Boehringer Ingelheim

Product information

1. NAME OF THE MEDICINAL PRODUCT

Bisolvon® tablets
8 mg/tablet

Active substance: Bromhexine hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 tablet contains 8 mg bromhexine hydrochloride.

Excipient: Lactose (see section 4.4)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets for oral use

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Secretolytic therapy of acute and chronic bronchopulmonary diseases associated with impaired mucus formation and transport

4.2 Posology and method of administration

Unless otherwise prescribed, the following dosages are recommended for Bisolvon tablets:

Adults and adolescents over 14 years:
1 - 2 tablets 3 times a day (equivalent to 24 - 48 mg bromhexine hydrochloride a day)

Children and adolescents between 6 and 14 years and patients under 50 kg bodyweight:
1 tablet 3 times a day (equivalent to 24 mg bromhexine hydrochloride a day)

More appropriate pharmaceutical forms of lower strength are available for children under 6 years of age.

Method of administration and duration of treatment

The duration of treatment should be determined on an individual basis depending on the indication and the course of the disease.

Bisolvon tablets should not be taken for more than 4 - 5 days without medical advice.

The tablets should be taken with plenty of liquid after meals.

4.3 Contraindications

Bisolvon tablets are contraindicated in patients with known hypersensitivity to any of the components.

4.4 Special warnings and precautions for use

In a very small number of cases, there have been reports of severe skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN) occurring in temporal association with the use of expectorants such as bromhexine. Most of these cases were attributable to the underlying disease and/or to other medication being taken concomitantly. In addition, during the early phase of Stevens-Johnson syndrome or TEN, patients may experience non-specific influenza-like prodromal symptoms such as fever, joint pain, rhinitis, cough and sore throat. Because of these non-specific influenza-like prodromal symptoms, symptomatic treatment with cough and cold medications, which is inappropriate, may be started. If new skin or mucosal lesions appear, therefore, medical advice should be sought immediately and the use of bromhexine discontinued.

In patients with impaired bronchial motility and copious secretions (as seen, for instance, in the rare syndrome of primary ciliary dyskinesia), Bisolvon tablets should be used with caution because of the risk that they may promote accumulation of secretions

In patients with impaired renal function or severe liver disease, Bisolvon tablets should be used with particular caution (i.e. at reduced doses or longer dosing intervals).

In patients with severe renal impairment, accumulation of the metabolites of bromhexine which are formed in the liver can be expected to occur.

Occasional monitoring of liver function is advisable, especially on longer-term use.

This medicine contains lactose (approx. 74 mg per tablet). Patients with the rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take Bisolvon tablets.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of Bisolvon tablets and cough suppressants may lead to the development of a dangerous accumulation of secretions owing to attenuation of the cough reflex and should be undertaken only after very careful risk-benefit assessment.

4.6 Fertility, pregnancy and lactation

Pregnancy
Bromhexine has been shown to cross the placental barrier in animal studies. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).
No data are currently available on the use of bromhexine in human pregnancy. Bisolvon should therefore be used in pregnancy only after careful risk-benefit assessment; its use in the first trimester is not recommended.

Lactation
Bromhexine has been shown to be excreted in the milk in animal studies. Use during lactation is not recommended.

Fertility
No studies on the effect of Bisolvon on fertility have been performed.

There is no evidence from the available preclinical studies to suggest that bromhexine has any effect on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effect of Bisolvon on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Frequencies of occurrence of undesirable effects are defined as:

Very common	≥ 1/10
Common	≥ 1/100 - < 1/10
Uncommon	≥ 1/1000 - < 1/100
Rare	≥ 1/10,000 - < 1/1000
Very rare	< 1/10,000
Not known	Frequency cannot be estimated from the available data

Immune system disorders / Respiratory, thoracic and mediastinal disorders / Skin and subcutaneous tissue disorders

Uncommon: Hypersensitivity reactions (skin rash, angioedema, dyspnoea, pruritus, urticaria)
Rare: Bronchospasm
Very rare: Anaphylactic reactions (including shock)

Gastrointestinal disorders

Uncommon: Nausea, abdominal pain (especially upper abdominal pain), vomiting, diarrhoea

General disorders and administration site conditions

Uncommon: Fever

4.9 Overdose

Symptoms of overdose
No hazardous symptoms of overdose are known to have occurred in man to date. The symptoms which have been observed on accidental or deliberate overdose to date are identical with the known undesirable effects and may require symptomatic treatment.

Management of overdose
Following massive overdose, cardiovascular monitoring and, where appropriate, symptomatic treatment are indicated. In view of the low toxicity of bromhexine, more intensive measures to reduce absorption or accelerate elimination are generally not required. In addition, the pharmacokinetic profile of the drug is characterised by a high distribution volume, slow redistribution processes and a high level of protein binding and elimination is therefore unlikely to be significantly affected by dialysis or forced diuresis.

In children aged 2 years and above, symptoms are likely to be relatively mild even after ingestion of quite large amounts of bromhexine hydrochloride and decontamination is therefore not required where the amount ingested is less than 80 mg (e.g. 10 Bisolvon tablets 8 mg). The corresponding threshold in children aged under 2 years is 60 mg (6 mg/kg).

In one published case review, it was reported that vomiting occurred in 4 out of 25 cases where excessive doses of bromhexine had been taken and that 3 toddlers had experienced impaired consciousne-

ss, ataxia, diplopia, mild metabolic acidosis and tachypnoea. Toddlers remained symptom-free, even without decontamination, after ingesting up to 40 mg bromhexine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Mucolytics
ATC code: R05CB

Bromhexine is a synthetic derivative of the herbal active ingredient vasicine. It has a secretolytic and secretomotor effect in the bronchial tract area and has been shown in clinical studies to ease cough and facilitate expectoration. In animal studies, it has been shown to increase the proportion of serous secretions in the bronchial tract. It enhances mucus transport by reducing mucus viscosity and activating the ciliated epithelium. Administration of bromhexine increases the concentrations of the antibiotics amoxicillin, erythromycin and oxytetracycline in sputum and bronchial secretions. The clinical relevance of this effect is unclear.

5.2 Pharmacokinetic properties

Bromhexine shows dose-proportional pharmacokinetics following oral administration of doses between 8 and 32 mg.

Absorption
Following oral administration, bromhexine is rapidly and completely absorbed from the gastrointestinal tract. Solid and liquid formulations show similar bioavailability following oral administration. The absolute bioavailability of bromhexine hydrochloride from Bisolvon tablets and solution is 22.2 ± 8.5% and 26.8 ± 13.1% respectively. Bromhexine is subject to significant first-pass metabolism (75 - 80%).
Concomitant intake of food leads to an increase in plasma bromhexine concentrations.

Distribution
Following intravenous administration, bromhexine is rapidly and widely distributed throughout the body, with a mean volume of distribution (V_{ss}) of 1209 ± 206 l (19 l/kg). Distribution of bromhexine in bronchial and parenchymal lung tissue was investigated after oral administration of 32 mg and 64 mg. Two hours post-dose, concentrations of bromhexine were 1.5 - 4.5 times higher in bronchial and bronchiolar tissue and 2.4 - 5.9 times higher in parenchymal tissue than in plasma. Bromhexine crosses the blood-brain barrier. It is 95% bound to plasma proteins (non-restrictive binding).

Metabolism
Bromhexine is almost completely metabolised to a variety of hydroxylated metabolites and dibromoanthranilic acid. Bromhexine and all its metabolites undergo conjugation, principally to N-glucuronides and O-glucuronides.
There is no evidence to suggest that the metabolic profile of bromhexine is altered by sulphonamides, oxytetracycline or erythromycin.
Relevant interactions with CYP450 2C9 or 3A4 are therefore considered unlikely.

Elimination
Bromhexine has a high clearance value of 843 - 1073 ml/min (similar to hepatic blood flow), indicating that it is a high hepatic extraction-ratio drug. The coefficient of variation for clearance values is > 30%.
Following oral administration of radiolabelled bromhexine, 97.4 ± 1.9% of the dose is recovered as radioactivity in the urine; less than 1% is present in unchanged form. Plasma concentrations of bromhe-

xine show a multiphasic decline. After administration of single oral doses between 8 and 32 mg, the terminal elimination half-life ranges between 6.6 and 31.4 hours.
The relevant half-life for the prediction of multiple-dose pharmacokinetics is about 1 hour; hence, no evidence of accumulation has been found after multiple dosing. The accumulation factor is 1.1.

Special populations
There have been no studies on the pharmacokinetics of bromhexine in the elderly or in patients with impaired renal or hepatic function. Experience following wide usage of the drug does not indicate any increased risk in these populations. Reduced clearance of the parent drug can be expected in patients with severe liver disease. The elimination half-life of bromhexine metabolites may be prolonged in patients with severe renal impairment.

Pharmacokinetic interactions
No interaction studies with oral anticoagulants or digoxin have been performed. Bromhexine pharmacokinetics are not affected by co-administration of ampicillin or oxytetracycline. A historical comparison has not indicated any relevant interaction between bromhexine and erythromycin.
The lack of any relevant interaction reports over the many years for which bromhexine has been in use suggests that it has no significant interaction potential with these drugs.

Nitrosation of bromhexine may occur in the stomach under physiological conditions.

5.3 Preclinical safety data

Bromhexine hydrochloride exhibits low acute toxicity. Oral LD_{50} values were > 5 g/kg in rats, > 4 g/kg in rabbits, > 10 g/kg in dogs and > 1 g/kg in newborn rats. The intraperitoneal LD_{50} in rats was 2 g/kg. The LD_{50} values for the syrup formulation were > 10 ml/kg in mice and rats. No specific signs of toxicity were observed at these doses.

In repeated-dose toxicity studies carried out in mice over 5 weeks, the no observed adverse effect level (NOAEL) was 200 mg/kg; at a dose of 2000 mg/kg, mortality was high and the few surviving animals showed a reversible increase in liver weight and serum cholesterol levels. In studies carried out in rats over 26 and 100 weeks, a dose of 25 mg/kg produced no adverse effects, whilst convulsions and deaths occurred at 500 mg/kg. The centrilobular hepatocytes were enlarged as a result of vacuolation. In a further two-year study, doses of up to 100 mg/kg were well tolerated, whilst convulsions occurred sporadically in a few animals at a dose of 400 mg/kg. In oral studies carried out in dogs over two years, doses of up to 100 mg/kg produced no adverse effects.

Bisolvon syrup (0.8 mg/ml) was well tolerated by rats when given at total doses of up to 20 ml/kg over 4 weeks. The doses used led to reversible centrilobular fatty change.

Bromhexine was haemolytic *in vitro*.

Mutagenic and tumorigenic potential
Bromhexine hydrochloride was not mutagenic in the bacterial mutation assay or the mouse bone marrow micronucleus test.

Bromhexine hydrochloride did not show any tumorigenic potential in studies carried out over two years in rats given doses of up to 400 mg/kg or dogs given doses of up to 100 mg/kg.

Toxicity to reproduction
Bromhexine hydrochloride did not show any evidence of teratogenic or embryotoxic potential at doses of up to 300 mg/kg in rats and 200 mg/kg in rabbits.

Fertility was not impaired at doses up to 300 mg/kg.

Peri- and postnatal development was not impaired. The NOAEL was 25 mg/kg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, maize starch, magnesium stearate

6.2 Incompatibilities

None known

6.3 Shelf life

3 years

6.4 Special precautions for storage

No special storage conditions are required.

6.5 Nature and contents of container

PVC/PVDC/aluminium blisters

Pack sizes:
Original pack containing 50 tablets (N2)
Hospital packs containing 250 (5 x 50) and 1000 (20 x 50) tablets

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim Pharma GmbH & Co. KG
Vertriebslinie Thomae
Binger Straße 173
55216 Ingelheim am Rhein
Germany
Tel.: 0 800/77 90 900
Fax: 0 61 32/72 99 99
info@boehringer-ingelheim.de

8. MARKETING AUTHORISATION NUMBER

6773.00.02

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

05.02.1986 / 22.08.2005

10. DATE OF REVISION OF THE TEXT

March 2012

11. GENERAL CLASSIFICATION FOR SUPPLY

Pharmacy only

Trans. 04717/D.J.Parker/12.4.2012