

BISOLVON®CHESTY

PRODUCT INFORMATION

DESCRIPTION

Proprietary Name:

BISOLVON CHESTY

Approved Name:

Bromhexine hydrochloride

Chemical Name:

N-(2-Amino-3,5-dibromobenzyl)-N-methylcyclohexanamine hydrochloride

Molecular formula:

$C_{14}H_{21}Br_2ClN_2$

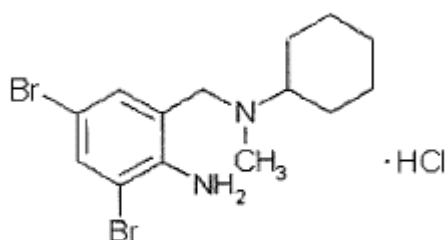
Molecular weight:

412.6

CAS number:

611-75-6

Bromhexine hydrochloride is a white or almost white crystalline powder, very slightly soluble in water and slightly soluble in alcohol and in methylene chloride. The structural formula for bromhexine hydrochloride is as follows:



BISOLVON CHESTY is available as oral liquids, tablets or soluble tablets for oral administration.

BISOLVON CHESTY Oral Liquid is available in two strengths:

- BISOLVON CHESTY and BISOLVON CHESTY KIDS Oral Liquid contains bromhexine hydrochloride 4 mg per 5 mL
- BISOLVON CHESTY FORTE Oral Liquid contains bromhexine hydrochloride 8 mg per 5 mL.

BISOLVON CHESTY and BISOLVON CHESTY FORTE Oral Liquids also contain Maltitol solution, sucralose, benzoic acid, menthol, chocolate flavour 96534-33, cherry flavour 96323-33 and purified water.

BISOLVON CHESTY KIDS Oral Liquid also contains maltitol solution, sucralose, benzoic acid, hydroxyethylcellulose, cherry flavour 96323-33, strawberry flavour 12006M and purified water.

BISOLVON CHESTY Tablets contain bromhexine hydrochloride 8 mg per tablet. Each tablet also contains lactose, maize starch and magnesium stearate.

BISOLVON CHESTY SOLUBLE Tablets contain bromhexine hydrochloride 8 mg per tablet. Each tablet also contains microcrystalline cellulose, crospovidone, tartaric acid, acesulfame potassium, macrogol 6000, fumaric acid, purified talc and the proprietary ingredients: Lemon Flavour 84260-51 (lemon flavour), Peppermint Naefco 957675 (peppermint flavour) and Beta-carotene 1% (beta-carotene).

PHARMACOLOGY

Bromhexine hydrochloride is a mucolytic. It has been shown to enhance the transport of mucus by reducing its viscosity and by activating the ciliated epithelium (mucociliary clearance). Preclinical studies have shown that bromhexine increases the amount of thin watery bronchial secretion. Clinical studies show that bromhexine has a secretolytic and secretomotor effect in the bronchial tract area, which facilitates expectoration and eases cough.

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

Pharmacokinetics

Following oral administration, bromhexine shows dose linear pharmacokinetics in the dose range of 8-32 mg. It is rapidly and completely absorbed from the gastrointestinal tract. The bioavailability after oral administration is substantially reduced by an extensive first-pass effect in the range of 75-80%. The absolute bioavailability of bromhexine hydrochloride is about $22.2 \pm 8.5\%$ and $26.8 \pm 13.1\%$ for Bisolvon tablets and solution, respectively. Concomitant food intake leads to an increase of bromhexine plasma concentrations.

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 of bromhexine in lung tissue (bronchial and parenchymal) was investigated after oral administration of 32 mg and 64 mg bromhexine. Bromhexine lung tissue concentrations two hours post-dose were 1.5 to 3.2 times higher in bronchiolo-bronchial tissues and between 3.4 and 5.9 times higher in pulmonary parenchyma compared to plasma concentrations. Bromhexine crosses the blood-brain barrier and only a small amount crosses the placenta. Unchanged bromhexine is 95% bound to plasma proteins.

Bromhexine is a high extraction ratio drug after intravenous administration (clearance is 843-1073 mL/min, within the range of the hepatic blood flow) resulting in high inter- and intra-individual variability ($CV > 30\%$). After administration of radiolabelled bromhexine, about $97.4 \pm 1.9\%$ of the dose was recovered in the urine, with less than 1% as the parent compound. Bromhexine plasma concentrations showed a multi-exponential decline. After administration of single oral doses

between 8 and 32 mg, the terminal half-life of bromhexine ranged between 6.6 and 31.4 hours. The relevant half-life to predict the multiple dose pharmacokinetics is about 1 hour. No accumulation was observed after multiple dosing (accumulation factor 1.1).

Bromhexine is almost completely metabolised to a variety of hydroxylated metabolites and to dibromanthranilic acid. Ambroxol is a metabolite of bromhexine.

There is no pharmacokinetic data available 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. However, reduced clearance of bromhexine parent substance may be expected in the case of severe liver disease; in the case of severe renal insufficiency, accumulation of metabolites cannot be ruled out.

Also, interaction studies with oral anticoagulants or digoxin were not performed. 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.

INDICATIONS

For use as a mucolytic to break down mucus and help clear the chest in conditions accompanied by excessive mucus secretions, such as in the common cold, influenza, infections of the respiratory tract or in other conditions where excess mucus is produced.

CONTRAINDICATIONS

BISOLVON CHESTY should not be used in patients known to be hypersensitive to bromhexine or any other component of the formulation.

In case of rare hereditary conditions that may be incompatible with an excipient of the product (refer to **Precautions**), the use of the product is contraindicated.

PRECAUTIONS

BISOLVON CHESTY should be used with caution in patients with severe liver disease and severe renal failure (refer Pharmacokinetics).

Use with caution in patients with gastric ulceration.

Patients should be advised to expect an increase in the flow of mucus secretions.

There have been very rare reports of severe skin lesions such as Stevens Johnson Syndrome and toxic epidermal necrolysis (TEN) in temporal association with the administration of mucolytic substances 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 should be discontinued as a precaution.

BISOLVON CHESTY Oral Liquid and BISOLVON CHESTY KIDS Oral Liquid contains at least 15 g of maltitol and up to 2.4 g of sorbitol per maximum recommended daily dose of 60 mL. BISOLVON CHESTY FORTE Oral Liquid contains at least 7.5 g of maltitol and up to 1.2 g of sorbitol per

maximum recommended daily dose of 30 mL. Products containing maltitol and sorbitol may have a laxative effect or cause diarrhoea in some people. This is more likely if several products containing maltitol, sorbitol or related substances are consumed simultaneously. Patients with rare hereditary fructose intolerance should not take these products.

BISOLVON CHESTY Tablets contains 444 mg of lactose per maximum recommended daily dose. Patients with rare hereditary galactose intolerance e.g. galactosaemia should not take this product.

BISOLVON CHESTY SOLUBLE tablets contain 31.6 mg of sucrose per maximum recommended daily dose. Patients with the rare hereditary condition of fructose intolerance should not take this medicine.

BISOLVON CHESTY SOLUBLE tablets do not contain lactose.

Use in Pregnancy

Category A: Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

Bromhexine crosses the placental barrier. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development.

Clinical experience to date has shown no evidence of harmful effects on the fetus during pregnancy. Nonetheless, the usual precautions regarding the use of drugs during pregnancy should be observed. Especially during the first trimester, the use of BISOLVON is not recommended.

Use in Lactation

Bromhexine is excreted in breast milk. Although unfavourable effects on breastfed infants would not be expected, BISOLVON CHESTY is not recommended for use in breastfeeding mothers.

Effects on ability to drive and use machines

When used as recommended and when there are no side effects, Bisolvon is not known to have any effect on the ability to drive or operate machinery.

INTERACTIONS WITH OTHER DRUGS

No clinically relevant unfavourable interactions with other medicines have been reported.

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

ADVERSE EFFECTS

Immune system disorder, skin and subcutaneous tissue disorders and Respiratory, mediastinal and thoracic disorders

Anaphylactic reaction including anaphylactic shock, angioedema, bronchospasm, rash, urticaria, pruritus and other hypersensitivity.

Gastro-intestinal disorders

Nausea, vomiting, diarrhoea, upper abdominal pain and other mild gastrointestinal side effects.

Nervous system disorders

Headache, dizziness, sweating.

Hepatic system disorders

A transient rise in serum aminotransferase values.

DOSAGE AND ADMINISTRATION

Do not use BISOLVON CHESTY in children under 6 years of age.

Use in children aged 6 to 11 years only on the advice of a doctor, pharmacist or nurse practitioner.

BISOLVON CHESTY Oral Liquid and BISOLVON CHESTY KIDS Oral Liquid

Adults & Children over 12 years: 10 mL (8 mg) three times a day. May be increased to 20 mL (16 mg) three times a day for the first seven days.

Children 6 - 11 years: 10 mL (8 mg) three times a day.

BISOLVON CHESTY FORTE Oral Liquid

Adults & Children over 12 years: 5 mL (8 mg) three times a day. May be increased to 10 mL (16 mg) three times a day for the first seven days.

Children 6 - 11 years: 5 mL (8 mg) three times a day.

The oral liquids are alcohol-free and sugar-free and therefore suitable for diabetics.

BISOLVON CHESTY Tablets

Adults & Children over 12 years: One tablet (8 mg) three times a day. May be increased to two tablets (16 mg) three times a day for the first seven days.

Children 6 - 11 years: One tablet (8 mg) three times a day.

BISOLVON CHESTY SOLUBLE Tablets

Adults and children over 12 years: One tablet (8 mg) three times a day. May be increased to two tablets (16 mg) three times a day for the first seven days.

Put tablet(s) in a mug or glass with either hot or cold water. Stir until dissolved and drink immediately.

BISOLVON CHESTY SOLUBLE Tablets are not recommended for children under 12 years of age.

For children between 6 to 11 years of age, use BISOLVON CHESTY Oral Liquid, BISOLVON CHESTY FORTE Oral Liquid or BISOLVON CHESTY Tablets.

When infection is present, specific treatment with antibiotics could be indicated in addition to BISOLVON CHESTY therapy.

Medical advice should be sought if symptoms do not improve rapidly.

OVERDOSAGE

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

In case of overdose, immediately call the Poisons Information Centre (telephone 13 11 26).

PRESENTATION

BISOLVON CHESTY Oral Liquid is a clear to almost clear and colourless to almost colourless solution with an aroma of chocolate and cherry, available in bottles of 250 mL. Each 5 mL contains 4 mg bromhexine hydrochloride.

BISOLVON CHESTY KIDS Oral Liquid is a clear to almost clear and colourless to almost colourless solution with a fruity aromatic odour of strawberry, available in bottles of 200 mL. Each 5 mL contains 4 mg bromhexine hydrochloride.

BISOLVON CHESTY FORTE Oral Liquid is a clear to almost clear and colourless to almost colourless solution with an aroma of chocolate and cherry, available in bottles of 200 mL and 250 mL. Each 5 mL contains 8 mg bromhexine hydrochloride.

BISOLVON CHESTY Tablets are round, white bevel-edged tablets. One side is scored and impressed with '51B' on both sides of the score. The other side is impressed with the company logo. BISOLVON CHESTY Tablets are available in blister packs of 10 (sample), 20, 30, 50 and 100 tablets. Each tablet contains 8 mg of bromhexine hydrochloride.

BISOLVON CHESTY SOLUBLE Tablets are square, cushion-shaped, shallowly convex, beige-yellow tablets with rounded edges and orange dots. BISOLVON CHESTY SOLUBLE Tablets are available in blister packs of 8 (sample), 16, 24, 32 and 48 tablets. Each tablet contains 8 mg of bromhexine hydrochloride.

Storage conditions

BISOLVON CHESTY Oral Liquids should be stored below 25°C.

BISOLVON CHESTY Tablets should be stored below 25°C.

BISOLVON CHESTY SOLUBLE Tablets should be stored below 30°C.

NAME AND ADDRESS OF SPONSOR

BOEHRINGER INGELHEIM PTY LIMITED
ABN 52 000 452 308
78 Waterloo Road
North Ryde NSW 2113

POISONS SCHEDULE

Schedule 2 –Pharmacy Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS:

BISOLVON CHESTY Oral Liquid	AUST R 133244	27/11/06
BISOLVON CHESTY KIDS Oral Liquid	AUST R 182576	28/04/11
BISOLVON CHESTY FORTE Oral Liquid	AUST R 133204	23/11/06
BISOLVON CHESTY Tablets	AUST R 125375	25/01/06
BISOLVON CHESTY SOLUBLE Tablets	AUST R 158944	29/01/09

DATE OF MOST RECENT AMENDMENT

Text approved by Therapeutic Goods Administration (TGA) on 17 APR 2012