Bisolvon®

Boehringer Ingelheim

Composition
1 tablet contains 8 mg
5 ml syrup contain 8 mg

N-cyclohexyl-N-methyl-(2-amino-3, 5-dibromobenzyl) amine hydrochloride (= bromhexine hydrochloride)

Excipients:
Tablets 8 mg: lactose monohydrate, maize starch, magnesium stearate.

Syrup 8 mg: Flavouring agents, benzoic acid, levomenthol, maltitol syrup (Ph.Eur.), sucralose, purified water.

Pharmacological properties

Pharmacodynamic properties:
Pharmacotherapeutic group: Mucolytic agents ATC code: R05CB

Bromhexine is a synthetic derivative of the herbal active substance vasicin. It has a mucolytic and secretomotor effect in the bronchial tract. It has been demonstrated in clinical studies that the substance relieves cough and makes expectoration easier. In animal studies it brings about an increase in the amount of serous bronchial secretion. It is thought to enhance mucus clearance by reducing viscosity and activating the ciliary epithelium. Administration of bromhexine increases the concentration of the antibiotics amoxycillin, erythromycin and oxytetracycline in the sputum and bronchial secretion. The clinical significance of this effect is still unclear.

Pharmacokinetic properties
Oral doses of between 8 and 32 mg bromhexine show dose-dependent pharmacokinetics.

Absorption
Following oral administration, bromhexine is absorbed rapidly and completely from the gastrointestinal tract. The bioavailability after oral administration is comparable with both the solid and the liquid form. The absolute bioavailability of bromhexine hydrochloride is 22.2 ± -8.5 % for the tablets and 26.8 ± -13.1 % for the solution. The first-pass effect is 75 – 80 %.
The plasma concentration of bromhexine increases when taken together with food.

Distribution
After intravenous administration, bromhexine is distributed rapidly through the body. The mean distribution volume (V_{ss}) is 1209 +/- 206 l (19 l/kg). Distribution to the bronchial and parenchymal lung tissue has been examined after oral administration of 32 and 64 mg bromhexine. Two hours after intake, the substance has been found to accumulate in the lung tissue, by a factor of 1.5 – 4.5 in the bronchial/bronchiolar tissue and by a factor of 2.4 to 5.9 in the pulmonary parenchyma, compared with the plasma level. Bromhexine enters the CSF. 95 % of bromhexine binds to plasma proteins; bromhexine shows a non-restrictive binding pattern.

Metabolism
Bromhexine is almost fully metabolized. A number of hydroxylated products and dibromoanthranilic acid are generated. Like the parent compound bromhexine, all the metabolites are converted primarily into N- and O-glucuronides.
There are no signs to suggest a change in the degradation route on combination with sulfonamides, oxytetracycline or erythromycin. It can thus be concluded that significant interactions with CYP 450 2C9 or 3A4 are unlikely.

Elimination
Clearance of bromhexine is 843 – 1073 mL/min and thus within the range of the hepatic circulation, suggesting that bromhexine has a high hepatic extraction coefficient. The coefficient of variation for clearance is > 30 %.
After oral administration of radioisotope-labelled bromhexine, 97.4 +/- 1.9 % of the dose is recovered in the urine; less than 1 % of which as parent compound. The bromhexine plasma concentration shows a multiphase decline. Following administration of single oral doses of between 8 and 32 mg bromhexine, the terminal half-life is between 6.6 and 31.4 hours.
The relevant half-life for estimation of the kinetics after multiple dosing is about 1 hour. Consequently, there were no signs of accumulation after multiple dosing. The accumulation factor is 1.1.

Special patient groups
No studies have been conducted to investigate the pharmacokinetics of bromhexine in elderly patients or in patients with liver or kidney failure. From experience with broad use of the substance, there are no signs to suggest this patient group is at greater risk. In the case of severe liver disease, clearance of the parent compound can be expected to be reduced. In severe renal failure, prolongation of the elimination half-life of the bromhexine metabolites cannot be ruled out.

Pharmacokinetic interactions
No studies have been conducted to investigate the interaction with oral anticoagulants or digoxin. Concomitant use of ampicillin or oxytetracycline has no effect on the pharmacokinetics of bromhexine. Even concomitant use of erythromycin was not found to cause any significant interactions on historical comparison.
As there were no reports of significant interactions during long-term use, it can be assumed that the potential for interactions with these drugs is low.

Bromhexine may undergo nitrozation in the stomach under physiological conditions.

Indications
Mucolytic treatment of acute and chronic bronchopulmonary diseases associated with impaired formation and transport of mucus.

Contraindications
Tablets: Bisolvon cough tablets should not be used where there is known hypersensitivity to one of the ingredients.

Syrup: Hypersensitivity to bromhexine hydrochloride, levomenthol or one of the other ingredients (see: Excipients).

In view of the high active ingredient content, Bisolvon cough syrup is not suitable for children below the age of 6 years. Other pharmaceutical forms and strengths are available for these patients.

Special warnings and precautions
In very rare cases severe skin disorders such as Stevens-Johnson's syndrome and Lyell's syndrome have been reported after concomitant administration of mucolytic substances (e.g. bromhexine); this was explained in most cases by the underlying disease or the concomitant medication. If new skin or mucosal lesions occur, medical advice should be sought immediately and treatment with bromhexine discontinued as a precaution.

In the case of disturbances of the bronchomotor system and excessive secretion (e.g. in the rare event of malignant ciliary syndrome) care should be taken when using Bisolvon Cough tablet or syrup as they can cause a build-up of secretion.

Care should be exercised when using Bisolvon cough Tablet or syrup in the case of impaired renal function or severe liver disease (i.e. longer intervals between doses or lower doses).

In severe renal failure an accumulation of the metabolites of bromhexine formed in the liver can be expected.

Occasional monitoring of hepatic function is advisable, particularly in the case of longer-term treatment.

For Tablets: This drug contains lactose (approx. 74 mg per tablet). Bisolvon cough tablet should not be used to treat patients with rare hereditary galactose intolerance, lactase deficiency or glucose-galactose malabsorption.

For Syrup: Bisolvon cough syrup should not be used to treat patients with the rare hereditary fructose intolerance. 5 ml Bisolvon cough syrup contains 2.5 g maltitol syrup equivalent to approx. 0.2 x 10-gram portions. This must be taken into consideration in patients with diabetes mellitus. The calorie count is 2.3 kcal/g maltitol syrup. Maltitol syrup can have a mild laxative effect.

Drug Interactions
If Bisolvon cough tablets or syrup are used together with antitussives, the reduced cough reflex can lead to a dangerous accumulation of mucus; this medicine should therefore only be used in combination with these medicinal products after very careful consideration.

Pregnancy and Lactation
In animal studies, bromhexine penetrated the placental barrier. Animal studies do not suggest any direct or indirect harmful effects on pregnancy, embryonic/fetal development, birth or postnatal development.

There is no previous experience with the use of bromhexine during human pregnancy. Consequently, Bisolvon should only be used during pregnancy after careful consideration of the benefit-risk ratio and is not recommended in the first three months.

The active ingredient bromhexine entered the breast milk in animal studies. Use during lactation is not recommended.

Effects on ability to drive and use machines:-
None known

Side Effects
The frequencies of undesirable effects are based on the following categories:

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)

Diseases of the immune system, diseases of the air passages, chest and mediastinum, diseases of the skin and hypodermis
Uncommon: Hypersensitivity reactions (skin rash, angiooedema, dyspnoea, pruritus, urticaria)
Rare: Bronchospasm
Very rare: Anaphylactic reactions, including anaphylactic shock

Gastrointestinal disorders
Uncommon: Nausea, abdominal pain, in particular epigastric pain, vomiting, diarrhoea

General diseases and disorders at the site of administration
Uncommon: Fever

Dosage and administration

Tablets 8 mg
Unless otherwise prescribed the following doses of Bisolvon cough tablets are recommended:

Adults and adolescents over 14 years: 1 – 2 Bisolvon cough tablets 3 times a day (equivalent to 24 to 48 mg bromhexine hydrochloride per day).

Children and adolescents between 6 and 14 years and patients under 50 kg body weight: 1 Bisolvon cough tablet 3 times a day (equivalent to 24 mg bromhexine hydrochloride per day).

More suitable pharmaceutical forms with a lower active substance content are available for children under 6 years of age.

Syrup 8 mg/5 ml (5 ml = 1 teaspoon)

Unless otherwise prescribed the following doses of Bisolvon cough syrup are recommended:
Adults and adolescents over 14 years: 5 – 10 ml Bisolvon cough syrup 3 times a day (equivalent to 24 to 48 mg bromhexine hydrochloride per day).

Children and adolescents between 6 and 14 years and patients under 50 kg in weight: 5 ml Bisolvon cough syrup 3 times a day (equivalent to 24 mg bromhexine hydrochloride per day).

Products with a lower active substance content are available for children under 6 years of age.

The measuring cup provided has the appropriate gradations.

Posology and method of administration
The duration of use depends on the patient's individual response and the nature and severity of the symptoms.

Tablets 8 mg
Bisolvon cough tablets should be taken for no more than 4 to 5 days without medical advice.
The tablets are to be taken after meals with plenty of liquid.

Syrup 8 mg /5ml
Bisolvon cough syrup should be taken for no more than 4 to 5 days without medical advice.
Note: Bisolvon cough syrup is suitable for diabetics.

Overdosage
Symptoms of overdose
There have been no known reports to date of dangerous intoxication following overdose in man. The symptoms observed to date following accidental or intentional overdose are exactly the same as the known side effects. These call for symptomatic treatment, if necessary.

Treatment of overdose
After an excessive overdose, circulation must be monitored and, if necessary, symptomatic treatment initiated. In view of the low toxicity of bromhexine, intensive measures to reduce absorption or accelerate elimination are not generally required. Furthermore, dialysis or forced diuresis are not expected to have much impact on elimination due to the pharmacokinetic properties (high distribution volume, slow redistribution processes, high protein binding).

Since only mild symptoms are to be expected in children aged 2 years and over even after the ingestion of large doses, decontamination is not considered to be necessary after ingestion of up to 80 mg of bromhexine hydrochloride (e.g. (e.g. ten 8 mg Bisolvon cough tablets or 50 ml of Bisolvon cough syrup); in younger children the equivalent limit is reported to be 60 mg of bromhexine hydrochloride (6 mg/kg body weight).

A case report was published according to which 4 of 25 cases of excessive doses of bromhexine led to vomiting and in 3 small children to diminished consciousness, ataxia, diplopia, mild metabolic acidosis and tachypnoea. Infants remained free of symptoms after ingestion of up to 40 mg bromhexine, even without decontamination.

Date of Package insert: August, 2009 (SPC)

Availability

Tablets 8 mg
Syrup 8 mg/5 ml

Storage instructions
Store below 30°C.
Store in Safe place out of the reach of children!

Manufactured by
Delpharm Reims/France
for Boehringer Ingelheim International GmbH,
Ingelheim am Rhein,
Germany

This is a medicament
- Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament
- The doctors and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicament out of reach of children!

Council of Arab Health Ministers - Union of Arab Pharmacists

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