Approved Professional Information

SCHEDULING STATUS

S1

1. NAME OF THE MEDICINE

UKASTYN 200 mg, Effervescent tablets.

UKASTYN 600 mg, Effervescent tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

UKASTYN 200 mg, Effervescent tablets.

Each effervescent tablet contains Acetylcysteine 200 mg.

Contains Sugar – Lactose 825,9 mg.

Contains Sweetener - Aspartame 3 mg.

UKASTYN 600 mg, Effervescent tablets.

Each effervescent tablet contains Acetylcysteine 600 mg.

Contains Sugar – Lactose 1919,5 mg.

Contains Sweetener - Aspartame 15 mg.

For full list of excipients, (see Section 6.1).

3. PHARMACEUTICAL FORM

UKASTYN 200 mg - White, beveled round tablets, plain on one side and with break line on the other side.

UKASTYN 600 mg - White, flat round, beveled tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

UKASTYN is used as a mucolytic, of non-infective secretions in cystic fibrosis and in respiratory conditions.

4.2. Posology and method of administration

Posology:

Children from 2 to 5 years of age:

UKASTYN 200 mg: 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:

UKASTYN 200 mg: 1 effervescent tablet twice daily (equivalent to 400 mg acetylcysteine/day).

Adults and adolescents from 14 years of age:

UKASTYN 200 mg: 1 effervescent tablet 2 to 3 times daily (equivalent to 400 to 600 mg acetylcysteine/day).

UKASTYN 600 mg: ½ effervescent tablet twice daily or 1 effervescent tablet once daily (equivalent to 600 mg acetylcysteine per day).

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

Method of administration

Oral use.

UKASTYN should be dissolved in a glass of water before use.

4.3. Contraindications

- Hypersensitivity to acetylcysteine or any of the other ingredients of **UKASTYN** effervescent tablets (see section 6.1).
- Safety in pregnancy has not been established. **UKASTYN** effervescent tablets should not be used during pregnancy (see section 4.6).
- Active peptic ulceration.
- **UKASTYN** is contraindicated in children below 2 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, as contained in **UKASTYN**.

If cutaneous and mucous membrane changes appear, medical advice should be sought immediately and the use of **UKASTYN** be stopped (see also section 4.8).

Patients with bronchial asthma should be closely monitored during therapy.

If bronchospasm occurs, **UKASTYN** should be stopped immediately and appropriate treatment must be instituted.

Caution is advised with the use of **UKASTYN** in patients with a history of ulcer, especially if, in addition, other medicines are taken that are irritating to the mucous membranes of the Gastrointestinal tract. Medicine-induced nausea and vomiting may occur and may increase the risk of gastrointestinal haemorrhage in patients predisposed to the condition. Mucolytics, including **UKASTYN** may disrupt the gastric mucosal barrier.

Caution should be exercised in patients with histamine intolerance. Long-term therapy of these patients should be avoided as acetylcysteine affects histamine metabolism and may lead to symptoms of intolerance (e.g. headache, runny nose, itching).

Use of **UKASTYN**, especially at the beginning of treatment, can cause a liquefaction and thus lead to an increase in the volume of the bronchial secretion. If the patient is unable to cough this up sufficiently, appropriate measures should be taken (e.g. postural drainage and suction).

Children under 2 years of age

UKASTYN must not be used in children under 2 years of age (see section 4.3).

UKASTYN contains sodium hydrogen bicarbonate 85 mg in **UKASTYN 200 mg** and 240 mg in **UKASTYN 600 mg**, corresponding to 4,25 % and 12 % of the WHO recommended maximum daily sodium intake with food of 2 g.

This should be taken into account in people taking controlled sodium (low-sodium / low-sodium) diet.

UKASTYN contains aspartame

Aspartame is a source of phenylalanine and can be harmful to patients with phenylketonuria.

UKASTYN contains lactose monohydrate

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take **UKASTYN.**

4.5 Interaction with other medicines and other forms of interaction

Interaction studies have only been conducted in adults.

With the combined use of mucolytic medicines such as acetylcysteine with antitussives (cough suppressants), a dangerous accumulation of secretion can arise due to the restricted cough reflex.

An especially careful diagnosis is required for this combination treatment.

The use of activated charcoal can reduce the effects of acetylcysteine.

Reports of inactivation of antibiotics (tetracycline with exception of doxycycline, aminoglycosides, penicillins) by acetylcysteine has so far only concerned in-vitro experiments in which the relevant substances were mixed directly. Oral antibiotics should be administered separately from **UKASTYN** and at least two hours apart.

Acetylcysteine / nitroglycerin

Concomitant administration of **UKASTYN** can possibly increase the vasodilatory effect of glycerol trinitrate (nitroglycerin).

If co-treatment with nitroglycerin and **UKASTYN** is considered necessary, the patient should be monitored for the development of hypotension that may be severe and be advised that headache may occur.

Simultaneous intake of **acetylcysteine and carbamazepine** can result in sub-therapeutic carbamazepine concentrations.

Changes in the determination of laboratory parameters

Acetylcysteine can influence the colorimetric determination of salicylates.

During urine tests, acetylcysteine can affect the results of the determination of ketone bodies.

Dissolving **UKASTYN** with other medicines is not recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

For acetylcysteine there are insufficient clinical data on exposed pregnant women.

Animal studies of reproductive toxicology do not indicate direct or indirect harmful effects. **UKASTYN** should not be used during pregnancy.

Breastfeeding

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

Fertility

There are no data on the influence of acetylcysteine on human fertility. In animal studies, no harmful effects on fertility were observed for therapy-relevant doses of acetylcysteine.

4.7. Effects on ability to drive and use machines

UKASTYN has no known influence on the ability to drive or use machinery.

4.8. Undesirable effects

The most common side effects associated with oral use of **UKASTYN** affect the gastrointestinal tract.

Hypersensitivity reactions, including anaphylactic shock, anaphylactic / anaphylactoid reactions, bronchospasm, angioedema, rash and itching were reported less frequently.

Tabulated list of adverse reactions

System Organ Class	**Frequency Category**
Immune system disorders	
Hypersensitivity reactions, angioedema Anaphylactic shock, Anaphylactic / anaphylactoid reactions	Less frequent
Nervous system disorders:	
Headache, convulsions, syncope	Less frequent
Ear and labyrinth disorders:	
Tinnitus	Less frequent
Eye disorders	
Blurred vision	Less frequent
Cardiac disorders	
Tachycardia	Less frequent
Vascular disorders	
Haemorrhage Hypertension	Less frequent
Respiratory, thoracic and mediastinal disorders	
Bronchial spasm, - predominantly in patients with hyperactive reactive bronchial system in association with bronchial asthma. Dyspnoea	Less frequent
Gastrointestinal disorders:	
Vomiting	Less frequent
Diarrhoea	
Stomach pain	

System Organ Class	Frequency Category
Stomatitis	
Nausea	
Dyspepsia	Frequency unknown
Skin and subcutaneous tissues disorders:	
Stevens-Johnson syndrome (see section 4.4), toxic epidermal necrolysis, exanthema, pruritus, flushing. Urticaria Rash Itching (pruritis)	Less frequent
General disorders and administration site conditions:	
Fever Hypotension	Less frequent
Facial oedema	Frequency unknown

Various studies have confirmed a decrease in platelet aggregation during the use of acetylcysteine. The clinical significance of this is so far unclear.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via The '6.04 Adverse Reactions Reporting Form'. Found 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: Mucolytics

ATC code: R05 CB 01

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 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 diacetylcystine, 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 aminoacid.
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.

Environmental Risk Assessment

UKASTYN is a well-established active ingredient used in pharmaceutical preparations for human use. Given the anticipated pattern of use and disposal of the product, the environmental exposure of the active substance and metabolites are expected to be very limited. The use of **UKASTYN** is not considered warranting any environmental concerns or requiring any special product labelling.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Acetylcysteine

Ascorbic acid

Citric acid (E 330)

Sodium bicarbonate

Crospovidone (Type B)

Lactose (Directly Compressible)

Orange flavor

Peppermint flavor

Aspartame

Leucine

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

Proposed Shelf-life is 24 months.

6.4. Special precautions for storage

Store at or below 25 °C.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5. Nature and contents of container

UKASTYN 200 mg are proposed to be marketed in the Polypropylene tube with moisture-proof LDPE assembling lid as a closure, containing silica gel as a desiccant Acetylcysteine Effervescent Tablets 200 mg packed in above tube packs will be further packed in preprinted cartons with package leaflet according to the approved pack size. Pack size -1 tube of 20's, 25's, 40's (2 tubes) in a carton.

UKASTYN 600 mg are proposed to be marketed in the Blister pack comprises of Paper/Al/PE composite film as forming and lidding material Acetylcysteine Effervescent Tablets 600 mg packed in above blister packs will be further packed in preprinted cartons with package leaflet according to the approved pack size.

UKASTYN 600 mg are proposed to be marketed in the Polypropylene tube with moisture-proof LDPE assembling lid as a closure, containing silica gel as a desiccant Acetylcysteine Effervescent Tablets 600 mg packed in above tube packs will be further packed in preprinted cartons with package leaflet according to the approved pack size. Pack size -1 tube of 15's in a carton, 1 blister of 10 tablets each and 2 blisters of 20 tablets each.

6.6. Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

7. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

AUROGEN SA (Pty) Ltd

Woodhill Office Park, Building 1, First Floor

53 Phillip Engelbrecht Avenue

Meyersdal, Ext. 12, 1448

Johannesburg

South Africa

8. REGISTRATION NUMBER

UKASTYN 200 mg: 56/10.3/0141.139

UKASTYN 400 mg: 56/10.3/0142.140

9. DATE OF FIRST AUTHORISATION

19 September 2023