Bisolvon® Solution 2mg/ml

SANOFI

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)
Excipients
tartaric acid, methyl paraben, purified water

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
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 i.v. (8 mg, 16 mg) and oral (32 mg, 64 mg) administration. After oral administration, lung-tissue concentrations two hours post dose 1.5 - 4.5 times higher in bronchiolo-bronchial tissues and between 2.4 and 5.9 times higher in pulmonary parenchyma compared to plasma concentrations. After i.v. administration, 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, oxytetracyclin or erythromycin. Thus relevant interactions with CYP 450 2C9 or 3A4 substrates are unlikely.
Elimination
Bromhexine is a high extraction ratio drug after i.v. administration in the range of the hepatic blood flow, 843-1073 mL/min resulting in high inter- and intraindividual 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. 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 8-32 mg following oral administration and 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. 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
Expectorant

Dosage and administration
The product should be used by physician prescription.
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.
In acute respiratory indications, medical advice should be sought if symptoms do not improve or worsen during course of therapy.

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 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 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 discontinued as a precaution.
BISOLVON solution for oral use and inhalation 2mg/ml contain the excipient methyl-parahydroxybenzoate, 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.
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, 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 and abdominal pain upper.

Overdose
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 at recommended doses and may need symptomatic treatment.

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 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. 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.
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 ~~in~~ (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
Solution for oral and inhalation use 2mg/ml: 4-4000 ml amber glass bottle pack.

Store below 30° C.
Store in a safe place out of the reach of children!

Manufactured by
PT. Boehringer Ingelheim Indonesia
Jl. Lawang Gintung No. 89
Bogor, Indonesia

20120106

氣舒痰®液2毫克/毫升 (印尼廠)
Bisolvon® Solution 2 mg/ml

SANOFI

衛署藥輸字第025729號

成分
每毫升含.....2毫克
N-cyclohexyl-N-methyl-(2-amino-3,5-dibromobenzyl)amine hydrochloride (= bromhexine hydrochloride)
賦形劑
tartaric acid, methyl paraben, purified water

藥理性質
Bromhexine為生藥主成分vasicine之合成衍生物。臨床前試驗顯示可增加支氣管分泌物漿液的比例，bromhexine可減少痰液黏稠度及活化呼吸道纖毛上皮細胞(即增加黏液纖毛的清除力)而加強痰液的清除。
臨床試驗中更顯示bromhexine在支氣管部位具有溶解痰液及刺激漿液分泌作用，進而促進排痰並緩解咳嗽。
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。

藥物動力學
吸收
Bromhexine可迅速且完全地被腸胃道吸收。
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±8.5%及26.8±13.1%。
首渡代謝(first pass metabolism)的量約為75-80%。
與食物同服，會增加bromhexine血漿濃度。
分布
靜脈注射後，bromhexine會迅速且廣泛地分佈至全身，平均分佈體積(Vss)可達1209±206L (19L/Kg)。曾研究靜脈注射(8毫克,16毫克)及口服(32毫克, 64毫克)後，在肺部組織的分佈(支氣管與肺實質組織)。
經口服投予，投藥2小時後，肺部組織的濃度比細支氣管-支氣管組織中的濃度高出1.5-4.5倍，而肺實質組織中的濃度則比血中濃度高出2.4至5.9倍。經靜脈注射投予，投藥2小時後的肺部組織濃度比細支氣管-支氣管組織中的濃度高出4.2-4.3倍，而肺實質組織中的濃度則比血中濃度高出3.0至4.3倍。
原型的bromhexine 95%與血漿蛋白質結合(非限定結合)。
代謝
Bromhexine幾乎完全被代謝成多種氫氧化代謝物及dibromanthranilicacid。所有代謝物及bromhexine本身大部分可經結合形成N-尿苷酸化合物及O-尿苷酸化合物。其代謝模式未曾因sulphonamide, oxytetracyclin或erythromycin而改變，因此與CYP450 2C9或3A4相關的交互作用不可能發生。
排除
Bromhexine是具高度抽提率(high extraction ratio)的藥物，靜脈注射後在肝臟血流範圍843-1073 mL/min下，有高的個體內及個體間差異(變異係數>30%)。服用有放射標記之bromhexine後，約97.4±1.9%有放射性劑量由尿排出，少於1%以原型化合物排出。Bromhexine血漿濃度呈現多重指數(multiexponential)下降。給與單次口服劑量8-32 mg後，末相之排除半衰期(terminal elimination half life)介於6.6至31.4小時。給與靜脈注射15-100 mg，末相之排除半衰期介於7.1至15.4小時。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，未見顯著藥物蓄積(藥物蓄積因子為1.1)。
一般
Bromhexine 在劑量範圍為8-32 mg口服給予與15-100 mg靜脈注射，呈現與劑量成比例之藥物動力學。
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對這族群尚未有藥物安全之影響。
迄今亦尚無本藥與口服抗凝血劑或digoxin的交互作用研究。
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也不曾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。

適應症
祛痰

用法用量
本藥須由醫師處方使用。
溶液8毫克/4毫升 (= 60滴)
口服
成人及14歲以上兒童：每次4 - 8毫升，每日三次。
6 - 14歲兒童：每次4毫升，每日三次。
6歲以下兒童：每次2毫升，每日三次。
開始治療時，成人每日總劑量可能需要增至48毫克。
吸入(使用噴霧裝置)
吸入前建議將溶液溫熱至體溫，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毫升，每日兩次。
2 – 6歲兒童：每次2 – 4毫升，每日兩次。
2歲以下兒童：每次2毫升，每日兩次。
溶液需以生理食鹽水以1:1的比例稀釋，為了避免混合溶液發生沈澱，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。

注意
正以bromhexine治療的病人，痰量排除會增加。
用於急性呼吸道適應症時，若症狀在治療期間未能改善或惡化，應儘速尋求醫療諮詢。

禁忌
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。

注意事項
有極少數的報告指出，發生如史帝文生-強生氏症候群 (Stevens Johnson syndrome)及毒性表皮溶解壞死症(toxic epidermal necrolysis，簡稱TEN)等的嚴重皮膚損害，與使用祛痰劑如bromhexine有時間關聯性，但這些案例通常與患者的潛在疾病及/或併用藥物有關。此外，在Stevens-Johnson症候群或TEN的早期階段，患者可能先出現類似流感的非專一性前兆症狀（如發燒、身體感覺疼痛、鼻炎、咳嗽及喉嚨痛）。若受這些類似流感之非專一性前兆症狀的誤導，一開始可能會使用咳嗽及感冒藥來作症狀治療。因此，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。
Bisolvon 供口服與吸入用溶液(2mg/ml)含有可能引起過敏反應(可能為延遲性過敏反應)的賦形劑methyl-parahydroxybenzoate。
交互作用
在臨床上未有與其他藥物有不利之交互作用的報告。

生育力、懷孕及哺乳
懷孕
於懷孕婦女使用bromhexine的相關資料仍極有限。
在生殖毒性方面，動物研究未顯示bromhexine具有直接或間接的有害作用。
但為了謹慎起見，最好避免於懷孕期間使用BISOLVON。
哺乳
目前還不清楚bromhexine/代謝物是否會分泌至人類乳汁。
現有的動物藥效學/毒理學資料顯示，bromhexine/代謝物會分泌至乳汁。
無法排除此藥物對哺乳嬰兒可能具有危險性。
不可於餵哺母乳期間使用BISOLVON。
生育力
尚未就BISOLVON對人類生育力的影響進行研究。
根據現有的臨床前經驗，並無跡象顯示bromhexine對生育力可能具有影響。

對駕駛與機器操作能力的影響
尚未就BISOLVON對駕駛與機器操作能力的影響進行研究。

副作用
免疫系統障礙、皮膚及皮下組織障礙、呼吸道、胸及縱膈障礙
過敏性反應(anaphylactic reaction)包括過敏性休克、血管性水腫、支氣管痙攣、皮疹、蕁麻疹、發癢及其他的過敏反應過度(hypersentivity)。
胃腸障礙
噁心、嘔吐、腹瀉及上腹部疼痛。

過量
至今尚未有用於人類之特定的過量症狀被報告。
根據意外過量(accidental overdose)及/或藥物失誤報告所觀察到的症狀，與在BISOLVON推薦劑量下已知的副作用一致，這些症狀有可能需要症狀治療。

毒物學
Bromhexine hydrochloride的急性毒性低，口服的LD50在大鼠大於5 g/kg，兔子大於4 g/kg，狗大於10 g/kg，新生大鼠則大於1 g/kg。而大鼠腹膜內注射之LD50大於2 g/kg。糖漿劑在小鼠與大鼠的LD50大於10 mg/kg。在這些劑量中並未有特定的臨床毒性徵狀被發現。
在一超過5週之口服重複劑量毒性研究中，老鼠對bromhexine hydrochloride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時死亡率高。存活的少數動物被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或100週耐受力，而劑量達500 mg/kg時，大鼠會發生全身性痙攣與死亡。且因為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劑量達100 mg/kg時，其耐受性良好，而達400 mg/kg時，少數動物偶而會發生全身性痙攣。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BISOLVON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的單純性脂肪改變。給予狗8毫克肌肉注射6週，無注射部位之局部過敏或全身毒性。對兔子及狗，動脈注射bromhexine單劑量4毫克，其耐受性佳。兔子肌肉注射後造成之傷口與注射生理食鹽水後的傷口相近。體外試驗顯示1毫升注射液與0.1毫升人血混合時，有溶血反應。
Bromhexine hydrochloride在妊娠階段II (Segment II)中，口服劑量達300 mg/kg (大鼠)及200 mg/kg (兔子)，並未發生胚胎毒性及畸胎。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，不造成任何不良副作用之劑量為25 mg/kg。
Bromhexine hydrochloride在細菌突變測定(bacterial mutation assay)及小鼠骨髓微細胞核試驗(mouse bone marrow micronucleus test)顯示無遺傳突變的潛在性。
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，Bromhexine hydrochloride未發生致癌性。

包裝
溶液(供口服或吸入用，2毫克/毫升)：4 – 4000毫升棕色玻璃瓶裝。

請存放於30°C以下。
請存放於兒童伸手不及處！

製造廠/廠址
PT. Boehringer Ingelheim Indonesia
Jl. Lawang Gintung No. 89
Bogor, Indonesia

藥商/地址
賽諾菲股份有限公司
台北市信義區松仁路3號7樓

20120106