 600 mg
Each effervescent tablet contains 600 mg acetylcysteine.

3. PHARMACEUTICAL FORM
Effervescent Tablet.

Acetylcysteine Sandoz Effervescent Tablet 200mg
White, round tablet, faultless surface, scored on one side, smell of blackberries, with a diameter of 18 mm. The effervescent tablet can be divided into equal doses.

Acetylcysteine Sandoz Effervescent Tablet 600mg
White, round tablet, faultless surface, scored on one side, smell of blackberries, with a diameter of 20 mm. The effervescent tablet can be divided into equal doses.

4. CLINICAL PARTICULARS
4.1 Therapeutics indication
Treatment of respiratory affections characterized by thick and viscous hypersecretions: acute or chronic bronchitis and its exacerbations, pulmonary emphysema, mucoviscidosis and bronchiectasis.

4.2 Posology and method of administration
Recommended Dosage

Acetylcysteine Sandoz Effervescent Tablet 200 mg:

Adult:	200 mg three times a day
Children >2 years:	100 - 200 mg two times a day

Acetylcysteine Sandoz Effervescent Tablet 600 mg:

Adult:	1 effervescent tablet daily

Duration of treatment: 5 to 10 days for acute cases.

Mode of Administration
Oral

Method of Administration
The effervescent tablets are taken dissolved in a glass of water after meals.

4.3 Contraindications
It is contraindicated
- in patients with hypersensitivity to acetylcysteine, or any of the excipients
- in children under 2 years of age
- severe asthma exacerbation
- chronic duodenal and gastric ulcer disease

4.4 Special warnings and precautions for use
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.

Care during use in patients with bronchial asthma and in patients with anamnestic ulcers.

Caution is advised in patients with histamine intolerance. Longer-term therapy should be avoided in these patients, as Acetylcysteine has an effect on histamine metabolism and may lead to symptoms of intolerance (e.g. headache, vasomotor rhinitis, itching).

One 200 mg effervescent tablet contains 3.6 mmol (82.9 mg) sodium. To be taken into consideration by patients on a controlled sodium (low-sodium/low-salt) diet.

One 600 mg effervescent tablet contains 6.03 mmol (138.8 mg) sodium. To be taken into consideration by patients on a controlled sodium (low-sodium/low-salt) diet.

This medicinal product contains lactose.
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicinal product contains traces of sorbitol.
Patients with rare hereditary problems of fructose intolerance should not take this medicine**.**

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 cough up enough of this, appropriate measures (such as postural drainage and aspiration) should be performed.

4.5 Interactions with other medicinal products and other forms of interaction
Interaction studies have only been performed in adults.

Combined use of Acetylcysteine with antitussives (cough-relieving agents) 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 (tetracyclines, aminoglycosides, penicillins) 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.

The use of activated charcoal may reduce the effect of acetylcysteine.

Co-administration of acetylcysteine can result in an enhancement of vasodilator and antiplatelet effects of glyceryl trinitrate (nitroglycerin).
If a common treatment with nitroglycerin and acetylcysteine is considered necessary, the patient should be monitored for a potential hypotension, which could be serious and may be indicated by headache.

Changes in the determination of laboratory parameters
• acetylcysteine may affect the colorimetric assay of salicylates.
• In urine tests, acetylcysteine may influence the results of the determination of ketone bodies.

4.6 Fertility, pregnancy and lactation
Pregnancy

No sufficient clinical 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.
Acetylcysteine should be used during pregnancy after strict assessment of the benefit-risk ratio.

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

4.7 Effects on ability to drive or use machine
Acetylcysteine has no influence on the ability to drive and use machines.

4.8 Undesirable Effects
The evaluation of undesirable effects is based on the following information on frequencies:
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)
Not known (cannot be estimated from the available data)

Immune system disorders	Uncommon Very rare	Hypersensitivity reactions Anaphylactic shock, anaphylactic / anaphylactoid reactions
Nervous system disorders	Uncommon	Headache
Cardiac disorders	Uncommon	Tachycardia
Vascular disorders	Uncommon Very rare	Hypotension Hemorrhage
Respiratory, thoracic and mediastinal disorders	Rare	Dyspnoea, bronchospasm – predominantly in patients with hyperreactive bronchial system in case of bronchial asthma
Gastrointestinal disorders	Uncommon Rare	Stomatitis, abdominal pain, nausea, vomiting, and diarrhoea Dyspepsia
Skin and subcutaneous tissue disorders	Uncommon	Urticaria, rash, angioedema, itching, rash
Ear and labyrinth disorders	Uncommon	Tinnitus
General disorders and administration site conditions	Uncommon Not known	Fever Facial edema

A very rare occurrence of serious 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 cases reported at least one other drug was administered at the same time, which may have possibly enhanced the described mucocutaneous effects.

In case of recurrence skin and mucosal lesions, medical advice should be sought at once and the use of acetylcysteine terminated immediately.

In addition, the occurrence of haemorrhages in association with the administration of acetylcysteine has very rarely been reported, partially with hypersensitivity reactions. A decreased blood platelet aggregation in the presence of acetylcysteine has been confirmed by various studies. The clinical relevance has not yet been clarified to date.

NPRA Directive
Immune System Disorders:
Anaphylactic/ anaphylactoid reaction

Skin and Subcutaneous Tissue Disorders:
Severe cutaneous adverse reactions (SCAR) e.g. erythema multiforme, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). In most of these cases reported at least one other drug was administered at the same time, which may have possibly enhanced the described mucocutaneous effects.

4.9 Overdose and Treatment
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 undesirable 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.

Therapeutic measures in case of an overdose
If necessary, according to the symptoms.

Experience gained from intravenous acetylcysteine treatment of paracetamol intoxication is available in humans with maximum daily doses of up to 30 g acetylcysteine. Intravenous administration of extremely high acetylcysteine concentrations led to partially irreversible "anaphylactoid" reactions, particularly in connection with rapid administration.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamics properties
Pharmacotherapeutic group: Cough and cold preparations; Mucolytics
ATC Code: R05C B01

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.

A protective effect on the frequency and severity of bacterial exacerbations – when acetylcysteine is administered prophylactically - is described in patients with chronic bronchitis/mucoviscidosis.

5.2 Pharmacokinetics 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. 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.

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

6. PHARMACEUTICAL PARTICULARS

6.1 Storage Conditions
Do not store above 30°C.

6.2 Dosage Forms and Packaging Available
Sachets: 10, 20, 50, 100 effervescent tablets.

Not all pack sizes may be marketed.

7. PRODUCT REGISTRATION HOLDER
Sandoz Products Malaysia Sdn. Bhd.
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8. DATE OF REVISION OF THE TEXT
Mar 2024