SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Siran 200 mg effervescent tablets

2. Qualitative and quantitative composition

Each Siran 200 mg effervescent tablet contains 200 mg acetylcysteine.
Each effervescent tablet contains aspartame and sodium hydrogen carbonate.
For a full list of excipients, see Section 6.1.

3. Pharmaceutical form

Effervescent tablet
White, round tablet with a breaking notch on one side.
The tablet can be divided into equal halves.

4. Clinical particulars

4.1 Therapeutic indications

Mucolytic in respiratory tract disorders where reduction of sputum viscosity is required.

4.2 Posology and method of administration

If not prescribed otherwise, the following dosage is recommended for Siran 200 mg effervescent tablets:

Adults and juveniles aged 14 and above: 1 effervescent tablet 2 - 3 times a day (corresponding to 400 - 600 mg acetylcysteine per day).

Children and juveniles from 6 - 14 years of age, 1 effervescent tablet twice a day (corresponding to 400 mg acetylcysteine per day).

Children from 2 - 5 years of age, ½ effervescent tablet 2 - 3 times a day (corresponding to 200 - 300 mg acetylcysteine per day).

Nature and overall duration of the application

Do not take Siran 200 mg effervescent tablets without medical advice for longer than 4 - 5 days.
Siran 200 mg effervescent tablets are taken dissolved in a glass of water after meals.

4.3 Contraindications

Siran 200 mg effervescent tablets may not be administered in the event of hypersensitivity against acetylcysteine or one of the other ingredients.

Siran 200 mg effervescent tablets may not be used for children under the age of 2 due to the high content of the active substance.

4.4 Special warnings and precautions for use

Very rarely, the occurrence of severe skin reactions such as Stevens-Johnson syndrome and Lyell syndrome has been reported in close connection with the application of acetylcysteine.

If new changes to the skin and the mucous membranes occur, medical advice should be obtained without delay and the application of acetylcysteine should be stopped.

Caution is advised in case of patients with histamine intolerance. Treatment of these patients over a longer period of time should be avoided because Siran 600mg effervescent tablets exert an influence on histamine metabolism and might cause symptoms of intolerance (e.g. headaches, rhinorrhea, pruritus).

Take care in use with patients suffering from Asthma bronchiale and patients with an ulcer anamnesis.

One effervescent tablet contains 6.37 mmol (146.5 mg) sodium. This is to be taken into account for persons on a sodium-controlled (low-sodium/low-salt) diet.

Contains aspartame as a source of phenylalanine and may be damaging for patients with phenylketonuria.

4.5 Interactions with other medicinal products and other forms of interaction

In combined application of Siran 200 mg effervescent tablets with antitussives (cough-relieving agents), a dangerous secretion congestion can result due to the limited coughing reflex, which means that the indication for this combination treatment should be made particularly carefully.

Reports on a deactivation of antibiotics (tetracycline, amino glycoside, penicillin) by acetylcysteine have been exclusively concerned with in-vitro tests up to now, in which the substances concerned were mixed directly. Nevertheless, for safety reasons, oral applications of antibiotics should be separate and with an interval of at least two hours. This does not apply to Cefixim and Loracarbef.

4.6 Pregnancy and lactation

No sufficient clinical data are available for acetylcysteine concerning exposed pregnant women. Experimental studies on animals give no indication of direct or indirect damaging effects on pregnancy, embryonic/foetal development, birth or post-natal development (see also 5.3). No information on excretion into the mother's milk is available. It should only be applied in pregnancy and lactation after a strict risk/benefit consideration.

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)
Not known (cannot be estimated from the available data)

General disorders and administration site conditions (uncommon ≥1/1.000 to < 1/100):
headache, fever, allergic reactions: itching, urticaria, exanthema, rash, bronchospasms, angio-oedema, tachycardia and drop in blood pressure.

Very rare (< 1/10,000): anaphylactic reactions, even shock

Respiratory, thoracic and mediastinal disorders (rare ≥1/10,000 to < 1/1,000):
dyspnoea, bronchospasms - mainly in patients with a hyperreactive bronchial system in Asthma bronchiale

Gastrointestinal disorders (uncommon ≥1/1,000 to < 1/100):
stomatitis, stomach pains, nausea, vomiting and diarrhoea

In addition, the occurrence of haemorrhages in connection with the administration of acetylcysteine has been reported very rarely (< 1/10,000), partly in connection with hypersensitivity reactions. A reduction of the blood platelet aggregation in the presence of acetylcysteine has been confirmed by various examinations. The clinical relevance has yet to be clarified.

4.9 Overdose

With oral forms of administration of acetylcysteine, no case of a toxic overdose has yet been observed. Volunteers were treated for 3 months with a dose of 11.6 g acetylcysteine/day without severe side-effects being observed. Oral doses of up to 500 mg acetylcysteine/day were tolerated without intoxication phenomena.

a) Symptoms of intoxication

Overdoses may lead to gastrointestinal symptoms such as nausea, vomiting and diarrhoea. With babies, there is the risk of hypersecretion.

b) Therapy measures for intoxications

If need be, symptomatically

From intravenous acetylcysteine treatment of paracetamol intoxication, experience with maximum daily doses of up to 30 g acetylcysteine is available for humans.

The i.v. application of extremely high acetylcysteine concentrations might cause „anaphylactoid“ responses, especially when rapidly applied. One case of epileptic seizures and cerebral oedema with fatal outcome after a massive i.v. overdose has been reported.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Mucolytics

ATC code: R05 CB01

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

An alternative mechanism of acetylcysteine is alleged to be based on 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 noxae. This explains its effect as an antidote in paracetamol intoxications.

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

5.2 Pharmacokinetic properties

Following oral administration, acetylcysteine is resorbed quickly and practically completely and metabolised in the liver to form cysteine, the pharmacologically active metabolite, and 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 1-3 hours, the maximum plasma concentration of the metabolite cystine being in the range of about 2 µmol/l. The protein binding of acetylcysteine was determined at about 50%.

Acetylcysteine and its metabolites occur in the organism in three differing forms: partly in a free form, partly bound to protein via instable 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. A limitation of the hepatic function therefore leads to prolonged plasma half-lives of up to 8 hours.

Pharmacokinetic examinations with intravenous administration of acetylcysteine resulted in a distribution volume of 0.47 l/kg (total) and 0.59 l/kg (reduced), plasma clearance being determined with 0.11 l/h/kg (total) and 0.84 l/h/kg (reduced). The elimination half-life after i.v. administration is 30-40 min., excretion following three-phased kinetics (alpha, beta and terminal gamma phase).

N-acetylcysteine passes the placenta and can be detected in the umbilical blood. There is no information about excretion into the mother's milk.

No information is available on the behaviour of acetylcysteine on the blood-brain barrier for application in human beings.

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

Examinations on 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.

Examinations on a carcinogenic potential of acetylcysteine have not been held.

d) Reproduction toxicology

In embryonic toxicity studies on rabbits and rats, no deformations were seen. Examinations of fertility and peri- and post-natal toxicity were negative.

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

6. Pharmaceutical properties

6.1 List of excipients

Aspartame , Lemon flavour , Sodium hydrogen carbonate, Citric acid, anhydrous

6.2 Incompatibilities

Also cf. interactions

6.3 Shelf life

The shelf life in polypropylene tubes is 3 years.

Do not use this medication used any more after the expiry date.

6.4 Specific precautions for storage

Keep in the original packaging. Do not store above 25°C

Close the tube again immediately after removing a tablet.

6.5 Nature and contents of container

Packets of 20 effervescent tablets.

6.6 Specific precautions for disposal and other handling

The drug may not be disposed of in waste water or household refuse. This measure helps to benefit the environment.

7. General classification for supply

Medicinal product not subject to medical prescription.

8. Manufacturer

Temmler Pharma GmbH

Marburg, Germany

9. License Holder

Megapharm Ltd.

P.O.B 519 Hod Hasharon 4510501

10. Marketing authorisation number

112-05-27057

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