



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

在使用bromhexine後，抗生素(如amoxicillin, erythromycin, oxytetracycline)在痰及肺部支氣管分泌物濃度會增加。

Bromhexine 呈現與劑量成比例之藥物動力學，可迅速且完全地從腸胃吸收。服用有放射性標記之 Bromhexine 後，約 $97.4 \pm 1.9\%$ 有放射性劑量由尿排出，少於 1% 以原型化合物排出。Bromhexine 藥物清除率高（清除率 $843-1073 \text{ ml/min}$ ），有高的個體內及個體間差異（變異係數 $>30\%$ ）。
口服固體製劑與液體製劑後之生體可用率相似。BISOLVON 錠劑與液劑之絕對生體可用率分別為 $22.5 \pm 8.5\%$ 及 $26.8 \pm 13.1\%$ 。

絲, 64公絲)後, 在肺部組織的分佈(支氣管與肺泡組織)。bromhexine在組織的濃度, 在給予劑量2小時

吸收後。

原型的bromhexine 95%與血漿蛋白質結合(非限定性結合)。

Bromhexine幾乎臨床被代謝成多種氫氧化代謝物及dibromanthranilic acid。所有代謝物及bromhexine本身大部分可經結合成N-尿苷酸化合物及O-尿苷酸化合物。少量bromhexine大多經由酵素cytochrome P450 3A4代謝成dibromanthranilic acid, 其代謝模式未曾因sulphonamide, oxytetracycline或erythromycin而改變, 因此與CYP450 2C9或3A4相關交互作用不可能發生。

Bromhexine血漿濃度呈現多重指數(multiexponential)下降, 由相關的半衰期預測多次劑量藥動學約1小時, 所以多次劑量後, 未見藥物蓄積(藥物蓄積因子為1.05)。

Bromhexine尚未有年老或腎或肝功能不全患者之藥動學資料, 但長期臨床使用經驗, bromhexine對這類人群未有藥物安全之影響。

與食物同服, 會增加bromhexine血漿濃度。

與ampicillin, oxytetracycline同時服用, bromhexine的藥動學不受影響。依據過去經驗的比較, bromhexine與erythromycin也不會發生相關之交互作用。

目前並未有與口服抗凝血劑及digoxin之交互作用的研究報告, 由於藥物已長期上市使用, 至今尚未有相關交互作用報告, 顯示應與這類藥物並無交互作用之可能性。

祛痰

醫師藥師藥劑生指示藥品。
溶液8公絲/4公撮(=60滴)

吸入(使用噴霧裝置)
 吸入前建議將藥液溫熱至體溫，對於患有支氣管氣喘之病人，吸入治療前需先實行其通常之支氣管解痙治療。
 成人及6歲以上兒童：每次4公撮，每日兩次。
 2-6歲兒童：每次2-4公撮，每日兩次。
 2歲以下兒童：每次2公撮，每日兩次。
 溶液需以生理食鹽水以1:1的比例稀釋，為避免混合液體發生沈澱，混合後請立刻使用。吸入與口服合併治療可加強效果，尤其適用於治療初期需迅速達到完全效果之病人。

正以bromhexine治療的病人，痰量排除會增加。

衛署藥製字第 028613 G-0314 號

已知對bromhexine或製劑中其他成分過敏者。
如有因罕見遺傳疾病不適合使用本品中之賦形劑時
(請見注意事項)，應避免使用本品。

有極少數的報告指出，發生如史蒂文生-強生氏症候群(Stevens Johnson syndrome)及毒性表皮溶解壞疽症(Lyell's syndrome)等的嚴重皮膚病表現，與使用化痰藥物如bromhexine有時間關聯性，但這些案例通常與潛在疾病的嚴重度或併用藥物有關。

如果皮膚或黏膜出現新的傷口，須立刻尋求醫療諮詢並停藥。

在臨床上未有與其他藥物有不利之交互作用的報告。

至今之臨床前研究及臨床上使用經驗，並未有對懷孕有不良影響之證據。但仍須注意懷孕時使用藥品之應注意事項，尤其是懷孕的前3個月，更應謹慎觀察。本藥預期會分泌於乳汁，所以哺乳期間應避免使用。

BISOLVON 的耐受性良好。曾有腹瀉、噁心、嘔吐及其他輕微胃腸副作用報告，也曾發生過敏反應包括皮膚紅疹、蕁麻疹、支氣管痙攣、血管性水腫及過敏性反應(anaphylaxis)。

至今尚未有過量症狀的報告。發生時，需給予症狀治療。

Bromhexine 的毒性指數極低，口服的 LD50 在大鼠大於 2 g/kg，兔大於 4 g/kg，狗大於 10 g/kg，新生大鼠則大於 1 g/kg。小鼠大鼠腹腔注射之 LD50 大於 2 g/kg。糖漿劑在小鼠與大鼠的 LD50 大於 10 ml/kg。在這些急性劑量中並未有臨床徵狀被發現。

在一個超過 500 天之重複劑量毒性研究中，老鼠的耐受劑量為 200 mg/kg 不造成任何不良副作用的劑量，no observed adverse effect level "NOAEL"，而劑量達 2000 mg/kg 時死亡率增高。存活的小白鼠少數發現有可逆性肝重量及血清中膽固醇增加。大鼠對 25 mg/kg 的劑量有超過 26 個週增加耐受力，而劑量達 500 mg/kg 時，大鼠會發生全身性皮癢與死亡。且因胃空泡改變而使肝小葉中心細胞增大。由另一兩年的研究中證實大鼠劑量 100 mg/kg 時，其耐受性良好，達 400 mg/kg 時，少數偶而會發生全身性皮癢，狗可以忍受口服 100 mg/kg 的劑量超過兩年 (NOAEL 不造成任何不良副作用的劑量)。

大鼠對於 BISOLOLON 糖漿 (0.8 mg/ml) 在劑量達 20 ml/kg 時，其耐受性良好。但曾有一例發生可逆性肝小葉中心細胞純脂肪改變。給予狗 8 公絲局部注射或全身性肌肉注射 6 週，其耐受性良好。

Bromhexine 在妊娠階段 II (Segment II) 中，口服劑量達 300 mg/kg (兔) 及 200 mg/kg (兔子)，並未發生胚胎毒性及嗜胎。在階段 I (Segment I) 劑量達 300 mg/kg，其生育力也未受損。在出生前後及出生後發育階段 III 中，也未造成任何不良副作用之劑量為 25 mg/kg。

對兔及狗，動脈注射 bromhexine 單劑量 6 公絲，其耐受性良好。兔子肌肉注射造成之傷口與注射生理食鹽水後的傷口相近。體外試驗經 1 公撮注射液與 0.1 公撮入血混合時，有溶血反應。

由兩個研究 (Ames 及 Micronucleus tests) 可顯示 bromhexine 無造成突變的潛在性。

由一個兩年的研究顯示給予大鼠劑量 400 mg/kg，狗達 100 mg/kg 時，未發生致癌性。

溶液(2公絲/公撮)：60-4000公撮瓶裝。
每瓶附有刻度為1至6公撮的量杯一個。

請存放於15-30°C。
請存放於兒童伸手不及處！

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20050805

Bisolvon® Solution 2 mg/ml
(bromhexine hydrochloride)

Composition
1 ml solution for oral and inhalation use contains 2 mg N-cyclohexyl-N-methyl-(2-amino-3,5-dibromobenzyl)amine hydrochloride (= bromhexine hydrochloride)

Pharmacological properties
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
Bromhexine shows dose proportional pharmacokinetics. It is rapidly and completely absorbed from the gastrointestinal tract. 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 is a high clearance drug (CL = 843-1073 mL/min) resulting in high inter- and intraindividual variability (CV > 30 %). After oral administration solid and liquid formulations show similar bioavailability. The absolute bioavailability of bromhexine hydrochloride was about 22.2 ± 8.5 % up to 26.8 ± 13.1 % for BISOLVON tablets and solution, respectively. Intravenous administrations showed a mean volume of distribution (V_d) of up to 1209 ± 206 L. The distribution in lung tissue (bronchial and parenchymal) was investigated after i.v. (8 mg, 16 mg) and oral (32 mg, 64 mg) administration. Bromhexine tissue concentrations two hours post dose were three to four times higher in lung tissue compared to plasma. Parenchymal tissue seemed to show a higher enrichment of bromhexine than bronchial tissue especially after oral absorption. Unchanged bromhexine is bound to plasma proteins by 95 % (non-restrictive binding). 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. A minor part of bromhexine is metabolised to dibromanthranilic acid most probably via cytochrome P450 3A4. There are no substantial hints for a change of the metabolic pattern by a sulphonamide, oxytetracyclin or erythromycin. Thus relevant interactions with CYP 450 2C9 or 3A4 substrates are unlikely. Bromhexine plasma concentrations showed a multiexponential decline. The relevant half-life to predict the multiple dose pharmacokinetics is about 1 hour, thus no accumulation was seen after multiple dosing (accumulation factor 1.05). 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. 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. Interaction studies with oral anticoagulants or digoxin were not performed. The lack of any relevant interaction reports during the long term marketing of the drug suggests no substantial interaction potential with these drugs.

Indications
Expectorant

Dosage and administration
The product should be used by physician or pharmacist instruction.
Solution 8 mg/4 ml (= 60 drops)
Oral
Adults and children over 14 years: 4 - 8 ml 3 times daily
Children 6 - 14 years: 4 ml 3 times daily
Children under 6 years: 2 ml 3 times daily
At commencement of treatment, it may be necessary to increase the total daily dose up to 48 mg in adults.
Inhalation (with aerosol apparatus)
It is generally recommended to warm inhalant solutions to body temperature before inhalation. Patients with bronchial asthma may be advised to commencing inhalation after they have taken their regular broncho spasmolytic therapy.
Adults and children over 6 years: 4 ml 2 times daily
Children 2 - 6 years: 2 - 4 ml 2 times daily
Children under 2 years: 2 ml 2 times daily
The solution may be diluted 1:1 with physiological saline solution. In order to avoid precipitation the solution should be inhaled immediately after mixing. The combined administration of inhalation and oral application intensifies the effect and is especially suited for the commencement of treatment in cases where the full effect is to be reached quickly.

Note
Patients being treated with BISOLVON should be notified of an expected increase in the flow of secretions.

Contraindications
BISOLVON should not be used in patients known to be hypersensitive to bromhexine or other components of the formulations.

In case of rare hereditary conditions that may be incompatible with an excipient of the product (please refer to "Special warnings and precautions") the use of the product is contraindicated.

Special warnings and precautions
There have been very rare reports of severe skin lesions such as Stevens Johnson syndrome and Lyell's syndrome in temporal association with the administration of mucolytic substances such as bromhexine. Mostly these could be explained by the severity of the underlying disease or concomitant medication. If new skin or mucosal lesions occur, medical advice should be sought immediately and treatment with bromhexine discontinued as a precaution.

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

Pregnancy and Lactation
Available preclinical studies as well as clinical experience to date have shown no evidence of ill-effects during pregnancy. Nonetheless, the usual precautions regarding the use of drugs during pregnancy, especially during the first trimester, should be observed. The drug is expected to enter breast milk and thus should be avoided during lactation.

Side Effects
BISOLVON is generally well tolerated. Diarrhoea, nausea, vomiting and other mild gastro-intestinal side effects have been reported. Allergic reactions including, skin rashes, urticaria, bronchospasm, angio-oedema, and anaphylaxis have also been reported.

Overdose
No symptoms of overdose have been reported in man to date. If they occur, symptomatic treatment should be provided.

Toxicology
Acutely, bromhexine hydrochloride has a very low index of toxicity: oral LD₅₀ 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. LD₅₀ in rats was 2 g/kg. The LD₅₀ values for the syrup formulation were > 10 ml/kg in mice and rats. No clinical signs were observed at these acute doses. In repeated oral dose toxicity studies over 5 weeks, mice tolerated 200 mg/kg ("no observed adverse effect level" NOAEL). At 2000 mg/kg, mortality was high. The few surviving mice 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 rats. 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, but there was a reversible centrilobular simple fatty change of liver. An i.m. dose of 8 mg injectable solution was locally and systemically well tolerated in dogs treated for 6 weeks. Bromhexine was neither embryotoxic nor teratogenic in segment II at oral doses up to 300 mg/kg (rat) and 200 mg/kg (rabbit). Fertility was not impaired in segment I at doses up to 300 mg/kg. The "NOAEL" during peri- and postnatal development in segment III was 25 mg/kg. A single i.a. injection of 4 mg bromhexine was well tolerated in rabbits and dogs. The lesions after i.m. injection in rabbits compared well with those after physiological saline solution. In vitro, 1 ml injectable solution showed a haemolytic action when mixed with 0.1 ml human blood. In two studies (Ames and micronucleus tests) bromhexine had no mutagenic potential. Bromhexine 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 for oral and inhalation use 8 mg/4 ml: 60-4000 ml bottle pack.

Store at 15-30°C.
Store in a safe place out of the reach of children!

Manufactured by
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