BISOLVON® Solution

Composition
1 ml solution contain
2 mg N-cyclohexyl-N-methyl-(2-amino-3,5-dibromobenzyl)amine hydrochloride
(= bromhexine hydrochloride)

Excipients
Tartaric acid, methyl parahydroxybenzoate, water purified.

Product Description
Clear, colourless solution

Indications

BISOLVON® acts as a mucolytic to facilitate productive cough.

Dosage and Administration
Solution drops 10mg/5ml (60 drops = 4 ml)

Children 5 – 10 years : 3 x 2 ml daily
Children 2 - 5 years : 2 x 2 ml daily

General
The solution is sugar-free and therefore suitable for diabetics and small children.
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 excipients of the formulations.

Special Warnings and Precautions
There have been very few reports of severe skin reactions such as erythema multiforme, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) and acute generalised exanthematous pustulosis (AGEP) associated with the administration of expectorants such as bromhexine hydrochloride. Mostly these could be explained by the severity of the patient's underlying disease or concomitant medication. In addition during the early phase of a Stevens-Johnson syndrome or TEN a patient may first experience non-specific influenza-like prodomes like e.g. fever, aching body, rhinitis, cough and sore throat. Misled by these non-specific influenza-like prodomes 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 hydrochloride discontinued as a precaution.

BISOLVON® solution for oral use 10mg/5ml contain 5mg of the excipient methyl-parahydroxybenzoate in each 5ml of oral solution, which may cause allergic reactions (possibly delayed).

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.
Pre-clinical studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section Toxicology).
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 pharmacodynamics/toxicological data in pre-clinical studies have shown excretion of bromhexine 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 (see section Toxicology).

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
The following CIOMS frequency rating is used, when applicable:
Very common ≥ 10%; Common ≥ 1 and < 10%; Uncommon ≥ 0.1 and <1%;
Rare ≥ 0.01 and < 0.1%; Very rare < 0.01%; Not known (cannot be estimated from available data).

Immune system disorders
Rare: hypersensitivity
Not known: anaphylactic reactions including anaphylactic shock

Respiratory, thoracic and mediastinal disorders
Not known: Bronchospasm

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

Skin and subcutaneous tissue disorders
Rare: rash
Not known: Severe cutaneous adverse reactions (including erythema multiforme, stevens-johnson syndrome/toxic epidermal necrolysis and acute generalized exanthematous pustulosis), angioedema, urticaria, pruritus.

Reporting of suspected adverse reactions
Report immediately if you experience any adverse reaction or undesirable condition during and after using the medicinal product to farmakovigilans@kalventis.com.

Overdose
Signs and Symptoms
No specific overdose symptoms have been reported in human.

Management
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).

Pharmacodynamics
Drug/ drug interactions in Pharmacodynamics and Pharmacokinetics
Following the administration of bromhexine antibiotic concentrations (amoxicillin, erythromycin, oxytetracycline) in the sputum and bronchopulmonary secretions are increased.

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.

Pharmacokinetics
Absorption
Bromhexine is rapidly and completely absorbed from the gastrointestinal tract.
After oral administration solid and liquid formulations show similar bioavailability.
The absolute bioavailability of bromhexine hydrochloride was about 22.2 ± 8.5 % and 26.8 ± 13.1 % for BISOLVON® tablets and solution, respectively.
The first pass metabolism amounts to about 75-80%.
Concomitant food leads to an increase of bromhexine plasma concentrations.

Distribution
After intravenous administrations 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 oral administration of 32 mg and 64 mg bromhexine. Lung-tissue concentrations two hours post dose were 1.5 - 3.2 times higher in bronchiolo-bronchial tissues and between 2.4 and 5.9 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 intravenous (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 administration of single oral doses between 8 and 32 mg, the terminal elimination half-life ranged between 6.6 and 31.4 hours. 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).

Linearity/Non-Linearity
Bromhexine shows dose proportional pharmacokinetics in the range of 8-32 mg following oral administration.

Special populations
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.

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

Nonclinical Safety Data
Single Dose Toxicity

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.
A single intraarticular injection of 4 mg bromhexine was well tolerated in rats and dogs. The lesions after intramuscular injection in rabbits compared well with those after physiological saline solution. Bromhexine hydrochloride was hemolytic in vitro.

Repeat Dose Toxicity
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 vacuolic 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.

Reproductive and Developmental Toxicity
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.

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

Carcinogenicity
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
Solution (drops) 2 mg/ml Bottle of 50 ml Reg. No. DTL1721206735A1

Store below 30°C, in a well-closed container.
Store in a safe place, out of the reach of children.

P No. 1
Awas! Obat Keras
Bacalah aturan memakainya

Manufactured by:
PT. Menarini Indria Laboratories
Bekasi, Indonesia

For:
PT. Kalventis Sinergi Farma
Jakarta, Indonesia

Under license from:
Opella Healthcare International SAS, France

HALAL INDONESIA
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Opella.

BISOLVON® Larutan

BISOLVON® Larutan mengandung bromheksin hidroklorida yang bekerja sebagai mukolitik untuk meredakan batuk berdahak.

Sediaan BISOLVON®	Kekuatan	Deskripsi Produk
Larutan 	2 mg/ml	Larutan bening dan tidak berwarna

Zat tambahan:
Tartaric acid, methyl parahydroxybenzoate, purified water.

Dosis dan Cara Pemberian BISOLVON® Larutan

Sediaan	Usia	Dosis per hari
Larutan 2 mg/ml*	Anak 5-10 tahun	3 x 2 ml
	Anak 2-5 tahun	2 x 2 ml

*larutan yang digunakan bebas gula sehingga cocok untuk penderita diabetes dan anak-anak

Cara Kerja BISOLVON® Larutan

Bromheksin hidroklorida yang terkandung dalam **BISOLVON® Larutan** dapat mengurangi kekentalan dahak, melancarkan dan memudahkan proses pengeluaran dahak.

Jangan Gunakan **BISOLVON® Larutan** jika alergi/hipersensitif terhadap bromheksin hidroklorida atau komponen lain dalam formula.

Perhatikan keadaan berikut pada penggunaan **BISOLVON® Larutan**

- Segera berkonsultasi ke dokter apabila gejala batuk tidak membaik atau semakin memburuk.
- Hentikan penggunaan obat ini dan hubungi dokter apabila muncul luka baru di kulit atau selaput lendir (misalnya pada mulut, hidung dan tenggorokan).
- Eksipien metilparahidroksibenzoat dapat menyebabkan reaksi alergi tipe lambat.
- Tidak ada interaksi klinis dengan obat lain.

Penggunaan BISOLVON® Larutan pada Ibu Hamil dan Menyusui

Penggunaan **BISOLVON® Larutan** dalam kehamilan dan menyusui sebaiknya dihindari, kecuali atas petunjuk dari dokter.

Tidak ada studi mengenai efek penggunaan **BISOLVON® Larutan** terhadap kemampuan mengemudi dan mengoperasikan mesin yang pernah dilakukan.

BISOLVON® Larutan dapat mempunyai efek samping yang jarang terjadi, berupa reaksi alergi, ruam, mual, muntah, diare, serta nyeri perut bagian atas. Selain itu terdapat kemungkinan efek samping (belum pernah dilaporkan/diketahui) berupa reaksi alergi berat (anafilaksis), kesulitan bernapas (bronkospasme) pembengkakan (angioedema), biduran, gatal-gatal (pruritus), dan reaksi alergi kulit berat (*erythema multiforme, Stevens-Johnson syndrome/toxic epidermal necrolysis dan acute generalized exanthematous pustulosis*). Jika mengalami gejala-gejala tersebut, segera berkonsultasi ke dokter.

Pelaporan efek samping

Segera laporkan apabila Anda mengalami keluhan efek samping atau kondisi tidak nyaman selama dan setelah penggunaan obat kepada farmakovigilans@kalventis.com. Anda dapat membantu memberikan informasi terkait keamanan obat ini.

Tidak terdapat gejala spesifik overdosis yang dilaporkan terjadi pada manusia. Gejala yang muncul sesuai dengan gejala efek samping **BISOLVON® Larutan**. Jika mengalami gejala-gejala tersebut, segera berkonsultasi ke dokter.

Kemasan & Cara Penyimpanan BISOLVON® Larutan

Larutan 2mg/ml Dus, botol 50 ml Reg. No. xxx

Simpan di bawah suhu 30° C, pada tempat tertutup rapat.

Simpan di tempat yang aman, jauh dari jangkauan anak-anak.

Diproduksi oleh:
PT Menarini Indria Laboratories
Bekasi, Indonesia

Untuk:
PT Kalventis Sinergi Farma,
Jakarta, Indonesia

Di bawah lisensi dari:
Opella Healthcare International SAS, France

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Opella.