PROFESSIONAL INFORMATION

Scheduling status: S1

1 NAME OF THE MEDICINE

ACC® 20 mg/ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of ACC 20 mg/ml ORAL SOLUTION contains 20 mg acetylcysteine

Excipients with known effects:

Contains sweetener (saccharin sodium 1 mg per ml)

Contains preservatives (methyl parahydroxybenzoate 1,30 mg and sodium benzoate 1,95 mg per ml)

Contains benzyl alcohol, an ingredient of cherry flavour (0,1 mg per ml)

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Oral solution

Clear, slightly viscous, colourless solution with a cherry flavour

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ACC 20 mg/ml Oral Solution is used as a mucolytic in acute respiratory conditions.

4.2 Posology and method of administration

Posology

The following dosage is recommended for ACC 20 mg/ml ORAL SOLUTION (if not otherwise prescribed):

Adults and adolescents over 14 years of age:

Take 10 ml oral solution 2 - 3 times daily (equivalent to 400 - 600 mg acetylcysteine per day).

Children and adolescents from 6 - 14 years of age:

Take 10 ml oral solution twice daily (equivalent to 400 mg acetylcysteine per day).

Children from 2 - 5 years of age:

Give 5 ml oral solution 2 - 3 times daily (equivalent to 200 - 300 mg acetylcysteine per day).

10 ml of oral solution is equivalent to half a measuring cup or the content of 2 filled syringes.

Method of administration

ACC 20 mg/ml ORAL SOLUTION is taken after meals.

It is taken by means of a syringe for oral preparation or measuring cup, included in the pack.

Duration of use:

ACC 20 mg/ml ORAL SOLUTION should not be taken for more than 14 days without consulting a doctor.

4.3 Contraindications

- Hypersensitivity to the active substance acetylcysteine, methyl-parahydroxybenzoate, sodium benzoate or to any of the inactive ingredients, see section 6.1
- Contraindicated in children below 2 years of age.
- Safety in pregnancy has not been established. ACC 20 mg/ml ORAL SOLUTION should not be used during pregnancy, see section 4.6.

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 ACC 20 mg/ml ORAL SOLUTION. If cutaneous and mucosal changes newly occur, medical advice should be sought without delay and the use of ACC 20 mg/ml ORAL SOLUTION be terminated, see section 4.8.

- Care should be exercised during use in patients with bronchial asthma and in patients with a history of ulcers.
- Caution is advised in patients with histamine intolerance. Longer-term therapy should be avoided in these patients as ACC 20 mg/ml ORAL SOLUTION affects the histamine metabolism and may lead to symptoms of intolerance (e.g. headache, vasomotor rhinitis, itching).
- 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.
- ACC 20 mg/ml ORAL SOLUTION contains methyl parahydroxybenzoate, sodium benzoate and benzyl alcohol.
- ACC 20 mg/ml ORAL SOLUTION contains 1,3 mg methyl parahydroxybenzoate in each ml. It may cause allergic reactions (possibly delayed).
- ACC 20 mg/ml ORAL SOLUTION contains up to 4,8 mg sodium in each ml, equivalent to 0,24 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.
- This medicinal product contains up to 0,1 mg benzyl alcohol in each ml. Benzyl alcohol may cause allergic reactions. Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called “gasping syndrome”) in young children. High volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis).
- Do not use continuously for more than 14 days without consulting a doctor.

- The safety and efficacy of ACC 20 mg/ml ORAL SOLUTION in children below 2 years has not been established. The use of ACC 20 mg/ml in children aged under 2 years is not recommended.
- 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.

4.5 Interactions with other medicines and other forms of interaction

Interaction studies have only been performed in adults.

Activated carbon in high doses:

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

Combination with antitussives:

Combined use of ACC 20 mg/ml ORAL SOLUTION 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.

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

Antibiotics:

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.

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 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 determination of ketone bodies.

4.6 Fertility, pregnancy and lactation

Fertility

Data concerning effects of acetylcysteine on human fertility are not available. In animal studies, no harmful effects on fertility were observed for therapy-relevant doses of acetylcysteine.

Pregnancy

There are no adequate clinical data from the use of acetylcysteine in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. The use of acetylcysteine during pregnancy is not recommended.

Breastfeeding

No information is available regarding excretion of acetylcysteine or its metabolites into breast milk. A risk for the breast-fed child cannot be excluded. The use of acetylcysteine during breastfeeding is not recommended.

4.7 Effects on ability to drive and use machines

ACC 20 mg/ml ORAL SOLUTION has no known effect on the ability to drive and use machines.

4.8 Undesirable effects

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: Stomatitis, abdominal pain, nausea, vomiting, diarrhoea and dyspepsia

Skin and subcutaneous tissue disorders:

***Less frequent*:** Stevens-Johnson syndrome and toxic epidermal necrolysis*, urticaria, rash, angioedema, pruritus, exanthema

Investigations:

Less frequent: Hypotension

General disorders and administration site conditions:

***Less frequent*:** Fever

Frequency Unknown: Facial oedema

*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. 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 various studies. The clinical relevance has not yet been clarified to date.

ACC 20 mg/ml ORAL SOLUTION contains methylparahydroxybenzoate. It may cause allergic reactions (possibly delayed).

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 providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

Suspected adverse reactions can also be reported directly to the HCR via Patientsafety.sacg@novartis.com.

4.9 Overdose

Overdoses may lead to gastrointestinal symptoms such as nausea, vomiting and diarrhoea. Infants are at risk of hypersecretion. Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Cough and cold preparations; mucolytics ATC code: R05C B01

5.1 Pharmacodynamic properties

Mechanism of Action

Acetylcysteine is a mucolytic agent that reduces the viscosity of non-infected bronchial secretions probably by the splitting of disulphide bonds in mucoproteins.

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 splits off the interconnecting disulphide bonds between the mycopolysaccharide chains and that it has a depolymerizing effect on DNA-chains (in purulent mucus). This leads to a reduction in the viscosity of the mucus.

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.

5.2 Phamacokinetic 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 diacetylcysteine, cysteine 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 body: 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 behavior of acetylcysteine at the blood-brain barrier in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carmellose sodium, cherry flavour (aldehyde C14, alpha-ionone, alpha-tocopherol, anisic aldehyde, benzaldehyde, benzyl acetate, benzyl alcohol, citric acid, dihydro coumarin, ethyl acetate, frambinon® , geranyl butyrate, isoamyl acetate mix, heliotropin/piperonal, maltol, vanillin, propylene glycol-1,2), disodium edetate, methyl parahydroxybenzoate, purified water, saccharin sodium, sodium benzoate, sodium hydroxide 10 % aqueous solution.

Contains sweetener (saccharin sodium 1 mg per ml).

Contains preservatives (methyl parahydroxybenzoate 1,30 mg and sodium benzoate 1,95 mg per ml).

Contains benzyl alcohol, an ingredient of cherry flavour (0,1 mg per ml)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

After first opening the bottle, ACC 20 mg/ml ORAL SOLUTION is stable for 15 days when stored at or below 25 °C.

6.5 Nature and contents of container

The prime container comprises of brown glass bottles with a screw-neck consisting of glass type III. The bottles are sealed with a polypropylene closure system containing an originality (temper evident) ring. The closure system (screw cap) contains a chlorobutyl sealing disk, which is assembled into the cap.

The bottles are equipped with a measuring device in the form of a polypropylene cup allowing withdrawal of 2,5, 5 and 10 ml or a polypropylene-dosing syringe allowing withdrawal of aliquots of up to 5 ml.

Pack sizes of 100 ml and 200 ml bottles.

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

48/10.3/0261

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05 October 2021

10 DATE OF REVISION OF THE TEXT

Not applicable

[1]Company Reg. No.: 1990/001979/07

Additional country registration details:

Country	*Product name*	*Scheduling status (or Category of distribution)*	*Registration number*
Botswana	ACC 20 mg / ml oral solution	S3	BOT1402654A/B
Namibia	ACC 20 mg / ml oral solution	NS1	17/10.2.2/0045

ATC Code: R05CB01 – Mucolytics

Name and address of manufacturer:

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Dornbersweg 35,
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