1 NAME OF THE MEDICINAL PRODUCT
Acetylcysteine 200 mg Powder for Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each sachet contains Acetylcysteine 200 mg.

Excipient(s) with known effect:
- aspartame (E951): 26 mg per sachet
- sorbitol (E420): 723.34 mg per sachet
- sunset yellow (E110): 0.66 mg per sachet

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Powder for oral solution.

White to slightly pink powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Mucolytic adjuvant in the therapy of respiratory disorders associated with thick, viscous, mucus hypersecretion.

4.2 Posology and method of administration
Posology

Adults and adolescents over the age of 12 years
200 mg (1 sachet) 3 times a day. Maximum recommended daily dose 600 mg/day.
The duration of therapy is dependent on the nature and severity of the illness, and should be decided by the doctor treating the patient for adults and adolescents. Abundant fluid intake supports the mucolytic effect of acetylcysteine.

**Method of administration**

Dissolve the contents of one sachet completely in a glass containing a little water just before use, stirring as needed with a teaspoon.

**4.3 Contraindications**

Acetylcysteine 200 mg Powder for Oral Solution must not be used when:

- Hypersensitivity to the active substance, other chemically similar substance (for example carbocisteine, erdosteine or mecysteine) or to any of the excipients listed in section 6.1, is present
- Phenylketonuria is present, as the product contains aspartame.

**4.4 Special warnings and precautions for use**

Patients with bronchial asthma should be closely monitored during therapy; if bronchospasm occurs, treatment with Acetylcysteine 200 mg Powder for Oral Solution should be discontinued immediately.

Administration of acetylcysteine, especially at the beginning of treatment, may liquefy bronchial secretions and, at the same time, increase their volume. If the patient is unable to expectorate efficiently, to avoid retention of secretions postural drainage and tracheal suction should be used.

There are no studies on the efficacy and safety of acetylcysteine 200 mg three times daily in adolescent population. However, mild to severe adverse reactions have been reported with the use of IV acetylcysteine in adults and adolescents.

This medicine contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

This medicine contains aspartame, which is a source phenylalanine. This may be harmful to people with phenylketonuria.

This medicine contains a colouring agent called sunset yellow (E110), which may cause allergic reactions.
Acetylcysteine can cause interference with the colorimetric assay method for the determination of salicylates.

Acetylcysteine can interfere with tests for ketones in urine.

Upon opening the sachet the powder may smell of sulphur (rotten egg smell). This is a normal characteristic of the active substance. Upon addition of water the solution will have a citrus odour.

4.5 Interaction with other medicinal products and other forms of interaction

Drug Interactions

Antitussive drugs and acetylcysteine should not be administered concomitantly because reducing the cough reflex may lead to a build-up of bronchial secretions.

Activated charcoal may reduce the effect of acetylcysteine.

It is advisable not to mix Acetylcysteine 200 mg Powder for Oral Solution with other medicinal products.

*In vitro* tests have shown that when cephalosporin antibiotics and acetylcysteine are mixed, there is a degree of antibiotic inactivation. It is precautionary to advise the administration of oral antibiotics at least two hours before or after acetylcysteine.

Concurrent administration of nitroglycerin and acetylcysteine causes significant hypotension and leads to temporal artery dilation with possible onset of headache. If concurrent administration of nitroglycerin and acetylcysteine is required, patients should be monitored and warned for hypotension that can be severe and accompanied by a headache.

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Acetylcysteine 200 mg Powder for Oral Solution during pregnancy.

Breastfeeding

There is insufficient information on the excretion of acetylcysteine in human milk. A risk to the newborns/infants cannot be excluded.
4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive or use machines have been performed. Acetylcysteine 200 mg Powder for Oral Solution has no known effect on the ability to drive and use machines.

4.8 Undesirable effects
Adverse reactions are listed below, by system organ class and frequency.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency/Adverse Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Tinnitus</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypotension</td>
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<tr>
<td>Respiratory, thoracic and mediastinal</td>
<td>Bronchospasm, dyspnœa</td>
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<tr>
<td>disorders</td>
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</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Vomiting, diarrhoea, stomatitis, abdominal pain, nausea</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Urticaria, rash, angioedema, pruritus</td>
</tr>
<tr>
<td>General disorders and administration site</td>
<td>Fever</td>
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<tr>
<td>conditions</td>
<td></td>
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<tr>
<td></td>
<td>Oedema of the face</td>
</tr>
</tbody>
</table>
The occurrence of serious skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have 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 effects.

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

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

A decreased blood platelet aggregation in the presence of acetylcysteine has been confirmed by various studies. The clinical relevance has not yet been clarified to date.

**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](http://www.mhra.gov.uk/yellowcard).

### 4.9 Overdose

An acute overdose of acetylcysteine can cause gastrointestinal symptoms such as nausea, vomiting and diarrhoea.

**Treatment of Overdose**

Treatment of overdose is to be symptomatic and supportive treatment as indicated by the patient’s clinical condition.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Mycolytics, ATC code: R05CB01

N-acetyl-L-cysteine (NAC), the active ingredient in Acetylcysteine 200 mg Powder for Oral Solution exerts an intense mucolytic-fluidizing action on mucous and mucopurulent secretions by depolymerizing the mucoproteic complexes and the nucleic acids which confer viscosity to the vitreous and purulent component of the sputum and other secretions.

Furthermore, acetylcysteine exerts a direct antioxidant action, having a free thiol (-SH) nucleophilic group that is able to interact directly with electrophilic groups of oxidant radicals. Of particular interest is the recent finding that acetylcysteine protects
α1-antitrypsin enzyme inhibiting elastase from inactivation by hypochlorous acid (HOCl), a powerful oxidant agent produced by the myeloperoxidase enzyme of activated phagocytes. Due to its molecular structure, acetylcysteine can readily cross cell membranes. Inside the cell, NAC is deacetylated to L-cysteine, an amino acid essential for glutathione synthesis (GSH).

GSH is a highly reactive tripeptide found ubiquitously in the various tissues of animals and is essential for the maintenance of functional capacity as well as cellular morphological integrity. It is the most important protective intracellular mechanism against oxidant radicals, both exogenous and endogenous, as well as toward numerous cytotoxic substances.

These features make Acetylcysteine 200 mg Powder for Oral Solution particularly suitable for the treatment of acute and chronic affections of the respiratory system, characterised by thick, viscous mucous and mucopurulent secretions.

There is no evidence on the efficacy and safety of mucolytics including acetylcysteine in acute bronchitis.

5.2 Pharmacokinetic properties

Absorption
Following oral administration, acetylcysteine is rapidly and almost completely absorbed and metabolised in the liver to cysteine (the pharmacologically active metabolite), diacetylcysteine, cysteine and further mixed disulphides.

Distribution
Due to the high first-pass effect, the bioavailability of orally administered acetylcysteine is very low (approximately 10%). In humans, maximum plasma concentrations are achieved after 1-3 hours with the maximum plasma concentration of the metabolite cysteine in the range of approximately 2 μmol/l. The protein binding of Acetylcysteine was determined to be about 50%.

Biotransformation
Acetylcysteine and its metabolites occur in three different forms in the organism: partially in free form, partially bound to proteins via labile disulphide bonds and partially as incorporated amino acid. 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 the 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 revealed a distribution volume 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 after intravenous administration is 30-40 minutes while excretion follows 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
Acute toxicity studies in rats and mice, by oral, intraperitoneal and intravenous administration showed acetylcysteine to be of low toxicity. LD50 values greater than 7 g / kg in mice and 6 g / kg in rats have been reported. Chronic toxicity studies with acetylcysteine in rats at doses up to 2000 mg / kg / day and dogs at doses up to 300 mg / kg / day for periods up to 52 weeks demonstrate that acetylcysteine is well tolerated, even at higher doses. In reproductive toxicity studies in rats and rabbits, the oral administration of doses up to 2000 mg / kg / day did not show changes in reproductive capacity, teratogenic effects or peri/postnatal toxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Aspartame (E951)
Sorbitol (E420)
Lemon flavour (contains maltodextrin, a form of glucose)
Sunset yellow (E110)

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

6.3 Shelf life
3 years

After reconstitution, the product must be administered immediately.
6.4 Special precautions for storage
Store in the original package to protect from moisture.

6.5 Nature and contents of container
Paper/aluminium/polyethylene sachet containing 1g powder for oral solution, packaged in a cardboard box, in the following pack sizes:

10, 18, 20, 30 sachets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements for disposal. Any unused product should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
NTC S.r.l.
Via Luigi Razza, 3-20124, Milan
Italy

8 MARKETING AUTHORISATION NUMBER(S)
PL 35730/0009

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
05/07/2016

10 DATE OF REVISION OF THE TEXT
05/07/2016