DocuSign Envelope ID: 9E29EF18-BCFE-4AB3-97EF-2C4DE9AE8339

Applicant	:	Sandoz SA (Pty) Ltd
Proprietary name	:	ACC 200 POWDER FOR ORAL SOLUTION
Dosage form and strength	:	Powder for oral solution. Each sachet contains 200 mg acetylcysteine.
Date of submission	:	13 February 2023

CLEAN PROPOSED PROFESSIONAL INFORMATION FOR ACC 200 POWDER FOR ORAL SOLUTION

SCHEDULING STATUS: S1

1. NAME OF THE MEDICINE:

ACC 200 Powder for Oral Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each sachet of the ACC 200 powder for oral solution contains 200 mg acetylcysteine.

Excipients with known effect:

Each sachet of the ACC 200 powder for oral solution contains sugar (2717,00 mg of Sucrose).

Each sachet of the ACC 200 powder for oral solution contains sweetener (8,00 mg of Saccharin).

For full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM:

ACC 200 powder for oral solution

Homogeneous, white powder, free from agglomerations of particles, smell of orange.

When an ACC 200 powder for oral solution is dissolved in a glass of water, the appearance is clear to slightly opalescent, colourless solution in water.

4. CLINICAL PARTICULARS:

4.1. Therapeutic indications:

Initials: DocuSigned by: NM
Signer Name: Nkosinathi Mbokane
Signing Reason: I approve this document
Signing Time: 24-Feb-2023 | 08:55:05 GMT
D22075D453FC4A80B696E2507679FFC4

Signature: DocuSigned by: Nkosinathi Mbokane
Signer Name: Nkosinathi Mbokane
Signing Reason: I approve this document
Signing Time: 24-Feb-2023 | 08:55:34 GMT

DocuSign Envelope ID: 9E29EF18-BCFE-4AB3-97EF-2C4DE9AE8339

Applicant	:	Sandoz SA (Pty) Ltd
Proprietary name	:	ACC 200 POWDER FOR ORAL SOLUTION
Dosage form and strength	:	Powder for oral solution. Each sachet contains 200 mg acetylcysteine.
Date of submission	:	13 February 2023

ACC 200 powder for oral solution is indicated as a mucolytic in acute respiratory conditions to reduce the viscosity of non-infective secretions for a maximum treatment period of 14 days.

4.2 Posology and method of administration:

Posology:

The following dosages are recommended for the treatment of respiratory disorders:

Children up to 2 years: one sachet once daily

Children 2 to 6 years: one sachet twice daily

Adults: one sachet three times daily

Method of administration:

For oral use.

The powder should be dissolved in a glass of water before administration.

4.3. Contraindications:

Hypersensitivity to acetylcysteine or any of the ingredients of ACC 200 powder for oral solution listed in section 6.1.

Safety in pregnancy has not been established. ACC 200 powder for oral solution should not be used during pregnancy (see section 4.6).

4.4. Special warnings and precautions for use:

Use with caution in elderly patients with respiratory insufficiency or in asthmatic patients. If bronchospasm occurs, treatment with ACC 200 powder for oral solution should be discontinued immediately.

Initials: DocuSigned by: NM
Signer Name: NkosinathiMbokane
Signing Reason: I approve this document
Signing Time: 24-Feb-2023 | 08:55:48 GMT
D22075D453FC4A80B696E2507679FFC4

Signature: DocuSigned by: Nkosinathi Mbokane
Signer Name: Nkosinathi Mbokane
Signing Reason: I approve this document
Signing Time: 24-Feb-2023 | 08:56:00 GMT

DocuSign Envelope ID: 9E29EF18-BCFE-4AB3-97EF-2C4DE9AE8339

Applicant	:	Sandoz SA (Pty) Ltd
Proprietary name	:	ACC 200 POWDER FOR ORAL SOLUTION
Dosage form and strength	:	Powder for oral solution. Each sachet contains 200 mg acetylcysteine.
Date of submission	:	13 February 2023

ACC 200 powder for oral solution should be used with caution in patients with recent gastroduodenal ulceration or in patients with a history of peptic ulcer disease as mucolytics may disrupt the gastric mucosal barrier.

Administration of ACC 200 powder for oral solution, especially at the beginning of treatment, may liquefy bronchial secretions and, at the same time, increase their volume. If the patient is unable to expectorate efficiently, to avoid retention of secretions postural drainage and tracheal suction should be used.

Acetylcysteine can cause interference with the colorimetric assay method for the determination of salicylates.

Acetylcysteine can interfere with tests for ketones in urine.

Upon opening the sachet, the powder may smell of sulphur (rotten egg smell). This is a normal characteristic of the active substance. Upon addition of water, the solution will have a citrus odour.

Excipients

ACC 200 powder for oral solution contains sucrose. Patients with the rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrase-isomaltase insufficiency should not take ACC 200 powder for oral solution.

ACC 200 powder for oral solution contains saccharin which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5. Interaction with other medicines and other forms of interaction:

Antitussive medicines and ACC 200 powder for oral solution should not be administered concomitantly because reducing the cough reflex may lead to a build-up of bronchial secretions.

Initials: DocuSigned by: NM
Signer Name: Nkosinathi Mbokane
Signing Reason: I approve this document
Signing Time: 24-Feb-2023 | 08:56:14 GMT
D22075D453FC4A80B696E2507679FFC4
Signature: DocuSigned by: Nkosinathi Mbokane
Signer Name: Nkosinathi Mbokane
Signing Reason: I approve this document
Signing Time: 24-Feb-2023 | 08:56:33 GMT

DocuSign Envelope ID: 9E29EF18-BCFE-4AB3-97EF-2C4DE9AE8339

Activated charcoal may reduce the effect of acetylcysteine.

It is advisable not to mix ACC 200 powder for oral solution with other medicines.

It is precautionary to advise the administration of oral antibiotics at least two hours before or after ACC 200 PWDER FOR ORAL SOLUTION.

Concurrent administration of nitroglycerin and ACC 200 POWDER FOR ORAL SOLUTION causes significant hypotension and leads to temporal artery dilation with possible onset of headache.
If concurrent administration of nitroglycerin and ACC 200 POWDER FOR ORAL SOLUTION is required, patients should be monitored and warned for hypotension that can be severe and accompanied by a headache.

Concurrent use of ACC 200 powder for oral solution and carbamazepine may result in sub-therapeutic carbamazepine levels.

4.6 Fertility, pregnancy and lactation:

Pregnancy

The safety of ACC 200 powder for oral solution in pregnancy have not been established (see section 4.3).

Breastfeeding

The safety of ACC 200 powder for oral solution in breastfeeding have not been established.

4.7. Effects on ability to drive and use machines:

ACC 200 powder for oral solution should be used with caution whilst driving and using machines as ACC 200 powder for oral solution may cause headaches.

DocuSign Envelope ID: 9E29EF18-BCFE-4AB3-97EF-2C4DE9AE8339

Applicant	:	Sandoz SA (Pty) Ltd
Proprietary name	:	ACC 200 POWDER FOR ORAL SOLUTION
Dosage form and strength	:	Powder for oral solution. Each sachet contains 200 mg acetylcysteine.
Date of submission	:	13 February 2023

4.8. Undesirable effects:

Blood and the lymphatic system disorders:

Frequency unknown: Haemoptysis

Immune system disorders:

Less frequent: Hypersensitivity, anaphylactic shock, anaphylactic/anaphylactoid reaction.

Nervous system disorders:

Less frequent: Headache.

Ear and labyrinth disorders:

Less frequent: Tinnitus.

Cardiac disorders:

Less frequent: Tachycardia.

Vascular disorders:

Less frequent: Hypotension, haemorrhage.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Bronchospasm, dyspnoea.

Frequency unknown: Rhinorrhoea.

Gastrointestinal disorders:

Less frequent: Vomiting, diarrhoea, stomatitis, abdominal pain, nausea, dyspepsia.

Initials: DocuSigned by: NM Signer Name: Nkosinathi Mbokane Signing Reason: I approve this document Signing Time: 24-Feb-2023 | 08:57:09 GMT D22075D453FC4A80B696E2507679FFC4
Signature: DocuSigned by: Nkosinathi Mbokane Signer Name: Nkosinathi Mbokane Signing Reason: I approve this document Signing Time: 24-Feb-2023 | 08:57:20 GMT

DocuSign Envelope ID: 9E29EF18-BCFE-4AB3-97EF-2C4DE9AE8339

Applicant	:	Sandoz SA (Pty) Ltd
Proprietary name	:	ACC 200 POWDER FOR ORAL SOLUTION
Dosage form and strength	:	Powder for oral solution. Each sachet contains 200 mg acetylcysteine.
Date of submission	:	13 February 2023

Skin and subcutaneous tissue disorders:

Less frequent: Urticaria, rash, angioedema, pruritus.

General disorders and administration site conditions:

Less frequent: Fever.

Frequency unknown: Oedema of the face, chills.

The occurrence of serious skin reactions such as Steven-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 medicine 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 use of acetylcysteine terminated immediately.

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 medicines is important. It allows continued monitoring of the benefit/risk balance of the medicines. 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

Initials: DocuSigned by: NM
Signer Name: Nkosinathi Mbokane
Signing Reason: I approve this document
Signing Time: 24-Feb-2023 | 08:57:33 GMT
D22075D453FC4A80B696E2507679FFC4
Signature: DocuSigned by: Nkosinathi Mbokane
Signer Name: Nkosinathi Mbokane
Signing Reason: I approve this document
Signing Time: 24-Feb-2023 | 08:57:46 GMT

DocuSign Envelope ID: 9E29EF18-BCFE-4AB3-97EF-2C4DE9AE8339

Applicant	:	Sandoz SA (Pty) Ltd
Proprietary name	:	ACC 200 POWDER FOR ORAL SOLUTION
Dosage form and strength	:	Powder for oral solution. Each sachet contains 200 mg acetylcysteine.
Date of submission	:	13 February 2023

4.9. Overdose:

An acute overdose of ACC 200 POWDER FOR ORAL SOLUTION can cause gastrointestinal symptoms such as nausea, vomiting and diarrhoea.

Treatment of overdose:

Treatment of overdose is to be symptomatic and supportive treatment as indicated by the patient's clinical condition.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

Category and class: A7.2 Respiratory System - Mucolytics

Pharmacotherapeutic group: Mucolytics

ATC code: R05CB01

N-acetylcysteine has mucolytic action on mucoid secretions in the respiratory tract. It acts mostly on the mucoproteins, through its free sulfhydryl groups, to open disulphide bonds and lower the viscosity of the mucus.

5.2. Pharmacokinetic properties

Absorption:

Following oral administration, acetylcysteine is rapidly and almost completely absorbed and metabolised in the liver to cysteine (the pharmacologically active metabolite), diacetylcysteine, cysteine and further mixed disulphides. Peak plasma concentrations occur about 0,5 to 1 hour after oral doses of 200 mg to 600 mg.

DocuSign Envelope ID: 9E29EF18-BCFE-4AB3-97EF-2C4DE9AE8339

Applicant	:	Sandoz SA (Pty) Ltd
Proprietary name	:	ACC 200 POWDER FOR ORAL SOLUTION
Dosage form and strength	:	Powder for oral solution. Each sachet contains 200 mg acetylcysteine.
Date of submission	:	13 February 2023

Distribution:

Due to the high first-pass effect, the bioavailability of orally administered acetylcysteine is very low (approximately 10 %). Maximum plasma concentrations are achieved after 1 - 3 hours with the maximum plasma concentration of the metabolite cysteine in the range of approximately 2 µmol/L. The protein binding of acetylcysteine is approximately 50 %.

Biotransformation:

Acetylcysteine and its metabolites occur in three different forms in the organism: partially in free form, partially bound to proteins via liabile disulphide bonds and partially as incorporated amino acid. Acetylcysteine is excreted almost exclusively in the form of inactive metabolites (inorganic sulphates, diacetylcysteine) 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 acetylcysteine); the plasma clearance was determined to be 0,11 L/h/kg (in total) and 0,84 L/h/kg (reduced acetylcysteine), 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 in breast milk.

Initials: DocuSigned by: NM
Signer Name: Nkosinathi Mbokane
Signing Reason: I approve this document
Signing Time: 24-Feb-2023 | 08:58:36 GMT
D22075D453FC4A80B696E2507679FFC4
Signature: DocuSigned by: Nkosinathi Mbokane
Signer Name: Nkosinathi Mbokane
Signing Reason: I approve this document
Signing Time: 24-Feb-2023 | 08:59:00 GMT

DocuSign Envelope ID: 9E29EF18-BCFE-4AB3-97EF-2C4DE9AE8339

Applicant	:	Sandoz SA (Pty) Ltd
Proprietary name	:	ACC 200 POWDER FOR ORAL SOLUTION
Dosage form and strength	:	Powder for oral solution. Each sachet contains 200 mg acetylcysteine.
Date of submission	:	13 February 2023

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

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose

Ascorbic acid

Saccharin

Orange Flavour Dry 1:1000 Sotteri 289

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months

6.4. Special precautions for storage

Store at or below 30 °C.

This medicine does not require any special storage conditions.

6.5. Nature and contents of container

Initials: DocuSigned by: NM Signer Name: NkosinathiMbokane Signing Reason: I approve this document Signing Time: 24-Feb-2023 | 08:59:18 GMT D22075D453FC4A80B696E2507679FFC4
Signature: DocuSigned by: Nkosinathi Mbokane Signer Name: Nkosinathi Mbokane Signing Reason: I approve this document Signing Time: 24-Feb-2023 | 08:59:34 GMT D22075D453FC4A80B696E2507679FFC4

Applicant	:	Sandoz SA (Pty) Ltd
Proprietary name	:	ACC 200 POWDER FOR ORAL SOLUTION
Dosage form and strength	:	Powder for oral solution. Each sachet contains 200 mg acetylcysteine.
Date of submission	:	13 February 2023

The ACC 200 powder for oral solution is packed into thermo-sealed sachets made of a triple layer foil out of polyethylene-aluminium-paper.

The sachets are packaged together with the leaflet into the cardboard carton.

The sachets are available in pack sizes of 10, 20, 25 or 40.

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]

Magwa Crescent West

Waterfall City

Jukskei View

Midrand

2090

8. REGISTRATION NUMBERS

To be allocated by SAHPRA upon registration.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: To be allocated by SAHPRA upon registration

10. DATE OF REVISION OF THE TEXT

Not applicable.

Initials: DocuSigned by: NM
Signer Name: Nkosinathi Mbokane
Signing Reason: I approve this document
Signing Time: 24-Feb-2023 | 09:00:43 GMT
D22075D453FC4A80B696E2507679FFC4

Signature: DocuSigned by: Nkosinathi Mbokane
Signer Name: Nkosinathi Mbokane
Signing Reason: I approve this document
Signing Time: 24-Feb-2023 | 09:00:58 GMT

DocuSign Envelope ID: 9E29EF18-BCFE-4AB3-97EF-2C4DE9AE8339

Applicant	:	Sandoz SA (Pty) Ltd
Proprietary name	:	ACC 200 POWDER FOR ORAL SOLUTION
Dosage form and strength	:	Powder for oral solution. Each sachet contains 200 mg acetylcysteine.
Date of submission	:	13 February 2023

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

Initials: DocuSigned by: NM
Signer Name: Nkosinathi Mbokane
Signing Reason: I approve this document
Signing Time: 24-Feb-2023 | 09:01:11 GMT
D22075D453FC4A80B696E2507679FFC4

Signature: DocuSigned by: Nkosinathi Mbokane
Signer Name: Nkosinathi Mbokane
Signing Reason: I approve this document
Signing Time: 24-Feb-2023 | 09:01:27 GMT