UNI-PHARMA
Pharmaceutical Laboratories S.A.

SUMMARY OF PRODUCT CHARACTERISTICS

(S P C)

TREBON-N®

✓ ***Gra.or.sus (in single dose) -100, -200 & -600 mg/sachet***

✓ ***Pd.or.sus -100 & -200 mg/5ml***

✓ ***Eff.tab 600 mg/tab***

1. NAME OF THE MEDICINAL PRODUCT

✓ TREBON-N® Gr.or.sd -100, -200 & -600 mg/sachet

✓ TREBON-N® Pd.or.sus -100 & -200 mg/5ml

✓ TREBON-N® Eff.tab 600 mg/tab

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

✓ ***Granules for oral suspension, in single dose***

Each sachet of granules for oral suspension contains 100, 200 & 600 mg of acetylcysteine, respectively.

Excipients with known effect (for all strengths): Sorbitol

(only for the 100 mg/sachet strength): Azo dye Ponceau 4R/Cochineal Red A (E124).

✓ ***Powder for oral suspension***

The powder for oral suspension, 100 mg/5ml and 200 mg/5ml after reconstitution according to the instructions, contains 100 mg or 200 mg of acetylcysteine in 5 ml of suspension, respectively.

Excipient with known effect: Sodium methyl para-hydroxybenzoate (E219), Glucose.

✓ ***Effervescent tablet***

Each effervescent tablet contains 600 mg of acetylcysteine.

Excipients with known effect: Sorbitol, sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

✓ Granules for oral suspension, in single dose.

✓ Powder for oral suspension.

✓ Effervescent tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

For all strengths

For the liquefaction of mucus secretions of the respiratory tract in cases of acute and chronic bronchopulmonary diseases (bronchitis, emphysema, tracheobronchitis, chronic asthmatic bronchitis).

If required, during acute exacerbations of bronchitis, a suitable antibiotic should be administered concurrently.

For 600 mg strength

Paracetamol toxicity.

In cases of paracetamol poisoning, intravenous administration of acetylcysteine is preferred, in accordance with the European protocol PRESCOTT and if this is not available, it should be administered orally.

4.2. Posology and method of administration

Posology

For the liquefaction of mucus secretions

Children aged 2-5 years:

100 mg two-three times per day.

Children aged 6-12 years:

100 mg three-four times per day or 200 mg twice per day.

Adults and children aged 12 years and older:

200 mg two-three times per day or 600 mg once per day.

Paediatric population

It should be administered under medical supervision to children aged 2 to 6 years.

Administration to children under 2 years of age is contraindicated. Therefore, acetylcysteine 100 mg should not be used in children under 2 years of age.

Acetylcysteine 200 mg, due to its high strength of active substance, should not be used in children under 6 years of age. There is a suitable 100 mg strength available.

Acetylcysteine 600 mg, due to its high strength of active substance, should not be used in children under 12 years of age. There are other suitable strengths available, 200 mg or 100 mg.

Method of administration

Oral use.

It should be taken with an adequate amount of water (preferably one glass of water).

This medicine is recommended to be taken after meals.

Patients should be informed about the expected increase in mucus secretions.

Consumption of plenty of liquids during the day is recommended.

Instructions for use

Granules for oral suspension

The content of each sachet is dissolved in half a glass of water.

Powder for oral suspension

The bottle should be shaken well to remove the powder from the walls of the bottle. Add volume of water to the marked line on the bottle. The vial should be well shaken until the formation of a homogeneous solution. If necessary, top up with water exactly to the line. Each teaspoon (5 ml) of TREBON-N is equivalent to 100 mg or 200 mg of acetylcysteine, respectively.

Effervescent tablets

One effervescent tablet is dissolved in half a glass of water and the whole solution should be drunk at once.

Patients with a reduced cough reflex (elderly and weakened patients) are recommended to take the effervescent tablet in the morning.

Duration of treatment

The advice of the treating doctor should be sought if the symptoms do not subside after 4-5 days or worsen during treatment.

The duration of treatment may be increased by the treating doctor based on an assessment of the treatment results.

Paracetamol toxicity (for 600 mg strength)

Loading dose: 140 mg/kg body weight preferably during the first 10 hours of poisoning.

Maintenance dose: 70 mg/kg body weight, every 4 hours up to 17 doses.

4.3. Contraindications

⏩ Hypersensitivity to the active substance (acetylcysteine), or other chemically similar substance (for example carbocisteine, or cysteine) or to any of the excipients listed in section 6.1.

⏩ Contraindicated in rare cases of hereditary conditions, in which the patient may develop incompatibility with any of the product's excipients (*see section 4.4*).

⏩ Exacerbated severe asthma.

⏩ Chronic duodenal ulcer.

⏩ Not to be administrated during pregnancy and lactation.

⏩ Contraindicated in children under 2 years of age.

Mucolytic drugs may cause bronchial obstruction in children under 2 years of age. In fact, the ability to cough up sputum may be limited in this age group, due to the physiological characteristics of the airway.

Therefore, acetylcysteine 100 mg should not be used in children under 2 years of age.

Acetylcysteine 200 mg, due to its high strength of active substance, should not be used in children under 6 years of age. There is a suitable 100 mg strength available.

Acetylcysteine 600 mg, due to its high strength of active substance, should not be used in children under 12 years of age. There are other suitable strengths available, 200 mg or 100 mg.

4.4. Special warnings and precautions for use

The advice of the treating doctor should be sought if the symptoms do not subside after 4-5 days or worsen during treatment.

Acetylcysteine 100 mg should be administered under medical supervision to children aged 2 to 6 years.
Mucolytic drugs may cause bronchial obstruction in children under 2 years of age. In fact, the ability to cough up sputum may be limited in this age group, due to the physiological characteristics of the airway. The ability to cough up mucus may be limited. Therefore, it should not be used in children under 2 years of age.

Administration of acetylcysteine, especially at the beginning of treatment, can lead to liquefaction of bronchial secretions thereby increasing their volume. In patients unable to expectorate efficiently, suitable procedures (such as postural drainage and tracheal suction) should be performed.

Re-assessment of the clinical condition is necessary in cases of thick, mucopurulent secretions, in the presence of fever or in case of chronic broncopulmonary disease. It should be administered with caution to asthma patients with a history of bronchospasm or severe respiratory failure or active tuberculosis.
Formation of cavitation has been observed when used in patients with bronchial asthma and in patients with a history of ulcer.

It should be administered with caution to patients with asthma due to the risk of bronchospasm.
If bronchospasm occurs when using acetylcysteine, its use should be discontinued immediately.

The combined use of bronchial expectorants and antitussives and/or substances that dry bronchial secretions or with medicines that have an anticholinergic effect is not recommended.

Caution is advised in patients that are histamine-intolerant. Longer treatments should be avoided in these patients, as acetylcysteine affects histamine metabolism and may lead to intolerance symptoms (e.g., headache, vasomotor rhinitis, pruritus).

This medicinal product should be administered with particular caution to patients with a history of peptic ulcer. Caution is advised in the elderly, in patients with a history of duodenal ulcers, or those that take at the same time drugs known to cause gastrointestinal haemorrhage. If gastrointestinal haemorrhage occurs, patients should discontinue treatment.

The occurrence of serious skin reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and acute generalised exanthematous pustulosis (AGEP), has been reported in association with the administration of mucolytic active substances. If there are symptoms or signs of a progressive skin rash (that sometimes is associated with blisters or mucosal lesions), treatment with acetylcysteine should be discontinued immediately and medical advice should be sought.

Most cases can be explained by the severity of other underlying illnesses and/or concomitantly administered medication. In addition, during the early phase of Steven-Johnson syndrome or toxic epidermal necrolysis, the patient may develop initially non-specific precursor influenza-like symptoms, such as fever, body aches, rhinitis, coughing and sore throat. These non-specific precursor

influenza-like symptoms are likely to mislead to the start of a symptomatic treatment for the cough and the cold.
Therefore, if new skin or mucosal lesions occur, medical advice should be sought immediately and as a precaution treatment with acetylcysteine should be discontinued.

In case of impaired renal function or severe liver disease, acetylcysteine may only be used after medical advice. As with all drugs that are metabolised by the liver and then excreted by the kidneys, an accumulation of acetylcysteine metabolites formed in the liver may occur when there is severe renal failure.

Effervescent tablet

TREBON-N 600 mg effervescent tablet contains 165.6 mg of sodium per tablet, equivalent to 8.3% of the WHO recommended maximum daily intake of 2 g sodium through diet by an adult. This should be taken into account by patients on a sodium-restricted or -free diet (sodium-low/salt-low).
TREBON-N 600 mg Effervescent tablet contains 400 mg of sorbitol per effervescent tablet. Sorbitol is a source of fructose. Patients with hereditary fructose intolerance (HFI) should not take this medicinal product. The cumulative effect of concomitant use of products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into consideration. The quantity of sorbitol in oral medicinal products can affect the bioavailability of other oral medicinal products when administered concurrently.

Powder for oral suspension

5 ml of TREBON-N powder for oral suspension 100 mg/5 ml and
200 mg/5 ml (per dose) contain 0.78 g glucose. Patients with rare malabsorption of glucose-lactose should not take this medicine. This should be taken into account in patients with diabetes mellitus. In chronic use, e.g., for two weeks or more, it may be harmful to the teeth.

TREBON-N 100 mg/5 ml and 200 mg/ 5 ml powder for oral suspension contains sodium methyl para-hydroxybenzoate (E219), which may cause allergic reactions (possibly with delay).

Granules for oral suspension, in single dose

TREBON-N Granules for oral suspension 100 mg/sachet contain 2.741 g of sorbitol per dose, TREBON-N Granules for oral suspension 200 mg/sachet contain 2.542 g of sorbitol per dose and TREBON-N Granules for oral suspension 600 mg/sachet contain 2.162 g sorbitol per dose. Sorbitol is a source of fructose. Patients with hereditary fructose intolerance (HFI) should not take this medicinal product. The cumulative effect of concomitant use of products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into consideration. The quantity of sorbitol in oral medicinal products can affect the bioavailability of other oral medicinal products when administered concurrently.

The granules for oral suspension, *only the 100 mg/sachet strength*, contain the azo dye Ponceau 4R red/Cochineal Red A (E124), which may cause allergic reactions.

4.5. Interaction with other medicinal products and other forms of interaction

Interaction studies have been carried out only in adults.

Co-administration of bronchial expectorants and antitussives and/or substances that dry bronchial secretions or with medicines that have an anticholinergic effect is not recommended. Co-administration of acetylcysteine with antitussives may cause a severe build-up of secretions due to a reduced cough reflex. For this reason, particularly careful diagnosis is required for this combined treatment.

Due to the possibility of chelate formation, the fact that the salts of certain minerals such as calcium, iron or gold may reduce the bioavailability of acetylcysteine should be taken into account. In this

case their administration is recommended after an interval of at least 2 hours.

To date, the inactivation of antibiotics (tetracyclines, aminoglycosides, penicillins), by acetylcysteine has been reported only in *in-vitro* tests, whereby the relevant substances were mixed directly with each other. However, for safety reasons oral antibiotics should be taken separately and after an interval of at least 2 hours. This does not apply to cefixime and loracarbef.

Use of activated charcoal may attenuate the effect of acetylcysteine.

Concomitant administration of acetylcysteine may lead to potentiation of the vasodilatory and antiplatelet effect of glyceryl trinitrate (nitroglycerin). If concomitant treatment of nitroglycerin and acetylcysteine is considered necessary, patients should be monitored for any signs of hypotension that could be severe and occur with symptoms of headache.

Concomitant use of acetylcysteine and carbamazepine may lead to subtherapeutic levels of carbamazepine.

Changes in determination of laboratory parameters

• Acetylcysteine may affect the colorimetric assay of salicylates.

• Acetylcysteine may affect the results of the determination of ketone bodies in urinalyses.

4.6. Fertility, pregnancy and lactation

Fertility

No effects on fertility were observed in animal studies.

Pregnancy

No sufficient clinical data on pregnant women exposed to acetylcysteine are available. Animal studies do not suggest direct or indirect harmful effects on pregnancy, embryonal/foetal development, parturition or postnatal development (see also section 5.3).

Acetylcysteine should be used during pregnancy after strict assessment of the benefit/risk balance.

Breast-feeding

No information is available on excretion in breast milk.

During breast-feeding, acetylcysteine should be used only after strict assessment of the benefit/risk balance.

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

Assessment of adverse reactions is based on the following information in relation to the frequency of their occurrence:

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 (frequency cannot be estimated from the available data)

System/organ class	**Frequency**	**Adverse reaction**
Immune system disorders	Uncommon	hypersensitivity reactions*
	Very rare	anaphylactic shock, anaphylactic/anaphylactoid reactions
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	dyspnoea, bronchospasm - mainly in patients with bronchial hypersensitivity in case of bronchial asthma
Gastrointestinal disorders	Uncommon	stomatitis, abdominal pain, nausea, vomiting, diarrhoea
	Rare	dyspepsia
Skin and subcutaneous tissue disorders	Uncommon	urticaria, angioedema, pruritus, rash
	Very rare	Stevens-Johnson syndrome and toxic epidermal necrolysis
General disorders and administration site conditions	Uncommon	fever
	Not known	facial oedema
Investigations	Uncommon	hypotension

The occurrence of severe skin reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, has been reported in temporal association with the use of acetylcysteine. In most of these cases reported at least one other drug was administered at the same time, which may have possibly enhanced the described mucocutaneous adverse effects.

In case of recurrence of skin and mucosal lesions, medical advice should be sought immediately and the use of acetylcysteine should be discontinued.

In addition, occurrence of haemorrhage has very rarely been reported in association with administration of acetylcysteine, partially with hypersensitivity reactions.

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

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

A decrease in platelet aggregation in the presence of acetylcysteine has been confirmed by various studies. To date, the clinical significance of this has not been determined.

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 directly via the national reporting system.

4.9. **Overdose**

To date no cases of toxic overdose have been observed with oral pharmaceutical forms of acetylcysteine. Volunteers were treated for 3 months with a dose of 11.6 g acetylcysteine per day without serious undesirable effects being observed. Oral doses of up to 500 mg acetylcysteine per kg of body weight were tolerated without symptoms of intoxication.

Symptoms of intoxication

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

There is a risk of hypersecretion in infants. The occurrence of rash with or without fever is rarely reported.

Treatment in the event of an overdose

If necessary, according to the symptoms.

Experience has been gained from the treatment of people with paracetamol intoxication who were given intravenous maximum daily doses of up to 30 g of acetylcysteine. Intravenous administration of extremely high concentrations of acetylcysteine led to “anaphylactoid” reactions partially non-reversible, in particular in cases of fast administration.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Cough and cold preparations - Mucolytics
ATC Code: **R05CB01**

Additionally for the 600 mg strength: *Pharmacotherapeutic group:* Various other therapeutic products - Antidotes, *ATC code:* **V03AB23**

Mechanism of action

The active ingredient is acetylcysteine, which is produced by acetylation of cysteine, a naturally-occurring amino acid.

Acetylcysteine is used as a mucolytic agent both in purulent and in non-purulent mucus. It reduces the viscosity of mucus without damaging the mucous membrane.

The viscosity of pulmonary secretions depends on the concentration of mucoproteins and to a lesser extent on DNA. The mucolytic action of acetylcysteine is due to its thiol group (-SH), which helps break the interconnecting disulphide bonds between the mucopolysaccharide chains and exerts a depolymerising effect on the DNA chains in purulent mucus, reducing its viscosity.
The mucolytic action of acetylcysteine does not change by the presence of DNA and increases as pH increases; it is significant in a pH of 7 to 9.
In vivo, acetylcysteine is deacetylated to cysteine or oxidised to diacetylcysteine.
Acetylcysteine given with antibiotics contributes to a reduction in recurrence that is caused by retention of bronchial secretions and airway failure. Acetylcysteine also facilitates expectoration because it increases the activity of the ciliated epithelium and reduces coughing. Acetylcysteine helps eliminate thick secretions, in particular bronchopulmonary ones, thus reducing the risk of complications

caused by retention of mucus. Its mucolytic action is similar on purulent and non-purulent mucus.

A protective effect of prophylactic acetylcysteine administration on the frequency and severity of bacterial exacerbations has been reported in patients with chronic bronchitis/mucoviscidosis.

An alternative mechanism of acetylcysteine is hypothesised to be based on the ability of its reactive SH group to bind chemical radicals thereby detoxifying the body from them.

Moreover, acetylcysteine contributes towards increased glutathione synthesis, which is important for the detoxification of poisonous substances, as it serves as a substrate for its synthesis in the body. This explains its effect as an antidote for paracetamol poisoning.

5.2. Pharmacokinetic properties

Absorption

Following oral administration, acetylcysteine is absorbed rapidly and almost completely by the gastrointestinal tract and is metabolised extensively. It is metabolised in the liver to cysteine, its pharmacologically active metabolite, as well as to diacetylcysteine, cysteine and other mixed disulphides.

Distribution

After oral administration, acetylcysteine is rapidly absorbed and distributed throughout the organism, with highest concentrations reached in the liver, kidneys and lungs.

Due to the high first-pass effect, the bioavailability of orally administered acetylcysteine is very low (approximately 10%).

Peak plasma concentrations are attained in humans after 1-3 hours with the peak plasma concentration of the metabolite cysteine being approximately 2μmol/l. The protein binding of acetylcysteine was determined to be approximately 50%.

Biotransformation

Acetylcysteine and its metabolites, such as diacetylcysteine and cysteine, occur in the plasma in their free form, or bound to proteins via labile disulphide bonds or incorporated in the chains of protein peptides. The bioavailability of orally administered acetylcysteine is low and mean values ranged from 4% to 10% depending on whether total acetylcysteine or only its reduced forms had been measured. The low oral availability is due to its metabolism in the intestinal wall and the first-pass metabolism in the liver.

Acetylcysteine is excreted almost exclusively in the form of inactive metabolites (inorganic sulphates, diacetylcysteine) via the kidneys. The plasma half-life of acetylcysteine is approximately 1 hour and is mainly determined by rapid hepatic biotransformation. Impaired hepatic function therefore leads to prolonged plasma half-lives of up to 8 hours.

Elimination

Pharmacokinetic studies with intravenous administration of acetylcysteine have shown a volume of distribution of 0.47 L/kg (in total) or 0.59 L/kg (reduced acetylcysteine). The plasma clearance was determined to be 0.11 L/h/kg (in total) and 0.84 L/h/kg (reduced acetylcysteine), respectively. The elimination half-life following intravenous administration is 30-40 minutes with excretion following three-phase kinetics (alpha, beta and terminal gamma phase).

Acetylcysteine crosses the placenta and is detected in cord blood. No information is available regarding excretion in breast milk.

No knowledge is available concerning the behaviour of acetylcysteine at the blood-brain barrier in humans.

5.3. Preclinical safety data

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

Acute toxicity

Acute toxicity in animal studies is low. For treatment of overdose see section 4.9.

Chronic toxicity

Studies in various animal species (rats, dogs), lasting for up to one year, showed no pathological changes.

Tumorigenic and mutagenic potential

Acetylcysteine is not expected to have a mutagenic effect. One *in-vitro* test result was negative.

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

Reproductive toxicology

In embryotoxicity studies performed in rabbits and rats no malformations were detected. Studies of fertility and perinatal or postnatal toxicity were negative.

Acetylcysteine crosses rat placenta and has been detected in amniotic fluid. The concentration of the L-cysteine metabolite in the plasma and foetus is above the maternal plasma concentration, for up to 8 hours after its oral administration.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

✓ ***Granules for oral suspension, in single dose***

-100 mg/sachet: Cherry essence (in powder), Powder Cochineal Red A Ponceau 4R CI 16255 (E124), Saccharin sodium, Macrogol 6000, Sorbitol.

-200 mg/sachet: Citric acid, Lemon juice flavour (in powder), Saccharin sodium, Macrogol 6000, Sorbitol.

-600 mg/sachet: Citric acid, Saccharin sodium, Macrogol 6000, Lemon juice flavour (in powder), Sorbitol.

✓ ***Powder for oral suspension***

100mg/5ml & 200 mg/5ml: Saccharin sodium, Glycine, Sodium citrate, Methyl-p-hydroxybenzoate sodium salt (E219), Glucose anhydrous, Orange flavour (in powder), B. Carotene 1% cws, Water.

✓ ***Effervescent tablet***

Sorbitol, Monosodium citrate anhydrous, Sodium hydrogen carbonate anhydrous, Potassium carbonate, Polyethylene glycol 6000, Magnesium sulfate, Lemon flavour (in powder), Sodium cyclamate, Sodium saccharine.

6.2. Incompatibilities

Acetylcysteine can react with rubber and metal (e.g., iron, nickel, copper). Use of glass and/or plastic delivery systems is recommended when administering via nasogastric or nasointestinal tube.

Do not mix antibiotics and acetylcysteine prior to administration, due to the possibility of *in-vitro* inactivation of the antibiotics (mainly β-lactam antibiotics).

6.3. Shelf life

✓ ***Granules for oral suspension, in single dose***

5 years.

After reconstitution, the medicinal product must be used immediately.

✓ ***Powder for oral suspension***

3 years.

For storage conditions after reconstitution, see section 6.4.

✓ ***Effervescent tablet***

2 years.

6.4. Special precautions for storage

✓ ***Granules for oral suspension, in single dose***

Do not store at a temperature above 25 °C.

✓ ***Powder for oral suspension***

Do not store at a temperature above 25 °C.

After reconstitution: 20 days in the refrigerator or 12 days at a temperature up to 25 °C.

✓ ***Effervescent tablet***

Do not store at a temperature above 25 °C.

6.5. Nature and contents of container

✓ ***Granules for oral suspension, in single dose***

1. Cardboard box containing 20 sachets (BT X 20 sachets) made of low-density polyethylene, paper, aluminium and surlin and a Package Leaflet.
2. Cardboard box containing 8 sachets (BT X 8 sachets) made of low-density polyethylene, paper, aluminium and surlin and a Package Leaflet.

Each sachet contains 3 g.

✓ ***Powder for oral suspension***

Cardboard box containing a clear glass vial of 150ml, with a plastic screw cap, containing 30.0 g of orange-coloured powder, which with the addition of 120 ml of water becomes an oral suspension *(Bottle x 120 ml)* and a Package Leaflet.

✓ ***Effervescent tablet***

1. Cardboard box containing 12 effervescent tablets packaged in 3 foists made of polyethylene and aluminium foil each containing 4 tablets (foists 3 x 4) and a Package Leaflet.

2. Cardboard box containing 20 effervescent tablets in 5 foists made of polyethylene and aluminium foil each containing 4 tablets (foists 5 x 4) and a Package Leaflet.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal

No special requirements.

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

7. MARKETING AUTHORISATION HOLDER

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8. **MARKETING AUTHORISATION NUMBER(S)**

✓ ***Granules for oral suspension, in single dose***

100 mg/sachet:

116586/03.11.2022.

200 mg/sachet:

116587/03.11.2022.

600 mg/sachet:

116588/03.11.2022.

✓ ***Powder for oral suspension***

100mg/5ml:

92770/13.09.2018,

200 mg/5ml:

1273/20.06.2022.

✓ ***Effervescent tablet***

600 mg/tab:

117364/02.12.2019.

9. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

✓ ***Granules for oral suspension***

Date of first authorisation: 19.06.1991.

Date of latest renewal: 06.02.2007.

✓ ***Powder for oral suspension***

Date of first authorisation: 11.07.2001.

Date of latest renewal:

100 mg/5ml: 06.02.2007,

200 mg/5ml: 16.03.2007.

✓ ***Effervescent tablet***

Date of first authorisation: 29.08.2006.

Date of latest renewal: 09.05.2012.

10. DATE OF REVISION OF THE TEXT

03.11.2022.