SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Acepiro 600 mg effervescent tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each effervescent tablet contains 600 mg acetylcysteine.

Excipients with known effect

Each effervescent tablet contains:

- 6.04 mmol (138.79 mg) sodium
- 70 mg of lactose
- 0.52 mg of sorbitol (E420)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Effervescent tablet

White, round tablets with a score line on one side. The effervescent tablets have a diameter of 20 mm.

The score line is not intended for breaking the tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Acepiro is indicated in adults as a mucolytic agent for the treatment of respiratory tract diseases in which a reduction in bronchial secretion viscosity is required to facilitate expectoration.

4.2 Posology and method of administration

Posology

Adults:

600 mg acetylcysteine once daily.

Paediatric population:

Children aged 2 years and older, and adolescents

The safety and efficacy of Acepiro in children aged 2 years and older, and adolescents, have not been established.

Children under 2 years of age

Acepiro is contraindicated in children 0 to 2 years (see sections 4.3 and 4.4).

Duration of therapy

Duration of therapy should be determined by the clinician, depending on the nature and severity of the condition

Method of administration

For oral use

Before oral use the tablet should be dissolved in half a glass of water.

Acepiro should be taken after food.

Hepatic and renal impairment

Hepatic and renal impairment can reduce clearance and increase acetylcysteine plasma levels which may results in an increase in adverse drug reactions due to drug accumulation.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Children less than 2 years of age (see section 4.4).

Due to the high active substance content Acepiro must not be used in children and adolescents. Other strengths are available.

4.4 Special warnings and precautions for use

Acepiro should be used with caution in patients with asthma or a history of bronchospasm. Should bronchospasm occur, use should be discontinued immediately.

Very rarely, serious skin reactions such as Stevens-Johnson syndrome and Lyell syndrome have been reported in temporal association with the use of acetylcysteine. Patients should be advised to seek immediate medical advice if new skin or mucosal lesions occur and use should be discontinued as a precaution.

Acepiro should be administered with caution in patients with a reduced cough reflex (e.g. elderly or frail patients). Particularly at the beginning of treatment, the volume of bronchial secretions may be increased due to liquefaction. In patients unable to cough up bronchial secretions effectively, postural drainage and broncho-aspiration should be performed.

The effervescent tablets should be dissolved fully before intake (see section 4.2). Not fully dissolved tablets present a risk of choking and aspiration, particularly to elderly patients.

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

Caution is required in patients with histamine intolerance. Prolonged treatment should be avoided in these patients because Acepiro influences histamine metabolism and may lead to symptoms of intolerance (e.g. headache, runny nose, itching).

Paediatric population

Mucolytic medicinal products may obstruct the airways of children below 2 years of age, due to infant physiology. The ability to cough up mucus may be limited. Mucolytic medicinal products must not be used in children under 2 years of age.

The safety and efficacy is not established children aged 2 years and older and adolescents.

Hepatic and renal impairment

Hepatic and renal impairment can reduce clearance and increase acetylcysteine plasma levels which may results in an increase in adverse drug reactions due to drug accumulation.

Excipients

This medicinal product contains 138.79 mg sodium per effervescent tablet, equivalent to 6.94% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine also contains 0.52 mg sorbitol (E420) in each effervescent tablet. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Antibiotics: *in vitro* tests indicate that certain antibiotics (tetracycline, aminoglycosides, penicillin) are inactivated when directly mixed with acetylcysteine. Where concomitant use of oral antibiotics is required, separate administration by an interval of at least two hours. This does not apply to cefixime and loracarbef.

Nitroglycerin: acetylcysteine may potentiate the vasodilatory effect of nitroglycerine. Monitor patient for hypotension in cases where concomitant treatment is necessary.

The use of activated charcoal may attenuate the effect of acetylcysteine.

Antitussives: do not administer concomitantly with antitussives, as cough suppression may result in dangerous secretory congestion.

Laboratory tests: may affect colorimetric assay of salicylates. Acetylcysteine may affect the results of the determination of ketone bodies in urinalyses.

Acetylcysteine has a possible chelating effect and may reduce the bioavailability of certain heavy metal salts. As a precaution, acetylcysteine and heavy metal salts should be taken separately at different times of the day.

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 do not indicate harmful effects on pregnancy, embryo/foetal development, parturition or postnatal development (see section 5.3).

Breast-feeding

No information is available on excretion of acetylcysteine in human milk.

Administration of acetylcysteine during pregnancy and lactation should take place only after a strict risk /benefit assessment

Fertility

Animal studies do not indicate harmful effects of acetylcysteine on fertility (see section 5.3)..

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The following table shows undesirable effects after oral use of acetylcysteine according to system organ class (SOC).

System organ class	Undesirable effect			
	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	Hypersensitivity reactions		Anaphylactic reactions, anaphylactic shock	
Nervous system disorders	Headache			
Ear and labyrinth disorders	Tinnitus			
Cardiac disorders	Tachycardia[1]			
Vascular disorders			Haemorrhage[1]	
Respiratory, thoracic and mediastinal disorders		Dyspnoea[2], bronchospasm[1,2]		
Gastrointestinal disorders	Stomatitis, abdominal pain, nausea, vomiting, diarrhoea	Dyspepsia		
Skin and subcutaneous tissue disorders	Pruritus[1], urticaria[1], exanthema[1], rash[1], angioedema[1]		Stevens-Johnson syndrome, Lyell syndrome	
General disorders and administration site conditions	Pyrexia			Facial oedema
Investigations	Lowered blood pressure[1]			

[1]Associated with hypersensitivity reactions
[2] Mainly in patients with a hyper-reactive bronchial system associated with asthma

There have been very rare reports of the occurrence of severe skin reactions such as Stevens-Johnson syndrome and Lyell's syndrome with a temporal connection to acetylcysteine administration.

In the majority of these reported cases, at least one other pharmaceutical substance that may possibly have potentiated the mucocutaneous effects described was being taken. Therefore, medical advice should be sought promptly and administration of acetylcysteine stopped if new skin and mucous membrane changes occur. Administration of acetylcysteine must be stopped immediately

A decrease in platelet aggregation in the presence of acetylcysteine has been confirmed in various studies. The clinical significance of this has not yet been established.

In patients with peptic ulcer or a history thereof, acetylcysteine may have an undesirable effect on the gastric mucosa.

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

Website: 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 reports of toxic overdose with oral pharmaceutical forms of acetylcysteine. No serious adverse reactions were observed in clinical study volunteers receiving oral doses of 11.6 g acetylcysteine per day for three months.

Overdose may lead to gastrointestinal effects such as nausea, vomiting and diarrhoea.

In the case of an overdose of acetylcysteine, management should be supportive.

Experience with maximum daily doses of up to

30 g acetylcysteine has been obtained from intravenous acetylcysteine treatment of paracetamol intoxication in humans.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Expectorants, excluding combinations with cough suppressants, mucolytics

ATC code: R05CB01

Mechanism of action and pharmacodynamic effects

Acetylcysteine depolymerises mucus *in vitro* by breaking the disulphide bonds between macromolecules present in the mucus, thereby reducing mucosal viscosity.

Acetylcysteine activates the ciliated epithelium. Thus, the fluidity and passage of bronchial secretions is improved, which facilitates expectoration and improves mucociliary clearance. In *in vitro* human respiratory tract model systems, acetylcysteine has been shown to inhibit the adherence of bacteria to ciliated epithelial cells.

Acetylcysteine acts as an antioxidant and is a precursor of cysteine, the rate-limiting amino acid for glutathione synthesis in most tissues. Glutathione is present in the epithelial lining fluid of the normal lower respiratory tract, where it is thought to play a major role in providing antioxidant protection to the epithelial cells. Oxidative mechanisms are involved in the pathogenesis of a number of pulmonary diseases.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, acetylcysteine is rapidly absorbed; however bioavailability is low (approximately 10%) due to extensive first-pass metabolism in the small intestine and liver. Following a single 600 mg oral dose of acetylcysteine in humans, peak plasma concentrations of 4.6 μM have been reported at 1 hour, with plasma concentrations rapidly declining to 2.5 μM at 90 minutes (plasma half-life approximately 2 hours). Virtually no acetylcysteine is detectable 10-12 hours post-administration.

Biotransformation

Acetylcysteine undergoes rapid deacetylation *in vivo* to yield the pharmacologically active substance cysteine, thereby entering the normal cysteine metabolic pathway. Acetylcysteine also undergoes oxidation to yield a variety of metabolites including diacetylcysteine. Hepatic impairment leads to a prolonged plasma half-life of up to 8 hours.

Acetylcysteine may be present in the plasma as the parent compound or as various oxidised metabolites, including N-acetylcysteine, and cysteine and either free or bound to plasma proteins, by labile disulphide bonds, or as a fraction incorporated

into protein peptide chains. Following administration of a 100 mg oral dose of acetylcysteine, 48% was measurable in lung tissue.

Protein binding of acetylcysteine is approximately 50%.

Elimination

Following oral administration of acetylcysteine, excretion is almost exclusively renal (22% - 30%), predominately in the form of inorganic sulphates, with only 3% excreted in the faeces. Total Body Clearance in healthy subjects is 6.5 L/hour. The mean terminal half-life is approximately 6 hours.

5.3 Preclinical safety data

Chronic toxicity studies in rats and dogs, lasting up to 1 year, showed no pathological changes.

Mutagenic effects of acetylcysteine are not to be expected. One *in vitro* test result was negative,

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

No malformations were observed in embryo toxicity studies in rabbits and rats. Studies on fertility and perinatal/postnatal toxicity were negative.

N-acetylcysteine crosses the placenta in rats and has been detected in amniotic fluid. The concentration of the L-cysteine metabolite in placenta and foetal plasma is above the maternal plasma concentration for up to 8 hours following oral administration.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid (E330)

Ascorbic acid (E300)

Sodium citrate dihydrate (E331)

Sodium cyclamate (E952)

Saccharin sodium (E954)

Mannitol (E421)

Sodium hydrogen carbonate (E500)

Sodium carbonate (E500)

Lactose

Lemon flavour (*contains* Natural flavouring preparations, Natural flavouring substances, Flavouring substances, Mannitol (E421), Maltodextrin, Gluconolactone (E575), Sorbitol (E420), Silica, colloidal anhydrous (E551))

6.2 Incompatibilities

Acepiro should not be mixed with antibiotics.

Acetylcysteine can damage rubber and metal (including iron, nickel and copper). Should administration be via a nasogastric or nasointestinal tube, it is recommended that a glass and/or plastic administration system be used.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Laminated aluminium paper foil strips

Pack sizes: 20 or 30 effervescent tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

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