PROPOSED PROFESSIONAL INFORMATION FOR ACTEFF 600

SCHEDULING STATUS

S1

1. NAME OF THE MEDICINE

ACTEFF 600 effervescent tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each effervescent tablet contains 600 mg acetylcysteine.

ACTEFF 600 is sugar free.

Contains sweetener (sucralose, 10 mg per effervescent tablet).

Contains salt (sodium, 115 mg per tablet).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

ACTEFF 600 effervescent tablets are round, flat, white to yellowish tablets with a score line.

When an **ACTEFF 600** effervescent tablet is dissolved in a glass of water, the appearance of the solution is clear with gas bubbles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ACTEFF 600 effervescent tablets are used as a mucolytic in acute respiratory conditions.

4.2 Posology and method of administration

Posology:

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:

ACTEFF 600 effervescent tablets are taken dissolved in a glass of water after meals.

Duration of use:

ACTEFF 600 effervescent tablets should not be taken for more than 14 days without medical advice.

Paediatric patients:

Due to the high content of active substance, acetylcysteine 600 mg should not be used in children less than 14 years of age.

4.3 Contraindications

- Hypersensitivity to acetylcysteine and/or the other ingredients of **ACTEFF 600** (see section 6.1).
- Safety in pregnancy has not been established. **ACTEFF 600** should not be used during pregnancy (see section 4.6).
- Active peptic ulceration.

4.4 Special warnings and precautions for use

ACTEFF 600 should be used with caution in asthmatic patients. If bronchospasm occurs, the use of acetylcysteine must be stopped immediately and appropriate treatment initiated.

ACTEFF 600 should be used with caution in patients with a history of peptic ulcer disease, both because drug-induced nausea and vomiting may increase the risk of gastrointestinal haemorrhage in patients predisposed to the condition, and because of a theoretical risk that mucolytics may disrupt the gastric mucosal barrier.

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 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 occur, the patient should consult their health care provider without delay and use of acetylcysteine be terminated (see section 4.8).

Intolerance

Caution is advised in patients with histamine intolerance. Treatment with acetylcysteine for longer periods should be avoided in such patients, as acetylcysteine affects histamine metabolism and can result in symptoms of intolerance (e.g., headache, runny nose, itching).

Excipient warnings

ACTEFF 600 contains 115 mg sodium per effervescent tablet. This is equivalent to 5,75 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction

Combined administration of **ACTEFF 600** 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.

Tetracycline hydrochloride (with the exception of doxycycline) and other oral antibiotics must be administered separately from **ACTEFF 600** and with an interval

of at least 2 hours.

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 concomitant treatment with glyceryl trinitrate and acetylcysteine 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 charcoal in high doses (as an antidote) can reduce the effectiveness of acetylcysteine.

Acetylcysteine can affect the colorimetric determination of salicylates. In urine tests, acetylcysteine can affect the results of determinations of ketone bodies. The dissolution of **ACTEFF 600** together with other medicines is not recommended.

4.6 Fertility, pregnancy and lactation

Safety and efficacy of acetylcysteine in pregnancy and lactation have not been established (see section 4.3).

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. **ACTEFF 600** should not be used during pregnancy.

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

ACTEFF 600 has no known effect on the ability to drive and use machines.

4.8 Undesirable effects

System Organ Class	Frequency	Side effects
Immune system disorders	Less frequent Frequency unknown	Hypersensitivity reactions Anaphylactic shock, anaphylactic / anaphylactoid reactions
Nervous system disorders	Less frequent	Headache, convulsions, syncope
Eye disorders	Less frequent	Blurred vision
Ear and labyrinth disorders	Less frequent	Tinnitus
Cardiac disorders	Less frequent	Tachycardia
Vascular disorders	Less frequent	Haemorrhage, hypertension
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea, bronchospasm - predominantly in patients with hyperactive reactive bronchial system in association with bronchial asthma
Gastrointestinal disorders	Less frequent Frequency unknown	Nausea, vomiting, diarrhoea, abdominal pain, stomatitis Dyspepsia

Hepato-biliary disorders	Less frequent	Disturbances of the liver function, acidosis
Skin and subcutaneous tissue disorders	Less frequent	*Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria, rash, angioedema, itching, exanthema, pruritus, flushing
Musculoskeletal, connective tissue and bone disorders	Less frequent	Arthralgia
General disorders and administration site conditions	Less frequent Frequency unknown	Fever, hypotension Facial oedema

*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, the use of acetylcysteine must be discontinued immediately.

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.

Reporting of suspected adverse reactions:

Reporting of suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care 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.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cough and cold preparations;

Mucolytics

ATC Code: R05CB01

Mechanism of action

Acetylcysteine is a mucolytic medicine 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 mucopolysaccharide chains and that it has a depolymerising 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 Pharmacokinetic properties

Absorption

Following oral administration, acetylcysteine is rapidly and almost completely absorbed and metabolised 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 %). Maximum plasma concentrations are achieved after 1 to 3 hours. 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 labile 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); 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid

Orange flavour (containing butylated hydroxyl anisole, citric acid, gum Arabic, maltodextrine, sweet orange essential oil and sweet orange essential oil terpenless)

Sodium bicarbonate

Sucralose.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

It is recommended that **ACTEFF 600** is used within 90 days after opening.

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original container, protected from moisture and light.

6.5 Nature and contents of container

One polypropylene tube with a white polyethylene cap, containing a desiccant cage, and placed in an outer carton. Each tube contains 10 effervescent tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in

accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Activo Health (Pty) Ltd.

Block B

Arena Office Park

272 West Avenue

Centurion

0157

South Africa

8. REGISTRATION NUMBER

50/10.2/0539

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of Registration: 27 September 2022