BISOLVON® Solution for Injection
Bromhexine hydrochloride

**Composition**
2 ml solution for injection contain
N-Cyclohexyl-N-methyl-(2-amino-3,5-dibromobenzyl)amine hydrochloride (= bromhexine hydrochloride) 4 mg

Excipients: tartaric acid, glucose anhydrous, water for injection

**Indications**
Secretolytic therapy in acute and chronic bronchopulmonary diseases associated with abnormal mucus secretion and impaired mucus transport.

**Dosage and Administration**

**Solution for injection (4mg/2ml)**
The administration of BISOLVON® solution for injection is recommended for the treatment and prevention of the most severe cases of post-operative respiratory complications caused e.g. by impaired mucus production and transport.

In severe cases as well as before and after surgical intervention, 1 ampoule i.v. (duration of injection 2-3 minutes) 2-3 times daily.

The injection solution can also be given as an i.v. infusion together with glucose, laevulose, physiological saline or Ringer's solution.

BISOLVON® should not be mixed with alkaline dilution agent, as the acid character of the drug solution (pH 2.8) may cause opalescence or flocculation.

**General:**
Patients being treated with BISOLVON® should be notified of an expected increase in the flow of secretions.

In acute respiratory indications, medical advice should be sought if symptoms do not improve or worsen during course of therapy.

**Contraindications**
BISOLVON® is contraindicated in patients known to be hypersensitive to bromhexine or other components of the formulation.
Special Warnings and Precautions

There have been very few reports of severe skin lesions such as Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN) in temporal association with the administration of expectorants such as bromhexine. Mostly these could be explained by the patient’s underlying disease and/or concomitant medication. In addition during the early phase of a Stevens-Johnson syndrome or TEN a patient can first experience non-specific influenza-like prodromes like e.g. fever, aching body, rhinitis, cough and sore throat. Misled by these non-specific influenza-like prodromes it is possible that a symptomatic treatment is started with a cough and cold medication. Therefore, if new skin or mucosal lesions occur, medical advice should be sought immediately and treatment with bromhexine discontinued as a precaution.

For solution for injection
BISOLVON® solution for injection 4mg/2ml contain 259 mg of glucose per maximum recommended daily dose.

Interactions
No clinically relevant unfavourable interactions with other medications have been reported.

Fertility, pregnancy and lactation

Pregnancy
There are limited data from the use of bromhexine in pregnant women.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.
As a precautionary measure, it is preferable to avoid the use of BISOLVON® during pregnancy.

Lactation
It is unknown whether bromhexine/metabolites are excreted in human milk.
Available pharmacodynamic/toxicological data in animals have shown excretion of bromhexine/metabolites in breast milk.
A risk to the breastfed infant cannot be excluded.
BISOLVON® should not be used during breast-feeding.

Fertility
No studies on the effect on human fertility have been conducted with BISOLVON®.
Based on available pre-clinical experience there are no indications for possible effects of the use of bromhexine on fertility.

Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed with BISOLVON®.

Side Effects

Immune system disorder
Hypersensitivity, anaphylactic shock, anaphylactic reaction

Respiratory, thoracic and mediastinal disorders
Bronchospasm

Gastro-intestinal disorders
Nausea, vomiting, diarrhoea and abdominal pain upper

Skin and subcutaneous tissue disorders
Rash, angioedema, urticaria, pruritus

Overdose
No specific overdose symptoms have been reported in human to date. Based on accidental overdose and/or medication error reports the observed symptoms are consistent with the known side effects of BISOLVON® at recommended doses and may need symptomatic treatment.

Pharmacological Properties
Pharmacotherapeutic group: Expectorants, excl. combinations with cough suppressants
ATC-Code: R05CB02

Bromhexine is a synthetic derivative of the herbal active ingredient vasicine. Preclinically, it has been shown to increase the proportion of serous bronchial secretion. Bromhexine enhances mucus transport by reducing mucus viscosity and by activating the ciliated epithelium (mucociliary clearance).

In clinical studies, bromhexine showed a secretolytic and secretomotor effect in the bronchial tract area, which facilitates expectoration and eases cough.

Following the administration of bromhexine antibiotic concentrations (amoxicillin, erythromycin, oxytetracycline) in the sputum and bronchopulmonary secretions are increased.

Pharmacokinetics
Distribution
After intravenous administration bromhexine was rapidly and widely distributed throughout the body with a mean volume of distribution (V[ss]) of up to 1209 ± 206 L (19 L/kg). The distribution into lung tissue (bronchial and parenchymal) was investigated after i.v. administration of 8 mg and 16 mg bromhexine. Lung-tissue concentrations two hours post dose were 4.2 - 4.3 times higher in bronchiolo-bronchial tissues and between 3.0 and 4.3 times higher in pulmonary parenchyma compared to plasma concentrations.

Unchanged bromhexine is bound to plasma proteins by 95 % (non-restrictive binding).

Metabolism
Bromhexine is almost completely metabolised to a variety of hydroxylated metabolites and to dibromanthranilic acid. All metabolites and bromhexine itself are conjugated most probably in form of N-glucuronides and O-glucuronides. There are no substantial hints for a change of the metabolic pattern by a sulphonamide, oxytetracycline or erythromycin. Thus relevant interactions with CYP 450 2C9 or 3A4 substrates are unlikely.

Elimination
Bromhexine is a high extraction ratio drug (CL after i.v. administration in the range of the hepatic blood flow, 843-1073 mL/min) resulting in high inter- and intra-individual variability (CV > 30 %). After administration of radiolabelled bromhexine about 97.4 ± 1.9 % of the dose were recovered as radioactivity in urine, with less than 1% as parent compound. Bromhexine plasma concentrations showed a multiexponential decline. After intravenous administration of 15-100 mg, the terminal elimination half-life ranged between 7.1 h and 15.4 h. The relevant half-life to predict the multiple dose pharmacokinetics is about 1 hour, thus no accumulation was seen after multiple dosing (accumulation factor 1.1).

General
Bromhexine shows dose proportional pharmacokinetics in the range of 15-100 mg following i.v. administration.

There are no data for bromhexine pharmacokinetics in the elderly or in patients with renal or liver insufficiency. Extensive clinical experience did not give rise to relevant safety concerns in these populations. Also, interaction studies with oral anticoagulants or digoxin were not performed.

Concomitant food leads to an increase of bromhexine plasma concentrations.

Bromhexine pharmacokinetics are not relevantly affected by co-administration of ampicillin or oxytetracycline. There was also no relevant interaction between bromhexine and erythromycin according to a historical comparison.

The lack of any relevant interaction reports during the long term marketing of the drug suggests no substantial interaction potential with these drugs.

**Toxicology**

Bromhexine hydrochloride showed 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 i.p. 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 clinical signs of toxicity were observed at these doses.

In repeat oral dose toxicity studies over 5 weeks, mice tolerated 200 mg/kg bromhexine hydrochloride representing the "no observed adverse effect level" (NOAEL). At 2000 mg/kg, mortality was high. The few surviving animals showed a reversible increase in liver weight and serum cholesterol. Rats tolerated 25 mg/kg over 26 or 100 weeks, while at 500 mg/kg, convulsions and deaths occurred. The centrilobular hepatocytes were enlarged due to vacuolar change. Another 2 year study confirmed that doses up to 100 mg/kg are well tolerated, while at 400 mg/kg, convulsions occurred sporadically in a few animals. Dogs tolerated 100 mg/kg (NOAEL) orally over 2 years.

BISOLVON® Syrup (0.8 mg/ml) was well tolerated up to 20 ml/kg in rats with a reversible centrilobular simple fatty change of liver. After intramuscular administration of 8 mg injectable solution in dogs for 6 weeks there was no local irritation or systemic toxicity. A single i.a. injection of 4 mg bromhexine was well tolerated in rats and dogs. The lesions after i.m. injection in rabbits compared well with those after physiological saline solution. Bromhexine hydrochloride was hemolytic in *vitro*.

Bromhexine hydrochloride was neither embryotoxic nor teratogenic (segment II) at oral doses up to 300 mg/kg in rats and 200 mg/kg in rabbits. Fertility (segment I) was not impaired at doses up to 300 mg/kg. The "NOAEL" during peri- and postnatal development (segment III) was 25 mg/kg.

Bromhexine hydrochloride had no mutagenic potential in the bacterial mutation assay and the mouse bone marrow micronucleus test.

Bromhexine hydrochloride did not show a tumorigenic potential in the 2-year studies on rats given up to 400 mg/kg, and on dogs given up to 100 mg/kg.

**Availability**

Ampoules 4 mg/2 ml

Box contains 10 ampoules of 2 ml.

Reg. No. Dki0600700143A1

Store in a safe place, out of the reach of children.

Only on Doctor’s Prescription.
Harus Dengan Resep Dokter.

Manufactured by:
Boehringer Ingelheim Espana S.A
San Cugat del Valles
Madrid, Spain
Imported by:
PT. Boehringer Ingelheim Indonesia
Bogor, Indonesia