SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Acetylcysteine 600mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 600 mg acetylcysteine.

Excipient with known effect

Sodium (less than 23mg per tablet)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White, round convex tablets 13mm in diameter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Acetylcysteine 600 mg tablet is a mucolytic agent for the adjunctive therapy of respiratory tract disorders characterised by excessive, viscous mucus, including chronic obstructive airways disease.

4.2 Posology and method of administration

In general the usual recommended dosage is:

Adults including elderly and adolescents 14 years and older: 600 mg (1 tablet) once daily.

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

Hepatic and Renal Impairment:

In patients with impaired kidney or liver impairment there is insufficient data on whether dosage adjustments are required. Hepatic and renal impairment can reduce clearance which may result in an increase in adverse drug reactions due to drug accumulation.

For oral use.

Swallow the tablet with a drink of water. The tablet should be taken after food.

4.3 Contraindications

Hypersensitivity to acetylcysteine or to any of the excipients listed in section 6.1.
These tablets should not be used in children under 14 years of age.

4.4 Special warnings and precautions for use

Allergic symptoms, including generalized urticaria, have been reported; discontinue administration if symptoms cannot be medically controlled.

Serious skin reactions such as Stevens-Johnson syndrome and Lyell's syndrome 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.

There are no studies on the efficacy and safety of once daily acetylcysteine 600 mg effervescent tablet in the adolescent population. However, mild, moderate or severe adverse reactions have been reported with the use of IV acetylcysteine in the adolescent population.

Patients with bronchial asthma should be closely monitored during treatment. If a bronchospasm occurs, acetylcysteine administration must be immediately stopped and appropriate treatment started.

Caution is advised in patients with peptic ulcer disease or history thereof, at risk of gastrointestinal bleeding (history of peptic ulcer, esophageal varices), particularly with the simultaneous administration of other drugs with a known irritating effect on the gastric mucosa. Drug monitoring, animal testing, and extensive experience with acetylcysteine, however, do not indicate an increased risk of irritation of the gastric

mucosa by acetylcysteine at a dosage up to 600 mg/day.

Acetylcysteine can increase the intensity of vomiting.

This product should be used with caution by patients with histamine intolerance. They should avoid long-term therapy because Acetylcysteine 600mg Effervescent Tablets affect the metabolism of histamine and can lead to symptoms of intolerance (e.g. headaches, rhinitis, itching).

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).

No specific studies have been performed in patients with renal or hepatic impairment. Hepatic and renal impairment can reduce clearance and increase acetylcysteine plasma levels which may result in an increase in adverse drug reactions due to drug accumulation.

This medicine contains less than 1 mmol sodium (23mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Analysis of interactions with other medicines has been performed only in adults.

Antitussives
If this product is used in combination with cough-relieving medicines (antitussives) the suppressed cough reflex may cause a dangerous build-up of secretions, which means that the indication for this combination treatment should be established particularly carful.

Carbamazepine
Simultaneous use of acetylcysteine and carbamazepine could lead to subtherapeutic carbamazepine blood levels.

Activated charcoal
Co-administration with activated charcoal can reduce the effectiveness of acetylcysteine.

Antibiotics
Reports of inactivation of antibiotics by acetylcysteine indicate that this inactivation occurs only when these substances are mixed directly together in vitro. These antibiotics include tobramycin, netilmicin, piperacillin, sodium-ampicillin, erythromycin lactobionate, cefsulodin, ceftazidime, imipenem. Orally administered acetylcysteine does not interfere, regarding bioavailability, with amoxicillin, erythromycin, doxycycline, bacampicillin, thiamphenicol, and amoxicillin in

combination with clavulanic acid. Nevertheless, administration of oral doses of antibiotics and acetylcysteine effervescent tablets should be separated by minimum period of two hours. This does not apply to the antibiotics cefixime or loracarbef.

Acetylcysteine and glyceryl trinitrate (nitroglycerin)
Simultaneous administration of these drugs may increase the vasodilatory and platelet aggregation-inhibiting effect of glyceryl trinitrate and increase dilation of the temporal artery. If such combined treatment is considered necessary, the patient should be monitored for possible hypotension, which can be serious and may be indicated by headaches.

Interface with the measurement of laboratory parameters
Acetylcysteine can influence the colourmetric assay of salicyclates.
Acetylcysteine can influence results when measuring ketones in urine.

Due to its chelating properties, acetylcysteine can reduce the bioavailability of salts of heavy metals such as gold and iron salts and of calcium salts. In the absence of exact data in this regard, it is advisable to separate the intake of acetylcysteine and these salts or to choose a different route of administration.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited data on the use of acetylcysteine in pregnant women. Animal studies do not indicate direct or indirect adverse effects on pregnancy, embryonic/foetal development, birth or postnatal development (see also section 5.3). As a precautionary measure, it is preferable to avoid the use of Acetylcysteine during pregnancy. Before use during pregnancy, the possible risks should be weighed against the possible benefits.

Breast-feeding
There is insufficient information on the excretion of acetylcysteine or its metabolites in human milk. Risk for infants cannot be excluded. Use during pregnancy and while breast-feeding should be subject to careful consideration of the risk/benefit balance.

Fertility
No human data on the effect of acetylcysteine are available. Animal studies do not indicate harmful effects regarding fertility in humans at the recommended dosages (see section 5.3).

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

Summary of the safety profile
The most common adverse reactions associated with oral administration of

acetylcysteine are gastrointestinal in nature. Hypersensitivity reactions, including anaphylactic shock, anaphylactic/anaphylactoid reactions, bronchospasm, angioedema, rash, and pruritus, have been reported less frequently.

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) Unknown (frequency cannot be estimated from the available data)

System/organ classes	**Adverse Reactions**			
	Uncommon	**Rare**	**Very rare**	**Not known**
Immune system Disorders	Hypersensitivity reactions		Anaphylactic shock, anaphylactic/ anaphylactoid reactions	
Nervous system Disorders	Headache			
Ear and labyrinth Disorders	Tinnitus		Vertigo	
Cardiac disorders	Tachycardia			
Vascular disease			Haemorrhage	
Respiratory, thoracic and mediastinal disorders		Bronchospasm, Dyspnoea		
Gastrointestinal Disorders	Vomiting, diarrhoea, stomatitis, abdominal pain, nausea	Dyspepsia		
Diseases of the skin and subcutaneous tissue	Urticaria, rash, angioedema, pruritus, Exanthema			
General disorders	Fever			Facial oedema
Investigations	Hypotension			

Serious skin reactions, such as Stevens-Johnson syndrome and Lyell's syndrome, have been reported whilst taking acetylcysteine, but these occur rarely. In most reported cases at least one further medicine was being taken simultaneously, so the described muco-cutaneous effects could be exacerbated. 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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There have been no cases of toxic overdose observed with orally-dosed acetylcysteine. No serious undesirable effects were observed in volunteer test subjects dosed over a 3-month period with 11.2g acetylcysteine per day. Oral doses of up to 500mg/kg of acetylcysteine were tolerated without toxic effects.

a) Symptoms of intoxication

Overdoses can cause gastrointestinal symptoms such as nausea, vomiting and diarrhoea. In infants, there is a risk of hypersecretion.

b) Treatments for overdose

There is no specific antidote for acetylcysteine. Treat symptomatically if applicable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Mucolytic agent ATC code: R05CB01

Acetylcysteine belongs to the group of amino acid cysteine derivate.

Mechanism of action and pharmacodynamic effects

Acetylcysteine exerts a mucolytic–fluidifying activity on mucous and mucopurulent secretions through depolymerization of mucoproteins and macromolecules of nucleic acids, which increase the viscosity of the glassy and purulent component of sputum and other secretions. Additional properties of acetylcysteine include a reduction of induced hyperplasia of mucus-producing cells, an increase in surfactant production through stimulation of type II pneumocytes, and stimulation of mucociliary activity, leading to improved mucociliary clearance.

This activity is linked to the thiol group, which breaks disulfide bonds and thereby reduces the viscosity of the secretions.
In this way, acetylcysteine facilitates the evacuation of viscous secretions that make expectoration difficult.

Acetylcysteine also has a direct antioxidant effect through the free nucleophilic thiol group (-SH), which can directly bind electrophilic groups of oxidizing radicals (free oxygen, superoxide anion, and the hydroxyl radical). In this way, acetylcysteine protects α1-antitrypsin, an elastase-inhibiting enzyme, against inactivation by hypochlorous acid (HOCl), a powerful oxidizing substance produced by the enzyme myeloperoxidase in activated phagocytes.

Thanks to its molecular structure, acetylcysteine can furthermore easily cross the cell membrane. Within the cell, acetylcysteine is deacetylated, producing L-cysteine, an amino acid that plays an important role in the synthesis of glutathione (GSH). GSH is a highly reactive tripeptide that is ubiquitous in the various tissues of animal organisms, where it is essential for maintaining the functional capacity of cells as well as morphological integrity. GSH is the principal intracellular defense mechanism against oxidizing radicals, both exogenous and endogenous, and against various cytotoxic substances, including paracetamol. Paracetamol exerts a cytotoxic effect through increased depletion of GSH. By maintaining adequate GSH reserves, acetylcysteine is a specific antidote in paracetamol intoxication.

The antioxidant effect of acetylcysteine was proposed as a possible explanation for the results described in the study by Stav et al. In this study, acetylcysteine 1200 mg per day for six weeks was compared with placebo in 24 patients with COPD. The results showed that acetylcysteine produced a significant improvement in inspiratory capacity and forced expiratory vital capacity (FVC), probably due to a reduction in air trapping.

The use of acetylcysteine 600 mg three times per day (oral or aerosol) in combination with prednisone and azathioprine was evaluated over one year in patients with idiopathic pulmonary fibrosis in the IFIGENIA study. In this study, acetylcysteine resulted in preservation of vital capacity and diffusion capacity for carbon monoxide. In the study by Tomioka et al., over 12 months, acetylcysteine was compared with bromhexine hydrochloride as a control group in the treatment of idiopathic pulmonary fibrosis. Acetylcysteine slowed disease progression as evidenced by exercise desaturation, high-resolution CT, and serum KL-6, but had no effect on lung function or quality of life.

In two studies, treatment with acetylcysteine was evaluated in patients with cystic fibrosis. In both studies, acetylcysteine was administered at very high doses (up to 3000 mg per day for 4 weeks), without significant toxicity. The antioxidant effect of acetylcysteine was accompanied by a pronounced reduction in elastase activity in sputum, the strongest predictor of lung function in patients with cystic fibrosis. Additionally, acetylcysteine reduced the number of neutrophils in airway inflammation, as well as the number of neutrophils actively secreting elastase.

Early treatment with acetylcysteine prevents hepatotoxicity, renal failure, and possible death induced by paracetamol intoxication. The mechanism of action in this context has not yet been fully elucidated. Acetylcysteine can maintain or restore glutathione concentrations, which were depleted by the reactive metabolite of paracetamol. By generating cysteine and glutathione, acetylcysteine promotes the excretion of toxic paracetamol metabolites, which are first conjugated with cysteine and glutathione. Acetylcysteine may also act as a sulfate source that conjugates with paracetamol, thereby enabling excretion.

Toxicity of paracetamol

At a therapeutic dose, paracetamol is extensively conjugated with sulfate and glucuronic acid, while a small fraction is metabolized by the cytochrome P450 system into a reactive metabolite—N-acetyl-p-benzoquinone imine (NAPQI). This metabolite is then conjugated either with cysteine or with glutathione, forming mercapturic acid,

which is excreted in the urine. The toxic metabolite is neutralized by glutathione, but at high doses of paracetamol, saturation of the conjugation system occurs. This leads to liver necrosis due to covalent binding of the toxic metabolite with hepatocellular macromolecules.

More than 8 g of paracetamol taken at once by an adult is a toxic dose, i.e., there is a risk of liver necrosis.

For children, this toxic dose is 150 mg/kg body weight. In cases of chronic alcoholism, medications that induce liver enzymes (such as antiepileptics), or pre-existing liver insufficiency, the toxicity threshold may be lower. The plasma concentration of paracetamol provides a better indication of the severity of intoxication. Measurement must be done at least 4 hours after paracetamol intake, and the result must be plotted on the Rumack-Matthew nomogram.
For reference, for a measurement 4 hours after paracetamol intake:

- Plasma concentration ≤ 120 µg/ml: no risk of liver necrosis
- Plasma concentration > 120 and ≤ 200 µg/ml: possible risk of liver necrosis
- Plasma concentration > 200 µg/ml: high risk of liver necrosis

Important note: the nomogram is not usable if paracetamol was taken in multiple doses or if the time of intake is unknown.

5.2 Pharmacokinetic properties

Absorption and metabolism

Acetylcysteine is absorbed rapidly and almost completely after oral administration. It is metabolized in the liver into a pharmaceutically active metabolite cysteine, inactive diacetylcystine and cystine and into the other disulfides. Due to the high first pass effect, the bioavailability of orally administered acetylcysteine is very low (approximately 10%).

In patients with various respiratory or cardiac diseases, the maximum plasma concentration is reached 2 to 3 hours after administration and the concentration remains high for a period of 24 hours. The maximum plasma concentration reached after oral administration of acetylcysteine is 2.6 mg/L.

Biotransformation

Acetylcysteine is rapidly and extensively metabolized in the intestinal wall and liver after oral administration. Acetylcysteine is metabolized by esterases in the intestine (after oral administration) and liver into inorganic sulfate, cysteine, cystine, and diacetylcysteine. Cysteine is considered an active metabolite.

Elimination

Metabolites are mainly eliminated via the urine. Renal clearance accounts for approximately 30% of total body clearance. Less than 1% of the initial dose is excreted unchanged.

After oral administration, the average half-life (t1/2) of total acetylcysteine is 6.25 hours (4.59–10.6 hours).

The corresponding half-life of the distribution phase is on average 0.12 hours and of the elimination phase 60 minutes.

Due to a significant first-pass effect, the elimination half-life may increase by up to 80% in cases of severe liver insufficiency.

Distribution
Acetylcysteine is distributed both in unmetabolized form (20%) and in metabolized (active) form (80%), mainly to the liver, kidneys, lungs, and bronchial secretions.

Acetylcysteine is found in the body in three forms: a free fraction (22%), a fraction bound to proteins via labile disulfide bonds (16–22%), and a fraction bound to proteins as an amino acid (58–64%).
The binding degree to plasma proteins is 82% in rats and 97% in dogs. No data are available in humans.

Up to three hours after oral intake of 600 mg, the glutathione content in bronchoalveolar lavage fluid is significantly increased. This demonstrates that this dose causes a relevant biological change.
The volume of distribution of acetylcysteine ranges from 0.33 to 0.47 L/kg. Protein binding is approximately 50% for 4 hours after dose administration and decreases to 20% after 12 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 marked increase in systemic exposure to acetylcysteine in the extreme case of 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 (see sections 4.2 and 4.4).

The elimination half-life of acetylcysteine was found to increase to eight hours 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.

Linearity/non-linearity
The pharmacokinetics of acetylcysteine are proportional to the administered dose in the dose range of 200–3200 mg/m² for AUC and Cmax.

5.3 Preclinical safety data

Non-clinical data do not indicate a special risk for humans. These data are derived from conventional studies in the areas of safety pharmacology, toxicity after repeated dosing, genotoxicity, and reproductive and developmental toxicity.

No studies have been conducted on the carcinogenic potential of acetylcysteine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose, Macrogol 6000,

Crospovidone

Lemon Flavour, Saccharin Sodium, Magnesium Stearate.

6.2 Incompatibilities

This medicinal product must not be mixed with antibiotics (see section 4.5).

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

24 Months.

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package to protect from moisture and light.

6.5 Nature and contents of container

Pack size of 30.

Tablets are packed in Al -PVC/PVDC blister packs. Blisters are place in carton boxes together with a patient leaflet.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Ennogen IP Ltd
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8 MARKETING AUTHORISATION NUMBER(S)

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