SCHEDULING STATUS: S1

1. NAME OF THE MEDICINE

ACC 200 (effervescent tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ACC 200 effervescent tablet contains: 200 mg acetylcysteine.

Contains sugar (lactose anhydrous 70 mg) and mannitol 60 mg.

Contains sweetener (saccharin sodium 6 mg).

3. PHARMACEUTICAL FORM

White round tablets, faultless, scored on one side (200 mg), smell of blackberries.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ACC 200 effervescent tablets are used as a mucolytic, of non-infective secretions in cystic fibrosis and in respiratory conditions.

4.2 Posology and method of administration

Posology

As a mucolytic:

Children from 2 to 5 years of age: ½ (half) an effervescent tablet 2 to 3 times daily (equivalent to 200 to 300 mg acetylcysteine/day).

Children from 6 to 14 years of age: 1 effervescent tablet twice daily (equivalent to 400 mg acetylcysteine/day).

Adults and adolescents from 14 years of age: 1 effervescent tablet 2 to 3 times daily (equivalent to 400 to 600 mg acetylcysteine/day).

Method of administration

The effervescent tablet should be dissolved in a glass of water before use.

Duration of use

Do not use continuously for more than 14 days without consulting a doctor.

4.3 Contraindications

- Hypersensitivity to acetylcysteine or to any of the excipients listed in section 6.1.
- Active peptic ulceration.
- Children below 2 years of age.

Safety in pregnancy has not been established. ACC 200 effervescent tablets should not be used during pregnancy.

4.4 Special warnings and precautions for use

Care during use in patients with bronchial asthma and in patients with anamnestic ulcers. If bronchospasm occurs, ACC 200 effervescent tablets should be discontinued 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 ACC 200 effervescent tablets, 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 ACC 200

effervescent tablets be terminated (see also section 4.8).

Caution is advised in patients with histamine intolerance. Treatment with ACC 200 effervescent tablets for longer periods should be avoided in such patients, as ACC 200 effervescent tablets 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 section 4.3 Contraindications).

Important information about some excipients

ACC 200 effervescent tablets contains lactose anhydrous, which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take ACC 200 effervescent tablets.

4.5 Interaction with other medicines and other forms of interaction

Combined administration of ACC 200 effervescent tablets 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 ACC 200 effervescent tablets 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 ACC 200 effervescent tablets 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 ACC 200 effervescent tablets.

Changes in the determination of laboratory parameters

ACC 200 effervescent tablets can affect the colorimetric determination of salicylates.

In urine tests, ACC 200 effervescent tablets can affect the results of determinations of ketone bodies.

The dissolution of acetylcysteine formulations together with other medicinal products is not recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety and/or efficacy has not been established. ACC 200 effervescent tablets should not be used during pregnancy.

Lactation

No information is available regarding excretion into breast milk. ACC 200 effervescent tablets 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 section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The evaluation of side effects is based on the following information on frequencies:

Frequent: ≥ 1/100.

Less frequent: < 1/10 000 up to < 1/100.

Frequency not known: cannot be estimated from the available data.

Immune system disorders:

Less frequent: Hypersensitivity reactions, anaphylactic shock, anaphylactic/anaphylactoid reactions

Nervous system disorders:

Less frequent: Headache

Ear and labyrinth disorders:

Less frequent: Tinnitus

Cardiac disorders:

Less frequent: Tachycardia

Vascular disorders:

Less frequent: Haemorrhage

Respiratory, thoracic and mediastinal disorders:

Less frequent: Dyspnoea, bronchospasm - predominantly in patients with hyper reactive bronchial system in association with bronchial asthma.

Gastrointestinal disorders:

Less frequent: Nausea, vomiting, diarrhoea, abdominal pain, stomatitis, dyspepsia

Skin and subcutaneous tissue disorders:

Less frequent: Urticaria, rash, angioedema, pruritus, exanthema

General disorders and administration site conditions:

***Less frequent*:** Fever

***Frequency not known*:** Facial oedema

Investigations:

Less frequent: 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 medicine 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 ACC 200 effervescent tablets 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.

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 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.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A 10.3 Medicines acting on the respiratory system – other

5.1 Pharmacodynamic properties

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.

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 to 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 to 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

Ascorbic acid, blackberry flavour "B", citric acid anhydrous, lactose anhydrous, mannitol, sodium hydrogen carbonate, sodium carbonate anhydrous, sodium citrate and saccharin sodium.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C in a cool dry place.

6.5 Nature and contents of container

1. Individually sealed laminated aluminium paper foil in an outer cardboard carton.
2. Polypropylene tube with a polyethylene stopper and desiccant in an outer cardboard carton.

Pack sizes of either 20, 25 or 40 effervescent tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Waterfall 5-Ir

Magwa Crescent West

Waterfall City

Jukskei View

2090

8. REGISTRATION NUMBER

29/10.2.2/0753

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07 November 1996

10. DATE OF REVISION OF THE TEXT

08 July 2020

Additional country registration details:

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Namibia	ACC 200	NS1	04/10.2.2/1307
Botswana	ACC 200	S3	BOT1202173
Zambia	ACC 200	P	039/001

ATC Code: R05CB01 – Mucolytics

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