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

Boehringer Ingelheim

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爲生藥主成分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
Bromhexine呈現與劑量成比例之藥物動力學，可迅速且完全地被腸胃道吸收。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藥物清除率高(清除率843-1073mL/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爲22.5±8.5%及26.8±13.1%。
靜脈注射後，平均分佈體積(Vss)可達1209±206L。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(支氣管與肺泡組織)。bromhexine在組織的濃度，在給予劑量2小時後，肺部組織高於血漿中三至四倍，而肺泡組織bromhexine濃度似乎比支氣管中更高，尤其是口服吸收後。
原型的bromhexine 95%與血漿蛋白質結合(非限定結合)。
Bromhexine幾乎完全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形成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, 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。
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(藥物蓄積因子爲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對這族群尚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，爲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。

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(Lyell's syndrome)等的嚴重皮膚損害，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。

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。

懷孕及哺乳
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。

副作用
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、蕁痲疹、支氣管痙攣、血管性水腫及過敏性反應(anaphylaxis)。

過量
至今尚未有過量症狀的報告。發生時，需給予症狀治療。

毒物學
Bromhexine的毒性指數極低，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。在這些急性劑量中並未有臨床徵狀被發現。
在一超過5週之重複劑量毒性研究中，老鼠的耐受劑量爲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。且因爲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達100 mg/kg時，其耐受性良好，而達400 mg/kg時，少數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 (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爲25 mg/kg。
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。
由兩個研究(Ames及Micronucleus tests)可顯示bromhexine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，未發生致癌性。

包裝
溶液(2毫克/毫升)：4-4000毫升瓶裝。

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
國外許可證持有者
Boehringer Ingelheim International GmbH
Ingelheim am Rhein, Germany

藥商/地址
台灣百靈佳殷格翰股份有限公司
台北市民生東路三段49/51號12樓

20050805

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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
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 (Vss) 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 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.

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 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 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 micro-nucleus 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 2 mg/ml: 4–4000 ml 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
for
Boehringer Ingelheim International GmbH
Ingelheim am Rhein, Germany

20050805

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