SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Aceteff 600mg Effervescent Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each effervescent tablet contains 600mg acetylcysteine.

Excipients with known effect:
Each effervescent tablet contains 20mg aspartame (E591) and 145mg sodium (as sodium hydrogen carbonate).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Effervescent tablet.

Circular white tablet approximately 18mm in diameter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Mucolytic therapy for adjunctive therapy of respiratory tract disorders associated with excessive, viscous mucous secretions in adults and adolescents 14 years of age and over.

4.2 Posology and method of administration

Posology

Unless prescribed otherwise, the following dosage is recommended for Aceteff 600mg Effervescent Tablets.

Adults and adolescents 14 years of age and over

One effervescent tablet daily (equivalent to 600mg acetylcysteine per day).

Aceteff 600 mg Effervescent Tablets are not recommended in children under 14 years of age for whom a lower strength formulation of acetylcysteine should be prescribed.

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.

Method of administration

Aceteff 600mg Effervescent Tablets are to be taken after meals. Dissolve one whole tablet completely in a glass of water. Aceteff effervescent tablets should not be subdivided.

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

Upon storage over time a slight odour of hydrogen sulfide occurs as a result of the normal aging process of the tablets. This is harmless and does not affect the tolerability or effectiveness of the product.

4.3 Contraindications

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

Aceteff 600mg Effervescent Tablets should not be administered to children under the age of 14 years in whom a lower dose of acetylcysteine is recommended.

4.4 Special warnings and precautions for use

Serious skin reactions such as Stevens-Johnson syndrome and Lyell 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 adolescent population. However, mild, moderate or severe adverse reactions have been reported with the use of IV acetylcysteine in adolescent population.

No specific studies have been performed in patients with renal and/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 product should be used with caution by patients with bronchial asthma and patients with a history of peptic ulcer disease.

This product should be used with caution by patients with histamine intolerance. They should avoid long-term therapy because Aceteff 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.

One effervescent tablet contains 6.3mmol (145mg) sodium. This should be taken into account for people following a controlled sodium diet (low-sodium/low-salt).

This product contains aspartame as a source of phenylalanine and can be harmful to patients with phenylketonuria.

Tablets in effervescent formulations present a risk of choking and aspiration, particularly to elderly patients, if swallowed whole. The tablet should therefore be dissolved fully before intake.

4.5 Interaction with other medicinal products and other forms of interaction

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

If Aceteff 600mg Effervescent Tablets are 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 carefully.

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

Reports of inactivation of antibiotics (aminoglycosides, penicillins, tetracycline) by acetylcysteine indicate that this inactivation occurs only when these substances are mixed directly together in vitro.
Nevertheless, administration of oral doses of antibiotics and Aceteff tablets should be separated by a minimum period of two hours. This does not apply to the antibiotics Cefixime or Loracarbef.

Acetylcysteine and glyceryl trinitrate

Simultaneous administration of these drugs may increase the vasodilatory and platelet aggregation-inhibiting effect of glyceryl trinitrate. 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.

Interference with the measurement of laboratory parameters

Acetylcysteine can influence the colorimetric assay of salicylates.

Acetylcysteine can influence results when measuring ketones in urine.

4.6 Fertility, pregnancy and lactation

There are no 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 post-natal development (see also section 5.3). There is insufficient information on the excretion of acetylcysteine or its metabolites in human milk. Use during pregnancy and while breast-feeding should be subject to careful consideration of the risk/benefit balance.

4.7 Effects on ability to drive and use machines

Aceteff 600mg Effervescent Tablets have no influence on the ability to drive and use machinery.

4.8 Undesirable effects

The following frequencies are used for the description of the occurrence of adverse reactions:

Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1000)
Very rare (< 1/10,000)
Not known (frequency cannot be estimated from the available data)

Systemic organ category	**Side effects**			
	Uncommon	**Rare**	**Very rare**	**Not known**
Disorders of the immune system	Hypersensitive reactions		Anaphylactic shock, anaphylactic/ anaphylactoid reactions	
Disorders of the nervous system	Headaches			
Disorders of the ear and inner ear	Tinnitus			
Heart disorders	Tachycardia			
Vascular disorders			Haemorrhaging	
Disorders of the respiratory tract, thoracic cavity and mediastinum		Bronchial spasms, dyspnoea		
Disorders of the gastro-intestinal tract	Vomiting, diarrhoea, stomatitis, stomach ache, nausea	Dyspepsia		
Disorders of the skin and subcutaneous cellular tissue	Urticaria, rash, angioedema, itching, exanthema			
General disorders and administration site conditions	Fever			Facial oedema
Tests	Hypotension			

Serious skin reactions such as Stevens-Johnson syndrome and Lyell 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 national reporting system listed in the Yellow Card Scheme.
Website: www.mhra.gov.uk/yellowcard

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 11.6g acetylcysteine per day. Oral doses of up to 500mg/kg of acetylcysteine were tolerated without toxic effects.

a) Symptoms of intoxication

Overdoses can cause gastro-intestinal symptoms such as nausea, vomiting and diarrhoea. There is a risk of hypersecretion in infants.

b) Treatment for overdose

Treat symptomatically if applicable.

Where acetylcysteine is administered intravenously to treat paracetamol intoxication, experience shows that the maximum daily dose for a human is up to 30g.

Intravenous administration of extremely high concentrations of acetylcysteine may result in “anaphylactoid” reactions, particularly if the dose is given within a short time period. In one case epileptic fits and cerebral oedema with fatal consequences were reported after massive intravenous overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Mucolytics ATC code: R05 CB01

Acetylcysteine is a derivative of the amino acid cysteine. Acetylcysteine increases and thins the secretions in the bronchial tract area. One theory is that it splits the disulfide bonds between the mucopolysaccharide fibres and exerts a depolymerising effect on DNA-rich fibres (in purulent mucus). These mechanisms are believed to reduce the viscosity of the mucus.

An alternative mechanism of action of acetylcysteine is said to be based on the ability of its reactive SH group to bind, and therefore detoxify, chemical radicals.

Furthermore, acetylcysteine contributes to increased glutathione synthesis, which is of significance for nitric oxide (NO) detoxification. This explains its effect as an antidote in the treatment of paracetamol intoxication.

A protective effect on the frequency and severity of bacterial exacerbations in patients with chronic bronchitis/cystic fibrosis is described where acetylcysteine is given prophylactically.

5.2 Pharmacokinetic properties

After oral administration acetylcysteine is rapidly and almost completely absorbed and metabolised by the liver into cysteine the active metabolite, diacetylcystine, cystine and other mixed disulfides.

The oral bioavailability of acetylcysteine is very low (approximately 10%) due to high first pass effect. In humans maximum plasma concentration is reached in 1 to 3 hours where the maximum plasma concentration of the metabolite cysteine is about 2µmol/l. Approximately 50% of acetylcysteine is protein bound.

Acetylcysteine is metabolised by rapid hepatic biotransformation with a plasma half-life of approximately 1 hour. The metabolites occur in three different forms: in free form, bound to protein via labile disulfide bonds and as integral amino acids. Excretion of inactive metabolites (inorganic sulfates, diacetylcystine) is via the kidneys. For these reasons restricted liver function causes the plasma half-life to increase up to 8 hours.

Pharmacokinetic studies of intravenously-administered acetylcysteine showed a distribution volume of 0.47 l/kg (total) or 0.59 l/kg (reduced), the plasma clearance was determined to be 0.11 l/h/kg (total) and 0.84 l/h/kg (reduced). The elimination half-life after IV administration is 30-40 min., with excretion occurring as three-phase kinetics (alpha, beta and terminal gamma phase).

Acetylcysteine crosses the placenta and can be detected in umbilical cord blood. No information is available on excretion into breast milk.

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

5.3 Preclinical safety data

a) Acute toxicity

Acute toxicity in animal experimentation is low. See section 4.9 for treatment of overdose.

b) Chronic toxicity

Studies on various animal species (rat, dog) over a period of up to one year did not show any pathological changes.

c) Tumorigenic and mutagenic potential

Mutagenic effects of acetylcysteine are not to be expected. An in-vitro test showed a negative result.
Studies of the tumorigenic potential of acetylcysteine have not been carried out.

d) Reproductive toxicology

No deformities were identified in embryo toxicity studies on rabbits and rats. Tests on fertility and peri/post-natal toxicity showed negative results.
Acetylcysteine crosses the placenta in rats and can be detected in amniotic fluid. Concentration of the metabolite L-cysteine is higher in the placenta and foetus than the maternal plasma concentration for up to 8 hours after oral administration.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydrogen carbonate
Anhydrous citric acid
Aspartame (E951)
Lemon flavouring

6.2 Incompatibilities

This medicinal product should not be mixed with certain 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

3 years.

6.4 Special precautions for storage

Store in original packaging to protect the contents from light and moisture. Do not store above 25°C.

Re-seal tubes immediately after removing tablets.

6.5 Nature and contents of container

White polypropylene tubes with a low density polyethylene tamper evident cap with integrated desiccant.

Packs containing 10, 20 or 30 (2 x15) 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

Dunelm Pharmaceuticals Limited
2 McMillan Close
Saltwell Business Park
Low Fell
GATESHEAD
NE9 5BF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 36892/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/10/2016

10 DATE OF REVISION OF THE TEXT

03/03/2020