Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Trebon 600 mg powder for oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet with powder used for the preparation of oral solution contains 600 mg of acetylcysteine.

Excipients with known effect
Each sachet contains 2,167.9 mg sorbitol and 9.5 mg sucrose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for oral solution

White powder with lemon flavour.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Trebon is indicated in adults as a mucolytic therapy in chronic bronchitis and other respiratory conditions associated with thick mucus hypersecretion.

4.2 Posology and method of administration

Posology
In general the usual recommended dosage is:
600mg once daily

The dosage may be increased according to the instructions of the treating doctor based on the assessment of treatment outcomes.

Duration of treatment
The duration of therapy is dependent on the nature and severity of the illness, and should be decided by the doctor.

Paediatric population
Children older than 2 years of age and adolescents
The safety and efficacy of Trebon is not established in children aged 2 years and older and adolescents (see section 4.4). Other products with lower strengths of acetylcysteine are more suitable for this age group.
Children under 2 years of age
Trebon is contraindicated in children aged under 2 years (see section 4.3).

Elderly
Limited data in patients over 65 years of age is available.

Renal and hepatic impairment
In patients with renal or hepatic impairment there is insufficient data on whether dosage adjustments are required. Renal and hepatic impairment can reduce clearance and increase acetylcysteine plasma levels which may result in an increase in adverse drug reactions due to drug accumulation (see section 5.2).
Method of administration
Dissolve the content of one sachet in half a glass of water. This produces a solution that should be consumed immediately.

4.3 Contraindications

-Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
-The product should not be used in children under 2 years of age.

4.4 Special warnings and precautions for use

Serious skin reactions have been reported whilst taking acetylcysteine, but these occur rarely. For this reason, medical advice should be sought immediately and the patient should stop taking acetylcysteine in the event of new-onset changes to the skin and mucous membranes. See also section 4.8.

This product should be used with caution by patients with a history of peptic ulcer disease.

Acetylcysteine can, especially at the start of treatment, cause thinning and increased volume of bronchial secretions. If the patient is not able to expectorate this adequately, appropriate supportive measures should be implemented (such as postural drainage and suction removal).
The medicine should be administered with caution to asthmatic patients, due to the risk of bronchospasm. In the event of bronchospasm the drug should be discontinued immediately.

This product should be used with caution by patients with histamine intolerance. They should avoid long-term therapy because Acetylcysteine affects the metabolism of histamine and can lead to symptoms of intolerance (e.g. headaches, rhinitis, itching).

Renal and hepatic impairment
In patients with renal or hepatic impairment there is insufficient data on whether dosage adjustments are required. Renal and hepatic impairment can reduce clearance and increase acetylcysteine plasma levels which may result in an increase in adverse drug reactions due to drug accumulation (see section 5.2).

There is no evidence of the efficacy of acetylcysteine in the management of cystic fibrosis.

Pediatric population
Mucolytic drugs may obstruct the airways of children under 2 years of age, due to the physiological characteristics of the airways in this age group. The ability to cough up mucus may be limited. Therefore, the product must not be used in children under 2 years of age.
The safety and efficacy of Trebon is not established in children aged 2 years and older and adolescents, due to the high content of acetylcysteine in this medicinal product. Other products with lower strengths of acetylcysteine are more suitable for this age group.

Sorbitol
This medicinal product contains 2,167.9 mg sorbitol in each sachet. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

Sucrose
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product. May be harmful to the teeth.

Sodium
This medicinal product contains less than 1 mmol sodium per sachet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

Antibiotics
In vitro experiments report an inactivation of certain antibiotics (tetracyclines, aminoglycosides, fluoroquinolones, carbapenem, cephalosporins, penicillins) due to acetylcysteine when the substances were directly mixed. Therefore, antibiotics should be administered separately and at an interval of at least 2 hours.

Antitussives
Combined use of antitussives (cough-relieving agents) with acetylcysteine may cause dangerous secretory congestion due to the reduced cough reflex.

Nitroglycerin
Administration of Trebon may lead to an increase in the vasodilatory and anti- platelet effect of glyceryl trinitrate. If the drugs are administered together the patient should be monitored for a hypotensive response.
Activated charcoal
Co-administration with activated charcoal can reduce the effectiveness of acetylcysteine.
Laboratory tests
Acetylcysteine may affect the recovery of salicylates in the colourimetric assay and also may give false-positive ketone bodies results in urinalysis (a biochemical parameter of the general urine test that is determined along with glucose in diabetic patients). This should be taken into account in patients having any blood or urine test, while taking acetylcysteine.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of acetylcysteine in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Trebon is not recommended during pregnancy.

Breast-feeding
It is unknown whether acetylcysteine /metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Trebon therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
There are no human data from the use of acetylcysteine in fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

In the evaluation of side effects following frequencies are defined as:
Very common (≥ 1/10);
Common (≥ 1 /100 to < 1/10);
Uncommon (≥ 1/1,000 to <1/ 100);
Rare (≥ 1/10,000 to < 1/1,000);
Very rare (< 1/10,000);
Not known (Cannot be estimated from the available data).

Immune system disorders
Uncommon: Hypersensitivity
Very rare: Anaphylactic shock, anaphylactic/anaphylactoid reaction
Nervous system disorders
Uncommon: Headache
Ear and labyrinth disorders
Uncommon: Tinnitus
Cardiac disorders
Uncommon: Tachycardia
Vascular disorders
Uncommon: Hypotension
Very rare: Haemorrhage
Respiratory, thoracic and mediastinal disorders
Rare: Bronchospasm, dyspnoea
Gastrointestinal disorders
Uncommon: Vomiting, diarrhoea, stomatitis, abdominal pain, nausea
Rare: Dyspepsia
Skin and subcutaneous tissue disorders
Uncommon: Urticaria, rash, angioedema, pruritus
General disorders and administration site conditions
Uncommon: Fever

Not known: Oedema

Acetylcysteine may have an undesirable effect on the gastric mucosa in patients with a history of peptic ulcer.

Serious skin reactions have been reported whilst taking acetylcysteine, but these occur rarely. For this reason, in the event of new onset changes of the skin and mucous membranes medical advice should be sought immediately and the patient should stop taking acetylcysteine.
A reduction of blood platelet aggregation in the presence of acetylcysteine has been confirmed by various studies. The clinical relevance is not yet understood.

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 professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

There have been no cases of toxic overdose observed with orally-dosed acetylcysteine. Oral doses of up to 500mg/kg of acetylcysteine were tolerated without toxic effects.

a) Symptoms of intoxication

The following symptoms have been reported after overdoses of intravenous acetylcysteine: anaphylactoid reaction, bronchospasm and gastro-intestinal symptoms such as nausea, vomiting and diarrhoea. Oral overdose may lead to gastrointestinal adverse effects, such as nausea, vomiting and diarrhoea.

b) Treatment for 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

Pharmacotherapeutic group: Mucolytics ATC code: R05 CB01

Mechanism of action
The mechanisms of action of NAC in these respiratory indications include mucolytic effects.
The mucolytic action is mediated by a reduction in the viscosity of bronchial mucus. This is explained by the depolymerisation with the disulfide bridges between the macromolecules in the mucus being opened.

5.2 Pharmacokinetic properties

Absorption
After oral administration acetylcysteine is rapidly and almost completely absorbed.

The oral bioavailability of acetylcysteine is very low (between 6 and 10%) due to high first pass effect. In humans maximum plasma concentration is reached in 1 to 3 hours after an oral dose.

Distribution
Approximately 50% of acetylcysteine is protein bound after oral administration.

There is no information available on the behaviour of acetylcysteine at the blood-brain barrier in humans.

Biotransformation
Acetylcysteine is metabolized by rapid hepatic biotransformation. The metabolites occur in three different forms: in free form into cysteine the active metabolite, bound to protein via labile disulfide bonds and as integral amino acids into diacetylcystine and cystine.

Elimination
Excretion of inactive metabolites (inorganic sulfates, diacetylcystine) is via the kidneys. The elimination half-life after oral administration is 6.25 hours.

Hepatic and Renal impairment
There is evidence that clearance of acetylcysteine can be significantly reduced up to 90 % in the subjects with end-stage renal disease. This could result in a dramatically longer half-life and a marked increase in systemic exposure to acetylcysteine in patients with end-stage renal disease. It is not known to what extent the results can be extrapolated to the less severe forms of renal impairment that are more likely to be encountered during routine use of the proposed product.
Restricted liver function causes the plasma half-life to increase up to 8 hours, based in one study of patients with chronic liver disease. The total clearance of acetylcysteine was found to be significantly reduced following an intravenous dose of 600 mg over three minutes in nine subjects with hepatic cirrhosis. See also section 4.2.

Elderly
Limited data in patients over 65 years of age is available.

5.3 Preclinical safety data

Reproductive toxicology
No evidence of teratogenicity was identified in non-standard embryo toxicity studies in rabbits and rats.
Acetylcysteine crosses the placenta in rats and can be detected in amniotic fluid.

There are no non-clinical data of relevance to the prescriber which are additional to that already included in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid (E330)
Lemon juice flavour in powder (contains: natural flavouring substances, maltodextrin (maize), modified starch (E1450) (waxy maize), sucrose)
Saccharin sodium (E954)
Macrogol (E1521)
Sorbitol (E420)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
After preparation, the solution should be used immediately.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Sachets consisting of paper, aluminum foil, and polyethylene.
Pack size: 10, 20 or 30 sachets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

UNI-PHARMA KLEON TSETIS PHARMACEUTICAL LABORATORIES S.A.
14th km National Road 1
GR-145 64 Kifissia
Greece

8 MARKETING AUTHORISATION NUMBER

PA1732/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th June 2020

10 DATE OF REVISION OF THE TEXT