定喘樂® 單一劑量吸入液 0.5毫克/2毫升
Atrovent® Nebuliser Solution 0.5 mg/2 ml in Unit Dose Vials

Boehringer Ingelheim

衛署藥輸字第018863號

成分
每單一劑量吸入液(2毫升)含 (8r)-3α-hydroxy-8-isopropyl-1αH,5αH-tropanium bromide (±)-tropate monohydrate (= ipratropium bromide) 522 mcg
相當於ipratropium bromide anhydrous 500 mcg
賦形劑
sodium chloride, hydrochloric acid, purified water

藥理性質
藥物類別：抗膽鹼性藥物。
ATC代碼：R03BB01
ATROVENT (ipratropium bromide)為四級銨鹽化合物，具有抗乙醯膽鹼的性質(anticholinergic)，能消除副交感神經作用(parasympatholytic)。非臨床的研究顯示ATROVENT能拮抗迷走神經所釋出之傳遞物質”乙醯膽鹼”(acetylcholine)的作用而抑制迷走神經所調節的反射作用。乙醯膽鹼能與位於支氣管平滑肌的毒蕈鹼性接受體(muscarinic receptor)作用，而增加鈣離子(Ca++)的濃度，抗膽鹼激素的藥物則可抑阻此現象。
鈣離子(Ca++)的釋放係由IP3 (肌醇三磷酸[inositol triphosphate])與DAG (二醯基甘油[diacylglycerol])等第二傳訊物質(second messenger)所媒介。
吸入ATROVENT(ipratropium bromide)之後產生的支氣管擴張作用，主要局限於肺部，而非全身性作用。
臨床前及臨床的研究證實
ATROVENT(ipratropium bromide)不會影響呼吸道黏膜之分泌、黏膜纖毛之清潔作用或氣體交換。
臨床試驗
針對慢性阻塞性肺疾(慢性支氣管炎及肺氣腫)併發支氣管痙攣之病人的為期85-90天的有對照組的研究，顯示本藥能在15分鐘內顯著改善肺功能，在1至2小時內可達最大效應，且療效能持續達4-6小時。
在對成人的研究中，已顯示ATROVENT之支氣管擴張作用，可治療氣喘所併發之急性支氣管痙攣。
在這些研究，ATROVENT多半與吸入性β作用劑併用。

藥物動力學
吸收
ATROVENT的療效是直接局部作用於呼吸道所產生。支氣管擴張作用之時間與全身性作用藥動學並非同時。
依藥物配方與吸入技術的不同，吸入後總劑量的10% - 30%會分布於肺中，大部分藥物會經口吞入並通過腸胃道。
分布於肺中的藥物會很快進入循環系統(數分鐘內)。
0-24小時原型化合物的累積腎臟排除量約佔靜脈注射劑量的46%，若爲口服劑量則佔1%以下，吸入劑量則約爲3至13%。根據這些數據估計，口服與吸入的ipratropium bromide，其全身總生體可用率分別爲2%與7至28%。據此考量，經口吞入的ipratropium bromide對全身性暴露量無顯著影響。
分佈
由靜脈注射後之血漿中濃度，可用來計算ipratropium分佈之動力學數據。
可觀察到ipratropium之血漿濃度會出現快速的雙相衰減(a rapid biphasic decline)，穩定狀態時的擬似分布體積(Vdss)約爲176 L(≈2.4 L/kg)。本藥與血漿蛋白的結合率很低(少於20%)。非臨床資料指出因ipratropium離子具有四級銨結構，所以ipratropium離子無法通過胎盤及腦血管障壁。
生物轉化(Biotransformation)
靜脈注射之後約60%之劑量會被代謝，主要經肝臟的氧化作用。
代謝物主要是經由水解，脫水或脫除tropic acid之 hydroxy-methyl基而形成，與毒蕈鹼接受體結合極爲微弱或無結合作用，因此這些代謝物應視爲沒有作用。
排除
末端排除半衰期約爲1.6小時，ipratropium的總清除率爲2.3 L/min，腎清除率爲0.9 L/min。
在一項排泄平衡研究中，靜脈注射給藥之後，放射標示相關藥品(包括原型化合物與所有代謝物)的累積腎臟排泄量(6天)佔72.1%，口服給藥爲9.3%，吸入給藥則爲3.2%。靜脈注射給藥之後，經糞便排泄的放射活性總量佔6.3%，口服藥物爲88.5%，吸入給藥則爲69.4%。靜脈注射給藥之後，放射標示相關藥品主要經由腎臟排泄。放射標示相關藥品(原型化合物與代謝物)的排除半衰期爲3.6小時。

適應症
慢性阻塞性支氣管炎，支氣管氣喘。

用法用量
本藥須由醫師處方使用。
劑量應調整以適合個人需要，病人爲於醫師監督下接受治療。無論是急性或維持治療，建議不要超過每日建議劑量。
若治療時不見明顯改善或病人情況變更糟時，應請教醫師，決定一個新的治療計畫。應指導病人萬一發生急性或急速惡化呼吸困難時應立即求診。以下是建議劑量：
- 維持性治療

成人(包括年長者)與12歲以上的青少年：每次1單一劑量小瓶，每天3至4次。
- 急性發作

成人(包括年長者)與12歲以上的青少年：1單一劑量小瓶，劑量可重複至病人症狀穩定。每單一劑量之間隔時間由醫師決定。
ATROVENT可與吸入性β作用劑併用。
成人與12歲以上之青少年，若一天劑量超過2 mg 的ipratropium bromide anhydrous時，應遵循醫囑使用。

使用方法
請詳細閱讀使用說明書，以確保用藥方法正確。
單一劑量吸入液僅能放入適當的噴霧裝置供吸入使用，不能口服或注射。
每1毫升的單一劑量可用生理食鹽水稀釋至2-4毫升或與BEROTEC吸入溶液併用。
定喘樂吸入液可經由市面上的噴霧裝置投與。如用有壓式氣氣時，投予本溶液流速最好是6-8公升/分鐘。
ATROVENT吸入液可同時與祛痰劑MUCOSOLVAN吸入液、BISOLVON吸入液或BEROTEC吸入液使用。
ATROVENT單一劑量吸入液不可與disodium cormoglycate吸入液加在相同的噴霧裝置內使用。

1. 準備好噴霧器，依照藥廠或醫師指示加入藥品。 (圖一)
2. 自長排中撕離一支塑膠小瓶。(圖一)
3. 扭轉小瓶頭部將小瓶打開。(圖二)
4. 擠壓塑膠小瓶，將溶液擠入噴霧器藥槽中。(圖三)
5. 用生理食鹽水稀釋至2-4毫升
6. 照指示裝置組合及使用噴霧器。
7. 使用噴霧器後，依其說明指示丟棄殘留在噴霧器藥槽中的溶液，並清洗乾淨


(圖一)

(圖二)

(圖三)

由於單一劑量吸入液不含保存劑，打開後應立即使用，每次投與均應使用新的小瓶，以免微生物污染。
部份使用過、已開過的或受損的單一劑量吸入劑應丟棄。

禁忌症
已知對阿托品及其衍生物(例如主成分ipratropium bromide)或本劑中其他成分有過敏反應者，忌用本藥。

特別注意
過敏
使用ATROVENT後，可能發生立即性過敏反應，在極少數之病例曾出現皮疹、蕁麻疹、血管性水腫、口咽部水腫、支氣管痙攣及急性過敏性反應。
逆理性支氣管痙攣
如同其他吸入性藥物，ATROVENT也可能導致逆理性支氣管痙攣，發生時可能危及生命，應立即停用ATROVENT並改用其他替代療法。
眼睛的併發症
狹角性青光眼患者(narrow-angle glaucoma)應小心使用ATROVENT。
曾有零星之報告當僅含ipratropium bromide之噴霧劑或合併有腎上腺素β$_2$興奮劑 (adrenergic β$_2$-agonist)之噴霧劑噴到眼睛時，發生眼部之併發症(如散瞳、眼球內壓增加、狹角性青光眼、眼睛疼痛)。
眼睛疼痛或不適、視力模糊、虹暈幻視(visual halos)或有色影像伴隨結膜充血的紅眼睛及角膜水腫等，可能是急性狹角性青光眼的徵兆。如出現前述症狀時，應給予縮瞳滴劑並立即尋求專家之建議。
必須指示病人正確使用ATROVENT吸入液。使用時應謹慎，避免溶液誤進眼內。應告訴病人經由口含器使用噴霧吸入液。萬一無口含器，應使用適合的面罩。對容易罹患青光眼者應特別警告他們必須保護他們的眼睛。
腎臟及泌尿系統作用
已有尿道受阻(例如前列腺肥大者[prostatic hyperplasia]或膀胱頸部阻塞者[bladder-neck obstruction])，應小心使用ATROVENT。
胃腸運動障礙
患有囊性纖維變性(cystic fibrosis)的病人，使用本藥較易出現胃腸運動障礙。

藥物交互作用
長期併用ATROVENT和其他抗乙醯膽鹼類藥物尚未經過試驗。因此不建議長期併用ATROVENT和其他抗乙醯膽鹼類藥物。
β-腎上腺素刺激劑與黃嘌呤類製劑可能增加ATROVENT之支氣管擴張效果。
曾報患窄角性青光眼的病人(請參考“特別注意”)同時使用Ipratropium bromide噴霧劑與β擬交感製劑時，可能有發生急性青光眼的危險。

生育力、懷孕與哺乳
懷孕
人類懷孕期間使用ATROVENT的安全性仍未建立。已確定或可能懷孕的病患使用ATROVENT時，需考量使用益處及其對未出生嬰兒可能造成的損害。非臨床研究顯示，由口腔或鼻內吸入高於人類建議劑量的本藥時，並未發現本藥具有胚胎毒性或致畸性。
授乳
Ipratropium bromide 尚未知是否會進入乳汁，雖然ipratropium bromide 不太可能在嬰兒體內達到具顯著作用的強度，特別是當採噴霧劑方式給藥時亦如此。然而，授乳婦女應小心使用ATROVENT。
生育力
目前ipratropium bromide尚無與生育力有關的臨床資料。
非臨床研究顯示，ipratropium bromide對生育力無不良影響(請參閱”毒物學”)。

對開車與機器操作能力的影響
目前尚未針對ipratropium bromide是否會影響開車與機器操作的能力進行研究。不過，應告知病患，他們可能於接受ATROVENT治療期間出現暈眩、眼睛調節異常、散瞳與視力模糊等不良副作用。因此，開車與機器操作時應特別謹慎。

副作用
ATROVENT的許多不良副作用均可歸因於其抗乙醯膽鹼的性質。與所有吸入性療法相同，ATROVENT亦可能出現局部刺激症狀。藥物不良反應已從臨床試驗與上市後藥物安全監測所取得的資料確認。
臨床試驗中最常發生的副作用爲頭痛、喉嚨刺激、咳嗽、口乾、腸胃道蠕動失調(包括便秘、腹瀉及嘔吐)、噁心與暈眩。

免疫系統異常
- 過敏
- 類過敏反應

神經系統異常
- 頭痛
- 暈眩

眼睛異常
- 視力模糊
- 散瞳
- 眼球內壓增加
- 青光眼
- 眼睛疼痛
- 虹視(halo vision)
- 結膜充血
- 角膜水腫
- 眼睛調節異常

心臟異常
- 心悸
- 上心室性心搏過速
- 心房顫動
- 心搏加速

呼吸、胸部與縱隔膜異常
- 喉嚨刺激
- 咳嗽
- 支氣管痙攣
- 逆理性支氣管痙攣 (bronchospasm paradoxical)
- 喉部痙攣
- 咽部水腫
- 喉嚨乾

腸胃異常
- 口乾
- 噁心
- 腸胃道蠕動失調
- 腹瀉
- 便秘
- 嘔吐
- 胃炎
- 口腔水腫

皮膚與皮下組織異常
- 皮疹
- 搔癢症
- 血管性水腫
- 蕁麻疹

腎臟與尿道異常
- 尿液滯留

過量
未曾有過量特定的症狀發生，由於ATROVENT有寬廣的治療範圍及其爲局部作用的吸入溶液，預期不會有嚴重的抗膽鹼激素症狀。輕微的抗膽鹼激素作用包括口乾，視覺調節異常及心跳過速可能發生。

毒物學
Ipratropium bromide的局部與全身性耐受性已在數種動物利用各種投藥途徑廣泛研究。
單一劑量毒性
曾在數種齒齒類與非齒齒類動物評估本藥之吸入、口服與靜脈注射的急性毒性。
吸入使用，雄性天竺鼠之最低致死劑量爲199 mg/kg，在大鼠，投與技術上能提供的最高劑量(0.05 mg/kg 4小時後，或每劑量含0.02 mg之ipratropium bromide 160定劑量)後，未觀察到死亡的情況。口服及靜脈給藥的LD$_{50}$比吸入之最低致死量要高出許多。
在小鼠、大鼠與兔子的口服LD$_{50}$分別爲1585、1925與1920 mg/kg。在小鼠、大鼠與兔子的靜脈注射LD$_{50}$則分別爲13.6、15.8與約18.2 mg/kg。臨床病徵包括散瞳、口腔黏膜乾燥、呼吸困難、顫抖、癱瘓與/或心搏過速。
重複劑量毒性
重複劑量毒性研究已經完成於老鼠、兔子、狗與恆河猴。老鼠、狗與恆河猴之吸入投與的研究達6個月，沒有不良反應發生之劑量(NOAEL)分別爲0.38 mg/kg/day，0.18 mg/kg/day與0.8 mg/kg/day。
在狗曾出現口腔黏膜乾燥與心搏過速的副作用。在支氣管肺部系統或任何其他器官，均未觀察到與本藥有關的組織病理性病變。老鼠口服18個月其沒有不良反應的劑量爲0.5 mg/kg/day。
使用其他配方(鼻內吸入劑型，以HFA 134a作爲推進劑及含乳糖粉末之配方)對大鼠及狗分別進行長達6個月與3個月的重複劑量毒性研究顯示，沒有任何ipratropium bromide新增的毒性資料。
一項針對狗所作長達6個月，以鼻內投藥方式的研究顯示，無不良副作用劑量高於0.2 mg/kg/day，此結果證實了之前所作爲期13週鼻內投藥的研究結果。
使用ipratropium bromide在重複劑量毒性試驗顯示：含HFA之處方與傳統含CFC之處方毒性相似。
局部耐受性
以吸入方式給予大鼠ipratropium bromide水性溶液(0.05 mg/kg) (一次，投與時間超過4小時)，其局部的耐受性佳。重複劑量毒性研究亦顯示，ipratropium bromide的局部耐受性佳。
免疫原性
在天竺鼠並未出現主動性過敏和被動性皮膚的過敏。
遺傳毒性及致癌性
在體外(Ames檢測法)與體內(微核檢測法[micronucleus test]、小鼠之顯性致死檢測法[dominant lethal test]、中國大鼠骨髓細胞進行的細胞遺傳學檢測法)研究，均未發現遺傳毒性證據。
大鼠與老鼠長期的研究中並未顯示有發生惡性腫瘤或癌症之作用。
生殖及發育毒性
曾對小鼠、大鼠和兔子進行有關ipratropium bromide對生育能力、胚胎及胎兒之毒性、出生前後及出生後之發育(peri-/postnatal development)等的研究。
高口服劑量(大鼠爲1000 mg/kg/day，兔子爲125 mg/kg/day)在這兩種動物均具有母體毒性，在大鼠亦具有胚胎/胎兒毒性，胎兒的體重下降，但未觀察到與治療有關的畸形發生。
技術上可行之定量噴霧劑之最大吸入劑量老鼠爲1.5 mg/kg/day與兔子1.8 mg/kg/day，也未有生殖的不良反應發生。

包裝
每一長排含10支單一劑量吸入液小瓶
100支以下盒裝

請存於避光30°C以下及兒童伸手不及處。

製造廠廠名/廠址
Laboratoire Unither
Z.I. Longpre, 10 rue Andre Durouchez
80084 Amiens Cedex 2, France
for
Boehringer Ingelheim International GmbH
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Atrovent® Nebuliser Solution 0.5mg/2ml in Unit-Dose Vials

Boehringer Ingelheim

Composition
1 unit dose vial (2 mL) solution for inhalation contains 522 mcg (8r)-3-hydroxy-8-isopropyl-1H,5H-tropanium bromide (±)-tropate monohydrate (= Ipratropium bromide) corresponding to 500 mcg ipratropium bromide anhydrous
Excipients
sodium chloride, hydrochloric acid, purified water

Pharmacological properties
Pharmacotherapeutic group: Anticholinergics
ATC Code: R03BB01
ATROVENT (ipratropium bromide) is a quaternary ammonium compound with anticholinergic (parasympatholytic) properties. In nonclinical studies, it appears to inhibit vagally mediated reflexes by antagonising the action of acetylcholine, the transmitter agent released from the vagus nerve. Anticholinergics prevent the increase in intracellular concentration of Ca++ which is caused by interaction of acetylcholine with the muscarinic receptor on bronchial smooth muscle. Ca++ release is mediated by the second messenger system consisting of IP3 (inositol triphosphate) and DAG (diacylglycerol).
The bronchodilation following inhalation of ATROVENT (ipratropium bromide) is primarily local and site specific to the lung and not systemic in nature.
Preclinical and clinical evidence suggest no deleterious effect of ATROVENT (ipratropium bromide) on airway mucous secretion, mucociliary clearance or gas exchange.
Clinical trials
In controlled 85 - 90 day studies in patients with bronchospasm associated with chronic obstructive pulmonary disease (chronic bronchitis and emphysema) significant improvements in pulmonary function occurred within 15 minutes, reached a peak in 1-2 hours, and persisted up to 4 - 6 hours.
The bronchodilator effect of ATROVENT in the treatment of acute bronchospasm associated with asthma has been shown in studies in adults. In most of these studies ATROVENT was administered in combination with an inhaled beta-agonist.

Pharmacokinetics
Absorption
The therapeutic effect of ATROVENT is produced by a local action in the airways. Time courses of bronchodilation and systemic pharmacokinetics do not run in parallel.
Following inhalation 10 to 30% of a dose is generally deposited in the lungs, depending on the formulation and inhalation technique. The major part of the dose is swallowed and passes the gastro-intestinal tract.
The portion of the dose deposited in the lungs reaches the circulation rapidly (within minutes).
Cumulative renal excretion (0-24 hrs) of the parent compound is approximated to 46% of an intravenously administered dose, below 1% of an oral dose and approximately 3 to 13% of an inhaled dose. Based on these data the total systemic bioavailability of oral and inhaled doses of ipratropium bromide is estimated at 2% and 7 to 28% respectively.
Taking this into account, swallowed dose portions of ipratropium bromide do not relevantly contribute to systemic exposure.
Distribution
Kinetic parameters describing the disposition of ipratropium were calculated from plasma concentrations after i.v. administration.
A rapid biphasic decline in plasma concentrations is observed. The apparent volume of distribution at steady-state (Vdss) is approximately 176 L (≈ 2.4 L/kg).
The drug is minimally (less than 20%) bound to plasma proteins. Nonclinical data indicate that quaternary amine ipratropium does not cross the place ntal or the blood-brain barrier.
Biotransformation
After intravenous administration approximately 60% of a dose is metabolised, the major portion probably in the liver by oxidation.
The known metabolites, which are formed by hydrolysis, dehydration or elimination of the hydroxy-methyl group in the tropic acid moiety, show very little or no affinity for the muscarinic receptor and have to be regarded as ineffective.
Elimination
The half-life of the terminal elimination phase is approximately 1.6 hours. Ipratropium has a total clearance of 2.3 L/min and a renal clearance of 0.9 L/min.
In an excretion balance study cumulative renal excretion (6 days) of drug-related radioactivity (including parent compound and all metabolites) accounted for 72.1% after intravenous administration, 9.3% after oral administration and 3.2% after inhalation. Total radioactivity excreted via the faeces was 6.3% following intravenous application, 88.5% following oral dosing and 69.4% after inhalation.
Regarding the excretion of drug-related radioactivity after intravenous administration, the main excretion occurs via the kidneys. The half-life for elimination of drug-related radioactivity (parent compound and metabolites) is 3.6 hours.

Indications
Chronic obstructive bronchitis and asthma

Dosage and Administration
The product should be used by physician prescription.
The dosage should be adapted to the individual requirements and the patients should be kept under medical supervision during treatment. It is advisable not to exceed the recommended daily dose during either acute or maintenance treatment.
If therapy does not produce a significant improvement or if the patient's condition gets worse, medical advice must be sought in order to determine a new plan of treatment. The patient should be instructed that in the case of acute or rapidly worsening dyspnoea a physician should be consulted immediately.
The following dosages are recommended:
- Maintenance treatment:
  Adults (including elderly) and adolescents > 12 years of age:
  1 unit dose vial (UDV) 3 to 4 times daily.
- Acute attacks:
  Adults (including elderly) and adolescents > 12 years of age:
  1 unit dose vial (UDV); repeated doses can be administered until the patient is stable.
  The time interval between the doses may be determined by the physician.
  ATROVENT can be administered combined with an inhaled beta-agonist.
  Daily doses exceeding 2 mg ipratropium bromide anhydrous in adults and adolescents >12 years of age should be given under medical supervision.

Instructions for use
Please read the instructions for use carefully, to ensure correct administration.
The unit dose vials are intended only for inhalation with suitable nebulising devices and should not be taken orally or administered parenterally.

The unit dose vials of 1 mL are to be diluted with physiological saline up to a final volume of 2 - 4 mL or may be combined with BEROTEC solution for inhalation.
ATROVENT solution for inhalation can be administered using a range of commercially available nebulising devices. Where wall oxygen is available the solution is best administered at a flow rate of 6 - 8 litres per minute.
ATROVENT solution for inhalation is suitable for concurrent inhalation with the secretomucolytics MUCOSOLVAN solution for inhalation and BISOLVON solution for inhalation or BEROTEC solution for inhalation.
ATROVENT solution for inhalation in unit dose vials and disodium cromoglycate solution for inhalation should not be administered simultaneously in the same nebuliser.

1. Prepare the nebuliser for filling, according to the instructions provided by the manufacturer or doctor.
2. Tear one unit dose vial from the strip.
3. Open the unit dose vial by firmly twisting the top.
4. Squeeze the content of the unit dose vial into the nebuliser reservoir.
5. Dilute with saline up to a final volume of 2 - 4 mL.
6. Assemble the nebuliser and use as directed.
7. After use throw away any solution left in the reservoir and clean the nebuliser, following the manufacturer's instructions.



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Since the unit dose vials contain no preservative, it is important that the contents are used soon after opening and that a fresh vial is used for each administration to avoid microbial contamination. Partly used, opened or damaged unit dose vials should be discarded.

Contraindications
ATROVENT is contraindicated in patients with known hypersensitivity to atropine or its derivatives (such as the active substance ipratropium bromide) or to any other component of the product.

Special warnings and precautions
Hypersensitivity
Immediate hypersensitivity reactions may occur after administration of ATROVENT, as demonstrated by rare cases of rash, urticaria, angio-oedema, oropharyngeal oedema, bronchospasm, and anaphylaxis.
Paradoxical bronchospasm
As with other inhaled medicines ATROVENT may result in paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs ATROVENT should be discontinued immediately and substituted with an alternative therapy.
Ocular complications
ATROVENT should be used with caution in patients predisposed to narrow-angle glaucoma.
There have been isolated reports of ocular complications (i.e. mydriasis, increased intraocular pressure, narrow-angle glaucoma, eye pain) when aerosolised ipratropium bromide either alone or in combination with an adrenergic beta$_2$-agonist, has come into contact with the eyes.
Eye pain or discomfort, blurred vision, visual halos or coloured images in association with red eyes from conjunctival congestion and corneal oedema may be signs of acute narrow-angle glaucoma. Should any combination of these symptoms develop, treatment with miotic drops should be initiated and specialist advice should be sought immediately.
Patients must be instructed in the correct administration of ATROVENT nebuliser solution. Care must be taken not to allow the solution or mist into the eyes. It is recommended that the nebulised solution is administered via a mouth piece. If this is not available and a nebuliser mask is used, it must fit properly. Patients who may be predisposed to glaucoma should be warned specifically to protect their eyes.
Renal and urinary effects
ATROVENT should be used with caution in patients with pre-existing urinary outflow tract obstruction (e.g. prostatic hyperplasia or bladder-neck obstruction).
Gastro-intestinal motility disturbances
Patients with cystic fibrosis may be more prone to gastro-intestinal motility disturbances.

Interactions
The chronic co-administration of ATROVENT inhalation with other anticholinergic drugs has not been studied. Therefore, the chronic co-administration of ATROVENT® with other anticholinergic drugs is not recommended.
Beta-adrenergics and xanthine preparations may intensify the bronchodilator effect.
The risk of acute glaucoma in patients with a history of narrow-angle glaucoma (see section Special warnings and precautions) may be increased when nebulised ipratropium bromide and beta-mimetics are administered simultaneously.

Fertility, Pregnancy and lactation
Pregnancy
The safety of ATROVENT during human pregnancy has not been established. The benefits of using ATROVENT during a confirmed or suspected pregnancy must be weighed against possible hazards to the unborn child. Nonclinical studies have shown no embryotoxic or teratogenic effects following inhalation or intranasal application at doses considerably higher than those recommended in man.
Lactation
It is not known whether ipratropium bromide is excreted into breast milk, but it is unlikely that ipratropium bromide would reach the infant to an important extent, especially when administered by inhalation. However, caution should be exercised when ATROVENT is administered to nursing mothers.
Fertility
Clinical data on fertility are not available for ipratropium bromide.
Nonclinical studies performed with ipratropium bromide showed no adverse effect on fertility (see section Toxicology).

Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. However, patients should be advised that they may experience undesirable effects such as dizziness, accommodation disorder, mydriasis and blurred vision during treatment with ATROVENT. Therefore, caution should be recommended when driving a car or operating machinery.

Side effects
Many of the listed undesirable effects can be assigned to the anticholinergic properties of ATROVENT. As with all inhalation therapy ATROVENT may show symptoms of local irritation. Adverse drug reactions were identified from data obtained in clinical trials and pharmacovigilance during post approval use of the drug.
The most frequent side effects reported in clinical trials were headache, throat irritation, cough, dry mouth, gastro-intestinal motility disorders (including constipation, diarrhoea and vomiting), nausea, and dizziness.
Immune system disorders
- hypersensitivity
- anaphylactic reaction
Nervous system disorders
- headache
- dizziness
Eye disorders
- vision blurred
- mydriasis
- intraocular pressure increased
- glaucoma
- eye pain
- halo vision
- conjunctival hyperaemia
- corneal oedema
- accommodation disorder
Cardiac disorders
- palpitations
- supraventricular tachycardia
- atrial fibrillation
- heart rate increased
Respiratory, thoracic and mediastinal disorders
- throat irritation
- cough
- bronchospasm
- bronchospasm paradoxical
- laryngospasm
- pharyngeal oedema
- dry throat
Gastrointestinal disorders
- dry mouth
- nausea
- gastrointestinal motility disorder
- diarrhoea
- constipation
- vomiting
- stomatitis
- oedema mouth
Skin and subcutaneous tissue disorders
- rash
- pruritus
- angioedema
- urticaria
Renal and urinary disorders
- urinary retention

Overdose
No symptoms specific to overdose have been encountered. In view of the wide therapeutic range and topical administration of ATROVENT, no serious anticholinergic symptoms are to be expected. Minor systemic manifestations of anticholinergic action, including dry mouth, visual accommodation disorder and increase of heart rate may occur.

Toxicology
Local and systemic tolerability of ipratropium bromide have comprehensively been investigated in several animal species using various administration routes.
Single-dose toxicity
The acute inhalation, oral and intravenous has been assessed in several rodent and non-rodent species.
When administered by inhalation, the minimum lethal dose in male Guinea pigs was 199 mg/kg. In rats, no mortality was observed up to the highest technically feasible dosages (i.e. 0.05 mg/kg after 4 h of administration or 160 puffs of ipratropium bromide, 0.02 mg/puff) .
The oral LD_{50} values for the mouse, rat and rabbit were 1585, 1925 and 1920 mg/kg, respectively. The intravenous LD_{50} for the mouse, rat and dog was, respectively, 13.6, 15.8 and about 18.2 mg/kg. Clinical signs included mydriasis, dry oral mucosa, dyspnoea, tremor, spasms and/or tachycardia.
Repeat-dose toxicity
Repeat-dose toxixty studies have been performed in rats, rabbits, dogs and Rhesus monkeys.
In inhalation studies up to 6 months in rats, dogs and Rhesus monkeys, the No-Observed Adverse Effect Level (NOAEL) was 0.38 mg/kg/day, 0.18 mg/kg/day and 0.8 mg/kg/day, respectively. Dry oral mucosa and tachycardia were noted in the dogs.
No substance-related histopathological lesions were observed in the broncho-pulmonary system or in any other organs. In the rat, the NOAEL after 18 months of oral administration was 0.5 mg/kg/day.
Repeated-dose inhalation toxicity studies in rats up to 6 months, and in dogs for up to 3 months with other formulations (intranasal formulation, alternative propellant HFA 134a and lactose powder formulation) revealed no additional information on the general toxicity profile of ipratropium bromide.
Intranasal administration for up to 6 months revealed a No Effect Level (NOEL) > 0.20 mg/kg/day in dogs and confirmed earlier studies with intranasal administration for up to 13 weeks.
Repeat-dose toxicity studies of ipratropium bromide have shown the toxicological profiles of the HFA formulation and the conventional CFC formulation to be similar.
Local tolerance
An aqueous solution of ipratropium bromide, (0.05 mg/kg), was locally well tolerated when administered to rats by inhalation (single administration over 4 h). In the repeated dose toxicity studies, ipratropium bromide, was locally well tolerated.
Immunogenicity
Neither active anaphylaxis nor passive cutaneous anaphylactic reactions were demonstrated in Guinea pigs.
Genotoxicity and carcinogenicity
There was no evidence of genotoxicity *in vitro* (Ames test) and *in vivo* (micronucleus test, dominant lethal test in mice, cytogenetic assay on bone marrow cells of Chinese hamsters).
No tumorigenic or carcinogenic effects were demonstrated in long term studies in mice and rats.
Reproductive and developmental toxicity
Studies to investigate the possible influence of ipratropium bromide, on fertility, embryo-fetotoxicity, and peri-/postnatal development have been performed on mice, rats and rabbits.
High oral dose levels, i.e. 1000 mg/kg/day in the rat and 125 mg/kg/day in the rabbit were maternotoxic for both species and embryo-/fetotoxic in the rat, where the fetal weight was reduced. Treatment-related malformations were not observed.
The highest, technically feasible doses for inhalation of the metered aerosol, 1.5 mg/kg/day in rats and 1.8 mg/kg/day in rabbits, showed no adverse effects on reproduction.

Availability
Pack of 100 unit-dose vials below in paper boxes.

Protect from direct sunlight!
Store below 30°C and in a safe place out of the reach of children!

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