SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Acetylcysteine Sandoz 100 mg effervescent tablets
Acetylcysteine Sandoz 200 mg effervescent tablets
Acetylcysteine Sandoz 600 mg effervescent tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Acetylcysteine Sandoz100 mg effervescent tablets
Each effervescenttabletcontains100mgofacetylcysteine
Excipientswithknowneffect:sorbitol,
Eacheffervescenttabletcontains75mgoflactose,anhydrous and 4,2mmolmmol(96mg)of sodium.

Acetylcysteine Sandoz 200 mg effervescent tablets: Each effervescent tablet contains 200 mg of acetylcysteine
Excipients with known effect: sorbitol
Eacheffervescenttabletcontains70mgoflactose anhydrous.
and 4,3mmol(99mg)ofsodium.

Acetylcystiene Sandoz 600 mg effervescent tabletsl Each effervescent tablet contains 600 mg of acetylcysteine
Excipients with known effect: sorbitol
Eacheffervescenttabletcontains75mgoflactose anhydrous.
6.03mmol(138.8mg)ofsodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Effervescent tablet

Acetylcystiene Sandoz 100 mg effervescent tablets white round tablet, faultless, smell ofblackberries

Acetylcystiene Sandoz 200 mg effervescent tablets
white, round tablet, faultless, scored on oneside,smellofblackberries
The effervescent tablet can be divided into equal doses

Acetylcystiene Sandoz 600 mg effervescent tablets
white,roundtabletscoredononeside,faultlesssurface smellofblackberries.
The effervescent tablet can be divided into equal doses

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

100 mg]
[Nationally completed name 100 mg effervescent tablets]:
Secretolytic therapy in acute and chronic bronchopulmonary diseases accompanied by impaired formation and transport of mucus in adults, adolescents and children from 2 years of age.

[200 mg]
[Nationally completed name 200 mg effervescent tablets]:
Secretolytic therapy in acute and chronic bronchopulmonary diseases accompanied by impaired formation and transport of mucus in adults, adolescents and children from 6 years of age (whole tablets) or children from 2-5 years of age (half tablets)..

[600 mg]
[Nationally completed name 600 mg effervescent tablets]:
Secretolytic therapy in acute and chronic bronchopulmonary diseases accompanied by impaired formation and transport of mucus in adults and adolescents from 14 years of age

4.2 Posology and method of administration

Posology

The following dosage is recommended for Nationally completed name 100 mg effervescent tablets]:

Adults and adolescents from 14 years of age
2 effervescent tablets 2-3 times daily (equivalent to 400-600 mg acetylcysteine per day)

Children and adolescents from 6-14 years of age
1 effervescent tablet 3-4 times daily (equivalent to 300-400 mg acetylcysteine per day)

Children from 2-5 years of age
1 effervescent tablet 2-3 times daily (equivalent to 200-300 mg acetylcysteine per day)

If not otherwise prescribed, the following dosage is recommended for Nationally completed name 200 mg effervescent tablets:
Adults and adolescents from 14 years of age 1 effervescent tablet 2-3 times daily (equivalent to 400-600 mg acetylcysteine per day)

Children and adolescents 6-14 years of age
1 effervescent tablet twice daily (equivalent to 400 mg acetylcysteine per day)

Children 2-5 years of age
½ effervescent tablet 2-3 times daily (equivalent to 200-300 mg acetylcysteine per day)

If not otherwise prescribed, the following dosage is recommended for Nationally completed name600 mg effervescent tablets.
Adults and adolescents from 14 years of age
½ effervescent tablet twice daily or 1 effervescent tablet once daily (equivalent to 600 mg acetylcysteine per day)

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

Duration of use
Acetylcystiene Sandoz 100 mg effervescent tablets] should not be taken for more than 4-5days without medical advice.
Acetylcysteine Sandoz 200 mg effervescent tablets:
should not be taken for more than 4-5 days without medical advice.
Acetylcystiene Sandoz 600mg effervescent tablets should not be taken for more than 4-5 days without medical advice.

4.3 Contraindications

-hypersensitivity to acetylcysteine or to any of the excipients listed in section 6.1.
-severe asthma exacerbation
-chronic duodenal and gastric ulcer disease
On account of the high content of active substance, Nationally completed name 100 mg effervescent tablets must not be used in children of less than 2 years of age.

On account of the high content of active substance, half tablets of Nationally completed name 200 mg effervescent tablets must not be used in children of less than 2 years of age and whole tablets of Nationally completed name 200 mg effervescent tablets must not be used in children of less than 6 years of age.

On account of the high content of active substance, Acetylcystiene Sandoz 600 mg effervescent tablets must not be used in children of less than 14 years of age.

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.

Cave 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 effervescent tablet contains 4,2 mmol (96 mg) sodium. To be taken into consideration by patients on a controlled sodium (low-sodium/low-salt) diet.

1 effervescent tablet contains 4,3 mmol (99 mg) sodium. To be taken into consideration by patients on a controlled sodium (low-sodium/low-salt) diet.

1 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 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 Interaction 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

Fertility
No effects on fertility were noted in animal studies.

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 (see also section 5.3).
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 and use machines

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 tract	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, exanthema

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.

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 listed in Appendix V*.

4.9 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 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 Pharmacodynamic properties

Pharmacotherapeutic group: Cough and cold prepartions; 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 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. 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.

5.3 Preclinical safety data

Acute toxicity
The acute toxicity in animal experiments is low. For the treatment of overdoses, see section 4.9.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acetylcysteine Sandoz 100 mg effervescent tablets
Acetylcystiene Sandoz 200 mg effervescent tablets
Citric acid, anhydrous
Sodium hydrogen carbonate
Sodium carbonate anhydrous
Mannitol
Lactose, anhydrous
Ascorbic acid
Sodium citrate
Saccharin sodium

Blackberry flavour "B" (contains vanillin; maltodextrin; gluconolactone; sorbitol; silica,colloidale anhydrous, mannitol, Magnesium carbonate

Acetylcystiene Sandoz 600 mg effervescent tablets Citric acid, anhydrous
Sodium hydrogen carbonate
Sodium carbonate, anhydrous
Mannitol
Lactose, anhydrous
Ascorbic acid
Sodium cyclamate
Saccharin sodium

Sodium citrate 2 H2O
Blackberry flavour "B" (contains vanillin; maltodextrin; gluconolactone; sorbitol; silica, colloidale anhydrous; mannitol; magnesium carbonate;

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Acetylcystiene Sandoz 100 mg effervescent tablets tubes: 2 years
sachets: 3 years

Acetylcystiene Sandoz 200mgeffervescenttablets
In tubes: 2 years
In sachets : 2 years

[Acetylcysteine Sandoz 600 mg effervescent tablets}
sachets: 3 years

tubes: 3 years
In use shelf life:
After first opening : 2 years

6.4 Special precautions for storage

Nationally completed name 100 mg effervescent tablets
tubes: Do not store above 25 °C
Keep the tube tightly closed in order to protect from moisture'
sachets: Do not store above 30 °C

Acetylcystiene Sandoz 200 mg effervescent tablets tubes:
Do not store above 25 °C
Keep the tube tightly closed in order to protect from moisture'
sachets: Do not store above 30 °C

Acetylcystiene Sandoz 600 mg effervescent tablets
tubes:Keepthetubetightlyclosedinordertoprotectfrommoisture'
tubesandsachets:Thismedicinalproductdoesnotrequireanyspecialtemperaturestorageconditions

6.5 Nature and contents of container

DE/H/3625/001/002]

- Polypropylene tubes closed with a polyethylene stopper with desiccant (molecular sieve)-
- sealed sachets made of triple layer foil (Laminated -aluminium-paper)

Pack sizes:

Nationally completed name 100 mg effervescent tablets
tubes: 20, effervescent tablets
sachets: 20, 40, 50, 80, 100 effervescent tablets

Acetylcystiene Sandoz 200 mg effervescent tablets:
tubes: 20, effervescent tablets
sachets : 20, 40, 50, 80, 100 effervescent tablets

[DE/H/3625/003]

- Polypropylene tubes closed with a polyethylene stopper with desiccant (silica gel and molecular sieve)
- sealed sachets made of triple layer foil (Laminated -aluminium-paper)

Packsizes:

Acetylcystiene Sandoz 600 mg effervescent tablets:
tubes: 10, 20, 30, 60 effervescent tablets
sachets :10,20,30,50,60effervescenttablets

[DE/H/3667-001]

- Polypropylene tubes closed with a polyethylene stopper with desiccant (molecular sieve)-
- sealedsachetsmadeoftriplelayerfoil(Laminated-aluminium-paper)

Packsizes:
Acetylcystiene Sandoz 200 mg effervescent tablets:
tubes:20,effervescenttablets
sachets :20,40,50,80,100effervescenttablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

SALUTAS PHARMA GMBH Germany
OTTO-VON-GUERICKE-ALLEE 1D-39179 BARLEBEN, GERMANY

8. MARKETING AUTHORISATION NUMBER(S)

03970/3928/NMR/2017

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Jul 31, 2018

10. DATE OF REVISION OF THE TEXT

Jul 31, 2018