Siran™600mg effervescent tablets - Acetylcysteine

1. Name of the medicinal product
Siran 600mg effervescent tablets

2. Qualitative and quantitative composition
Siran 600mg effervescent tablet contains 600mg acetylcysteine. Also contains aspartame and sodium hydrogen carbonate. For a full list of excipients, see Section 6.1.

3. Pharmaceutical form
Effervescent tablet, round and white, scored on one side. The tablet can be divided into equal halves.

4. Clinical particulars

4.1 Therapeutic indications
To liquefy mucus and to facilitate expectoration in bronchitis induced by a cold.

4.2 Posology and method of administration
If not prescribed otherwise, the following dosage is recommended for Siran 600mg effervescent tablets:

- Adults and juveniles aged 14 or more, half an effervescent tablet twice a day (corresponding to 300 - 600mg acetylcysteine per day)

or

- One effervescent tablet once a day (corresponding to 600mg acetylcysteine per day).

Nature and overall duration of therapy:
Do not take Siran 600mg effervescent tablets without medical advice for longer than 4 - 5 days.
Siran 600mg effervescent tablets are taken dissolved in a glass of water after meals.

4.3 Contraindications
Do not take Siran 600mg effervescent tablets in the event of hypersensitivity to acetylcysteine or one of the other ingredients.

Siran 600mg effervescent tablets may not be used for children less than 2 years of age due to the high content of the active substance.

4.4 Special warnings and precautions for use
Do not use in patients with hepatic or renal failure, in order to avoid excessive intake of nitrogen.

Very rarely, severe skin reactions such as Stevens-Johnson syndrome and Lyell syndrome have been reported during use of acetylcysteine.
If new changes to the skin and the mucous membranes occur, medical advice should be obtained without delay and the use of acetylcysteine stopped.

Use cautiously in patients suffering from Asthma bronchiale or in patients with a history of gastric ulceration.

As one effervescent tablet contains 6.3mmol (145mg) sodium exercise caution with patients on a sodium-controlled (low-sodium/low-salt) diet.

The tablets also contain aspartame, a source of phenylalanine, and may thus be damaging for patients with phenylketonuria.

**4.5 Interactions with other medicinal products and other forms of interaction**

Siran 600mg effervescent tablets used with antitussives (cough remedies) may reduce the coughing reflex, leading to congestion.

Reports of in-vitro tests involving direct mixing of the compounds indicate deactivation of antibiotics (tetracycline, amino glycoside, penicillin). Therefore oral intake of antibiotics and acetylcysteine should be separated by at least two hours. This does not apply to Cefixim and Loracarbef.

**4.6 Pregnancy and lactation**

No data are available on use of acetylcysteine in pregnant women.

Experimental studies in animals give no indication of direct or indirect effects on pregnancy, embryonic/fetal development, birth or post-natal development (see also 5.3).

There are no data on excretion into breast milk.

Acetylcysteine should only be used in pregnancy and lactation after careful consideration of the risk and benefit.

**4.7 Effects on the ability to drive and use machines**

None known.

**4.8 Undesirable effects**

In the assessment of side-effects, the following categories are used as a basis:

- **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)

**General disorders and site of administration conditions (occasionally ≥1/1.000, < 1/100):**

- headache, fever, allergic reactions: itching, urticaria, exanthema, rash, bronchospasm, angioedema, tachycardia and fall in blood pressure.

**very rare (< 1/10,000):**

- anaphylactic reactions, even shock.

**Respiratory, thoracic and mediastinal disorders (rarely ≥1/10,000, < 1/1,000):**

- dyspnoea, bronchospasm - mainly in patients with a hyper-reactive bronchial system in Asthma.

**Gastrointestinal disorders (uncommon ≥1/1,000, < 1/100):**

- stomatitis, stomach pains, nausea, vomiting and diarrhoea.
In addition, haemorrhage whilst using acetylcysteine has been reported very rarely (- < 1/10,000), partly in connection with hypersensitivity reactions.

The reduction in platelet aggregation in the presence of acetylcysteine, confirmed by various studies, has not been shown to clinically relevant.

4.9 Overdose

In oral administration of acetylcysteine, no cases of toxic overdose have been observed.

Volunteers were treated for 3 months with a dose of 11.6 g Acetylcysteine per day with no severe side-effects observed.

Oral doses of up to 500mg Acetylcysteine per day were tolerated without intoxication.

a) Symptoms of intoxication

Overdose can lead to gastrointestinal symptoms such as nausea, vomiting and diarrhoea. In babies there is the risk of hyper-secretion.

b) Therapeutic measures for intoxication

Experience during intravenous treatment of paracetamol poisoning in humans at maximum daily doses of up to 30g acetylcysteine showed partly irreversible "anaphylactoid" reactions in particular during rapid administration.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Mucolytics

ATC code: R05 CB

Acetylcysteine is a derivative of the amino acid cysteine. Acetylcysteine has a secretolytic and secreto-motorial effect in the bronchial tract. It is suspected of disrupting disulfide bridges between mucopolysaccharide fibres and a depolymerising effect on DNA fibres (in the purulent mucus). By this mechanism, the viscosity of the mucus is said to be reduced.

An alternative mechanism is alleged to be based upon the ability of its reactive SH group to bind and thus to detoxify chemical radicals.

Further, acetylcysteine contributes to glutathione synthesis, which is important for the detoxification of noxious agents. This explains its effect as an antidote in paracetamol intoxication.

In patients with chronic bronchitis/cystic fibrosis, undergoing prophylactic administration of Acetylcysteine, a protective effect has been described on the frequency and severity of bacterial exacerbations.

5.2 Pharmacokinetic properties

Following oral administration, acetylcysteine is rapidly and almost completely resorbed and metabolised in the liver to form cysteine, the pharmacologically active metabolite. Also formed are diacetylcystine, cystine and further mixed disulfides. As a result of the high first-pass effect, bio-availability of orally administered acetylcysteine is very low (approx. 10%).

In humans, the maximum plasma concentrations are reached after 1 to 3 hours, the maximum plasma concentration of the metabolite cystine being about 2 μmol/l. The protein binding of acetylcysteine was determined at about 50%.

Acetylcysteine and its metabolites occur in the body in three differing forms: partly in a free form, partly bound to protein via unstable disulfide bridges and partly as an integrated amino acid. Excretion
is almost exclusively in the form of inactive metabolites (inorganic sulphates, diacetylcystine) via the kidneys.

The plasma half-life of acetylcysteine is about 1 hour and is mainly determined by the fast hepatic biotransformation. Reduced hepatic function therefore leads to prolonged plasma half-lives of up to 8 hours.

Pharmacokinetic studies following the intravenous administration of acetylcysteine show a volume of distribution of 0.47 l/kg (total) and 0.59 l/kg (reduced), plasma clearance being 0.11 l/h/kg (total) and 0.84 l/h/kg (reduced). The elimination half-life after intravenous administration is 30-40 minutes with excretion following three-phase kinetics (alpha, beta and terminal gamma phase).

N-acetylcysteine crosses the placenta and can be detected in the umbilical blood. There is no information about excretion into breast milk.

No data are 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 tests is low. Treatment of overdoses, see section 4.9.

b) Chronic toxicity

Studies in various species of animals (rats, dogs) with a duration of up to one year showed no pathological changes.

c) Carcinogenic and mutagenic potential

Mutagenic effects of acetylcysteine are not to be expected. An in-vitro test was negative. Studies of the carcinogenic potential of acetylcysteine have not been performed.

d) Reproductive toxicology

In embryonic toxicity studies in rabbits and rats, no deformities were seen. Studies of fertility and peri- and post-natal toxicity were negative.

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

6. Pharmaceutical properties

6.1 List of excipients

Aspartame
Lemon aroma
Sodium hydrogen carbonate
Water-free citric acid (Ph Eur)

6.2 Incompatibilities

See interactions

6.3 Shelf life

The shelf life is 3 years. Do not use this medicine after the expiry date.

6.4 Specific precautions for storage

Keep in the original packaging. Do not store above 30°C.

Close the tube immediately after removing a tablet.
6.5 **Nature and contents of container**

White polypropylene tube with a polyethylene tamper-evident closure.

Pack of 10, 20 and 30 effervescent tablets.

6.6 **Specific precautions for disposal and other handling**

Do not discard in waste water or household refuse. This measure helps the environment.

7. **Distributor**

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8. **Authorisation number**

WL 36892

9. **Date of revision of the text**

August 2011