SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bisolaclar 600 mg bruistabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each effervescent tablet contains 600 mg acetylcysteine.

Excipients with known effect:
Each effervescent tablet contains 6.03 mmol of sodium, which is equivalent to 138.8 mg of sodium.
Each effervescent tablet contains 70 mg lactose.
Each effervescent tablet contains the maximum of 40 mg sorbitol.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Effervescent tablet.

Round, white tablets with faultless surface, a score line on one side and diameter of 20 mm.

The score line is only to facilitate breaking for ease of dissolving and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Acetylcysteine is indicated in adults for the treatment of airway diseases in which a reduction in the viscosity of the bronchial secretions is required to facilitate expectoration, especially during periods of acute bronchitis.

4.2 Posology and method of administration

Posology

One 600 mg effervescent tablet once daily.

Paediatric population
Bisolaclar 600 mg effervescent tablets are contraindicated for use in children aged under 2 years (see section 4.3) and are not suitable for use in children and adolescents.

Method of administration
The effervescent tablet has to be dissolved in half a glass of water. Once the tablet has dissolved, the liquid can be drunk immediately.

Acetylcysteine is used for symptomatic treatment and should not be used longer than 8 to 10 days without seeking for medical advice.

4.3 Contraindications

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

Children aged under 2 years.

4.4 Special warnings and precautions for use

Administer with caution to asthmatic patients, or those with a history of bronchospasm. If a bronchospasm occurs, use of Bisolaclar should be stopped immediately.

Caution is required in patients with a history of peptic ulcer, especially if the patient is using other medicines that are known to irritate the mucosa of the gastrointestinal tract.

Very rarely, serious skin reactions such as Stevens-Johnson syndrome and Lyell syndrome have been reported in temporal association with the use of acetylcysteine. Mostly these could be explained by the patient's underlying disease and/or concomitant medication. If new skin or mucosal lesions occur, medical advice should be sought immediately and treatment with acetylcysteine discontinued as a precaution.

Administer with caution in patients with a reduced cough reflex (e.g. elderly or frail patients) as primarily at the beginning of acetylcysteine treatment, bronchial secretion may increase in volume as a result of the liquefaction. When a patient is unable to cough up the secretions effectively, postural drainage and broncho-aspiration should be performed.
Mucolytics may obstruct the airways of children under 2 years due to the physiological characteristics of the airways in this age group. The ability to cough up mucus may be limited. Therefore, mucolytics should not be used by children younger than 2 years.

Interaction with laboratory tests
Acetylcysteine can affect colorimetric determination of salicylate and the determination of ketones in the urine.

The presence of a mild sulphurous odour does not indicate any change in the preparation but is specific to the active substance.

Excipients
This medicinal product contains 70 mg lactose per tablet. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicinal product contains up to 40 mg sorbitol per tablet, which is equivalent up to 0.57 mg/kg/day.

This medicinal product contains 138.8 mg sodium per tablet, equivalent to 6.94% of the WHO recommended maximum daily intake of 2 g sodium for an adult. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions with other medicinal products
Dissolving Bisolaclar 600 mg effervescent tablets together with other medicinal products is not recommended.

The inactivation of antibiotics (tetracycline, aminoglycosides, penicillin) by acetylcysteine has been reported up to now only in *in vitro* tests whereby the relevant substances were mixed directly with each other. However, if oral antibiotics are required, it is advised that these should be taken two hours before or after Bisolaclar.

Acetylcysteine may potentiate the vasodilatory effect of nitro-glycerine. If concomitant therapy is necessary caution is required and the patient's blood pressure has to be monitored in terms of hypotension that can become serious.

Acetylcysteine has a possible chelating effect and may therefore reduce the bioavailability of certain heavy metal salts such as gold-, iron- and potassium salts. Bisolaclar and such salts should not be taken concomitantly but at a different time of the day.

Activated charcoal can decrease the effect of acetylcysteine due to reduced absorption.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is a limited amount of data from the use of acetylcysteine in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Acetylcysteine crosses the placenta. Available data do not indicate a risk to the baby. As a precautionary measure, it is preferable to avoid the use of Bisolaclar during pregnancy.

Breast-feeding
It is unknown whether acetylcysteine/metabolites are excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Bisolaclar therapy considering the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
Based on available pre-clinical experience, there are no indications for possible effects of the use of acetylcysteine on fertility.

4.7 Effects on ability to drive and use machines

Acetylcysteine has no or negligible 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 shock, anaphylactic/ anaphylactoid reactions	
Nervous system disorders	Headache			
Ear and labyrinth disorders	Tinnitus			
Vascular disorders			Bleeding	

Gastrointestinal disorders	Stomatitis, abdominal pain, nausea, vomiting, diarrhoea	Dyspepsia		
Skin and subcutaneous tissue disorders				Facial oedema
General disorders and administration site conditions	Pyrexia			
Investigations	Lowered blood pressure			

*Hypersensitivity reactions include bronchospasms, dyspnoea, pruritus, urticaria, skin rash, angioedema and tachycardia.

Description of selected adverse reactions
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 national reporting system <to be completed nationally>.

4.9 Overdose

No toxic overdose has yet been observed with oral pharmaceutical forms of acetylcysteine.
Voluntary study subjects were treated for three months with a dose of 11.6 g acetylcysteine per day without any serious undesirable effects being observed.
Oral doses of up to 500 mg acetylcysteine per kg body weight are tolerated without any signs of poisoning.

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

Management
Symptomatic treatment if necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cough and cold preparations, expectorants, excl. combinations with cough suppressants, mucolytics.
ATC code: R05CB01

Mechanism of action and pharmacodynamic effects
Acetylcysteine is a mucolytic agent that reduces the viscosity of mucosal secretions. Its mucolytic effect is explained by depolymerisation, whereby disulphide bridges between macromolecules

present in the mucus are broken. At the same time it activates the ciliated epithelium. Thus, the fluidity and passage of bronchial secretion is improved, which facilitates expectoration and improves mucociliary clearance.

Acetylcysteine is also a precursor of glutathione as it is a derivative of the natural amino acid cysteine. Cysteine serves as a substrate in the body for the synthesis of glutathione. Apart from the fact that acetylcysteine is able to normalise a state of glutathione depletion, it is able to conjugate with various toxic compounds.

5.2 Pharmacokinetic properties

Absorption and distribution
Following oral administration, acetylcysteine is rapidly and nearly completely absorbed and distributed throughout the whole body. The highest tissue levels are reached in the liver, kidneys and lungs. In humans the maximum plasma concentrations are reached after 1-2 hours. A peak plasma concentration of 4.6 µM was achieved at 60 min after an oral dose of 600 mg of acetylcysteine and plasma levels rapidly declined to 2.5 µM at 90 min. Due to the high first pass effect, the bioavailability of orally administered acetylcysteine is very low.
The volume of distribution of total acetylcysteine was reported to range between 0.33 and 0.47 l/kg, with little inter-individual variation.
Protein binding of acetylcysteine is about 50%.

Biotransformation
Acetylcysteine is mostly deacetylated in the liver to the pharmacologically active substance cysteine as well as to diacetylcystine, cystine and other mixed disulphides. Cysteine is primarily involved in the amino acid metabolism. Reversible disulphide bonds are also formed with amino acids and proteins with free sulphhydryl groups.

The half-life of acetylcysteine in plasma is approx. 2 hours and is mainly affected by the rapid hepatic biotransformation. Hepatic impairment leads to prolonged plasma half-life up to 8 hours.

Elimination
Following oral or intravenous doses of 600 mg n-acetylcysteine, virtually no n-acetylcysteine is detectable in plasma at 10-12 h. The total clearance of n-acetylcysteine was 0.286 l/kg/h in healthy adults after oral administration. High doses are mainly converted to inorganic sulphate and excreted via the kidneys, in which the excretion follows a tri-phasic kinetic (alpha-, beta- and terminal gamma-phase). The plasma clearance was determined as 0.11 l/h/kg (total) as well as 0.84 l/h/kg (reduced). The elimination half-life after intravenous administration is 30-40 min.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Single-dose toxicity
Single-dose toxicity is very low in animal studies.

Repeat-dose toxicity
Studies on different animal species (rats, dogs) with a duration of up to one year revealed no pathological changes.

Genotoxic and carcinogenic potential
Mutagenic effects of acetylcysteine are not to be expected. An *in vitro* test was negative.
No studies have been performed concerning the carcinogenic potential of acetylcysteine.

Reproductive and developmental toxicity
In developmental toxicity studies with rabbits and rats no malformations could be observed. Examinations on fertility and peri- and postnatal toxicity were negative. In rats acetylcysteine crosses the placenta and can be detected in amniotic liquor. Up to eight hours after oral administration, the concentration of the metabolite l-cysteine is higher in the placenta and the foetus than in the plasma of the dam.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid, anhydrous
Ascorbic acid
Sodium citrate
Sodium cyclamate
Saccharin sodium
Mannitol
Sodium hydrogen carbonate
Sodium carbonate, anhydrous
Lactose, anhydrous
Magnesium stearate

Flavour Lemon "AU", code 132 consisting of: natural lemon oil, natural / nature identical lemon oil, mannitol (E421), maltodextrin, gluconolactone (E575), sorbitol (E420), silica, colloidal anhydrous (E551)

6.2 Incompatibilities

Acetylcysteine can damage rubber and metal (including iron, nickel and copper). When administering 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.

Laminated aluminium paper foil package
No special temperature storage conditions required.

Polypropylene tubes with polyethylene stoppers containing desiccant package
Do not store above 30°C.

6.5 Nature and contents of container

Each effervescent tablet is either sealed separately into an aluminium paper foil packed in a folding box or the unsealed tablets are packed in a plastic polypropylene tube with polyethylene desiccant stoppers filled with molecular sieve.

Pack sizes:

Boxes with 10 and 20 tablets.
Polypropylene tubes with 10, 20 and 25 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

Opella Healthcare France SAS
157 avenue Charles de Gaulle
92200 Neuilly-sur-Seine
Frankrijk

8. MARKETING AUTHORISATION NUMBER(S)

RVG 115427

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 3 augustus 2015
Datum van laatste verlenging: 18 juni 2020

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft de rubriek 7: 15 juli 2023