冠喘衛®單一劑量吸入液
Combivent® UDV Inhalation Solution

衛署藥輸字第 023357 號

成分

每單一劑量吸入液(2.5 ml/瓶)含
(8r)-3α-hydroxy-8-isopropyl-1αH, 5αH-tropanium bromide (±)-tropate monohydrate (= ipratropium bromide monohydrate) 0.52 mg 相當於 ipratropium bromide anhydrous 0.5 mg
di[(RS)-2-tert-butylamino-1-(4-hydroxy-3-hydroxymethyl-phenyl)ethanol] sulphate (= salbutamol sulphate) 3.01 mg 相當於 salbutamol base 2.5 mg
賦形劑
氯化鈉、鹽酸、純水

性質

藥物分類：擬交感神經劑與抗乙醯膽鹼類藥物合併療法，用於阻塞性呼吸道疾病。
解剖學治療學化學分類系統編碼 (ATC Code)：R03AL02
作用機轉與藥效學
Ipratropium bromide 為四級銨鹽化合物，具有抗乙醯膽鹼性質，能解除副交感神經作用(parasympatholytic)。非臨床試驗顯示 ipratropium bromide 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。乙醯膽鹼由迷走神經釋出，抗膽鹼藥物抑制此現象，能與支氣管平滑肌上的毒蕈接受體作用，進而減少細胞內之 Ca++濃度增加。釋出 Ca++之作用的媒介為由 IP3 (三磷酸肌醇)與 DAG (二醯基甘油)所構成的二級訊息傳遞系統。
Iprotropium bromide 吸入後，其支氣管擴張作用主要是局部且特定作用於肺部而非全身。
Salbutamol sulphate 為一β_2擬交感神經劑(beta 2-adrenergic agent)，作用於呼吸道之平滑肌使其鬆弛。Salbutamol 可鬆弛所有氣管及支氣管平滑肌，拮抗所有支氣管收縮而具保護作用。
COMBIVENT 含有 ipratropium bromide 及 salbutamol，可以同時產生加成

作用在肺部之毒蕈鹼接受體與β_2腎上腺素激性接受體(adrenergic receptor)上，使支氣管舒張，其作用比任何單一成分效果更好。

臨床試驗

對患有可逆性支氣管痙攣病人進行有對照組之研究，顯示 COMBIVENT 之支氣管擴張療效大於其任一成分，但不會增加其不良反應。

兒科族群

COMBIVENT 目前尚未在兒科族群進行試驗。

藥物動力學

Ipratropium

吸收

靜脈注射，口服給藥，吸入給藥後 Ipratropium (原型成分)的累積腎臟排泄量(0-24 小時)分別為給藥劑量的 46%、＜1%、及吸入劑量的 3-13%。根據這些數據，ipratropium bromide 之口服劑量與吸入劑量的生體可用率分別約為 2%與 7 至 9%。從這點來看，ipratropium bromide 被吞下的劑量並不會使全身暴藥量明顯升高。

分佈

ipratropium 的分佈，排除的藥動參數乃藉由靜脈注射後的血漿濃度計算而得。其血中濃度會以雙相模式快速下降。穩定狀態表面分佈體積(Vdss)約為 176 升(≈ 2.4 升/公斤)。此藥物的血漿蛋白結合率極低(低於 20%)。以大鼠和狗所進行的非臨床試驗發現，屬於四級胺化合物的 ipratropium 並不會通過血腦障蔽。

生物轉化

靜脈注射給藥之後，約 60%的劑量會經代謝，可能主要是在肝臟進行氧化代謝。尿中的主要代謝物與毒蕈鹼接受體結合的作用極為微弱，因此這些代謝物應視為不具活性。

排除

其終端排除相的半衰期約為 1.6 小時。Ipratropium 的總廓清率為 2.3 升/分鐘，腎臟清除率為 0.9 升/分鐘。在一項排除平衡研究中，靜脈注射之後，放射線標示物質 (包括原型成分與所有代謝物)的累積腎臟排除量(6 天)為 72.1%，口服投予後為 9.3%，吸入投予後則為 3.2%。靜脈注射之後，經由糞便排泄的總放射活性為 6.3%，口服投予後為 88.5%，吸入投予後則為 69.4%。在靜脈注射後之放射線標示物質，主要的排除途徑為腎臟。放射線標示物質(原型成分與代謝物)的排除半衰期為 3.6 小時。

Salbutamol

吸收及分佈

Salbutamol 經口吸入後無論是在氣道或吞入的部分均可迅速且完全地被吸收，且口服吸收的生體可用率約為 50%。吸入 COMBIVENT 之後，

salbutamol 可於 3 小時內達到 492 pg/ml 的平均最高血中濃度。藥動參數乃藉由靜脈注射後的血漿濃度計算而得。其表面分佈體積(Vz)約為 156 升(≈ 2.5 升/公斤)。只有 8%的藥物會與血漿蛋白結合。Salbutamol 可穿透腦血管障壁，其濃度大約為血漿濃度的 5%。

<u>生物轉化與排泄</u>

Salbutamol 會以共軛結合的方式被代謝成 salbutamol 4'-O-sulphate。

Salbutamol 的 R(-)鏡像異構物(levosalbutamol)較易被代謝，因此也會比 S(+)鏡像異構物更快自體內清除。靜脈注射之後，尿液排泄會在約 24 小時後完成。大部份的劑量會以原型排出體外(64.2%)，有 12.0%會以硫酸鹽結合物的型態排出體外。口服投予之後，經由尿液排泄的原型藥物與硫酸鹽結合物分別相當於投予劑量的 31.8%與 48.2%。在單次吸入投予之後，約有 27%的口含器劑量會以原型排泄 24 小時累積尿液中。平均終端半衰期約為 4 小時，平均總廓清率為 480 毫升/分鐘，且平均腎臟廓清率為 291 毫升/分鐘。

Ipratropium bromide 與 salbutamol sulphate 合併投予並不會增加個別的全身性吸收，而且 COMBIVENT 療效加成是因為吸入後兩種主成分對肺部的局部作用相加所致。

適應症

用於治療阻塞性呼吸道疾病併發的可逆性支氣管痙攣需要一種以上支氣管擴張劑治療者。

用法用量

本藥需由醫師處方使用。

應告知病人，如果發生急性或快速惡化的呼吸困難症狀，且額外吸入 COMBIVENT 也無法產生適當的改善效果時，應立即向醫師或最近的醫院諮詢。

若病人需要持續使用高於建議劑量的 COMBIVENT 來控制症狀，則醫師應審視病人的治療計畫。

治療氣喘時，應考慮合併使用抗發炎藥物。

以下的 COMBIVENT 劑量為成人(包括老年病人)的建議劑量：

COMBIVENT 單一劑量吸入液可經由適當的噴霧機或間歇性的正壓呼吸器給藥。

應在醫療人員的監督下開始及給予治療，例如在醫院中。在特殊情況下(症狀嚴重或需要較高劑量，且曾有使用經驗)，若低劑量速效β-促效支氣管擴張劑已無法有效緩解氣喘時，於諮詢治療經驗豐富的醫師之後可考慮居家治療。

使用單一劑量瓶吸入液進行治療，務必從最低建議劑量(1UDV)開始。在極

嚴重的情況下，可能需要兩單位劑量才能緩解症狀。症狀獲得充分緩解時應停止給藥。

治療急性發作

對大多數病人，一瓶單一劑量吸入液即可迅速緩解症狀。

情況嚴重的病人，若一瓶單一劑量吸入液無效，可能需要投予第二瓶單一劑量吸入液，但在這些情況下，病人應立刻諮詢醫師或前往就近的醫院。

持續性治療

每次一瓶單一劑量，每日三至四次。

特殊族群

肝功能或腎功能不全病人

目前尚未針對肝功能或腎功能不全的病人進行過 COMBIVENT 的研究。對此類病人使用本品時應謹慎。

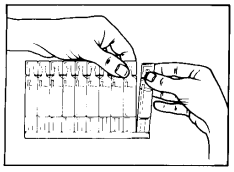
兒童族群

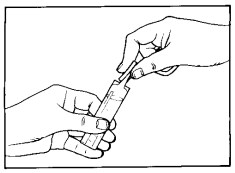
由於兒童方面的資料不足，因此 COMBIVENT 並不適用於兒童病人。

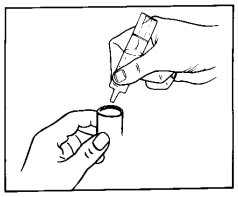
用法

單一劑量吸入液只可用適當噴霧機以吸入方式使用，不可口服或注射。

單一劑量瓶的內容物並不須稀釋即可用於噴霧給藥。







1.根據醫師或製造廠指示，準備好噴霧機來充填藥品。
2.打開鋁箔包裝並撕下一個單一劑量瓶。
3.用力旋轉頂部以打開單一劑量瓶。
4.將單一劑量瓶的內容物擠入噴霧器的藥槽中。
5.裝妥噴霧機，並依照指示使用。
6.使用完畢後將藥槽中的殘留液體丟棄，依照指示清潔噴霧器。

因為單一劑量瓶中不含有保存劑，所以打開後瓶中的內容物需很快用完。每次用藥均需使用新的小瓶，以避免被微生物感染。所以使用後剩餘部份、已開或單一劑量瓶已損壞者需丟棄。

絕不可將 COMBIVENT 吸入性溶液與其他藥物混合於同一噴霧機中。

禁忌

COMBIVENT 禁用於：

- 肥大阻塞性心肌病變或心搏過速性心律不整的病人
- 已知對 atropine 或其衍生物或對本品之任何其它成分過敏的病人。

特別注意

過敏

使用 COMBIVENT 後可能立即發生過敏，如：蕁麻疹、血管性水腫、皮疹、支氣管痙攣以及口咽部水腫。

逆理性支氣管痙攣

如同其他吸入性藥物，COMBIVENT 可能會造成致命性的逆理性支氣管痙攣。發生時，應立即停用 COMBIVENT 並改用其他療法。

眼科併發症

曾有個別案例，ipratropium bromide 噴霧劑單獨使用或與一種腎上腺素β_2-促效劑合用時，若不慎進入並接觸眼睛，會發生眼部併發症，如：散瞳、眼內壓升高、窄角性青光眼、眼痛。

眼睛痛或不舒服、視力模糊、視界出現光暈或有色彩、伴隨因結膜充血而造成的紅眼、角膜水腫等可能是窄角性青光眼的症狀。若有任一項以上的上述症狀發生，應立即使用縮瞳劑治療並請教醫師。

必須指示病人正確地使用 COMBIVENT，並避免讓溶液或灰塵進入眼睛。可能罹患青光眼的病人使用時，須特別告知其注意保護眼睛。建議利用含口器投予 COMBIVENT 單一劑量瓶 (UDV) 吸入液，若沒有含口器，則可使用噴霧器的面罩。

全身性作用

COMBIVENT 使用於下列情況下，且劑量超過推薦劑量時，應謹慎評估其使用益處勝過危險時，方得使用：

未完全控制病情之糖尿病、最近患有心肌梗塞、嚴重心臟或血管病變、甲狀腺機能亢進、親鉻細胞瘤、可能罹患窄角性青光眼、前列腺肥大或膀胱頸阻塞。

心血管作用

使用擬交感神經作用劑(包括 COMBIVENT)時可能會出現心血管影響。

從一些上市後的資料及發表的文獻證據顯示 salbutamol 與引起心肌缺血有關，但相當罕見。對於正接受 salbutamol 治療呼吸道疾病又合併嚴重心臟疾病(例如：缺血性心臟病、心搏過速或嚴重的心臟衰竭)的病人，須告知若出現胸痛或心臟病惡化的其他症狀，應尋求醫師的建議。應審慎評估呼吸困難及胸痛這類的症狀，因為它們可能是呼吸道問題所致，也可能是心臟問題所致。

低血鉀症

β_2-作用劑可能會造成嚴重的低血鉀症，此外，缺氧會使低血鉀症惡化。此時建議監測血清鉀濃度。

胃腸道蠕動障礙

纖維囊腫的病人可能更容易發生胃腸道蠕動障礙。

呼吸困難

若發生急性且快速惡化的呼吸困難，病人應立即就醫。

干擾實驗室檢驗或其他診斷測量

使用 COMBIVENT 可能會使非臨床物質濫用的檢驗因 salbutamol 而呈現陽性反應的結果，例如在運動員表現提升之情況下所進行的檢驗(禁藥檢測)。

乳酸中毒

使用高劑量靜脈注射劑型及霧化劑型的短效型β促效劑療法曾有乳酸中毒之報告，主要發生在因嚴重氣喘或慢性阻塞性肺病導致急性支氣管痙攣惡化而接受治療的病人。乳酸濃度增高可能導致呼吸困難及代償性過度換氣，而可能被誤解為氣喘治療失敗的徵象，因而導致不當提高短效型β促效劑的劑量。因此建議在此情形時，應監測病人是否出現血清中乳酸濃度升高以及隨之發生的代謝性酸中毒狀況。

藥物交互作用

長期併用 COMBIVENT 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 COMBIVENT 和其他抗乙醯膽鹼類藥物。

同時使用β-擬交感神經劑、黃嘌呤衍生物及抗乙醯膽鹼類藥物可能增加 COMBIVENT 的副作用。

β_2-擬交感神經作用劑(beta-adrenergic agonists)所引發之低血鉀症機率會因併用黃嘌呤衍生物、皮質類固醇及利尿劑而增加，尤其是患有嚴重的呼吸道阻塞病人應特別注意。

低血鉀症會造成使用 digoxin 之病人易發作心律不整。

這種情況下，建議監測病人血漿中鉀離子的濃度。

與β-阻斷劑併用時可能會大幅降低支氣管擴張的效果。

單胺氧化酶抑制劑(monoamine oxidase inhibitor)及三環抗鬱藥會使β_2-擬交感神經作用劑的作用增強，併用時須小心。

含鹵素原子的吸入性碳氫麻醉劑，如：halothane、trichloroethylene 及 enflurane 會加強β-作用劑的心血管作用。

生育力、懷孕與哺乳

懷孕

懷孕期間使用 COMBIVENT 的安全性尚未建立。應注意 COMBIVENT 會抑制子宮收縮。在確定或疑似懷孕期間，如果要使用 COMBIVENT，必須將治療的效益與對未出生之嬰兒所可能造成的危害放在一起權衡得失。通

常懷孕期間用藥需加以觀察，尤其是懷孕第一期。
就 ipratropium bromide 而言，在非臨床試驗中，吸入給藥或鼻內給藥較人類建議劑量高得多的劑量之後，並未發現任何胚胎毒性作用或致畸作用。
就 salbutamol sulphate 而言，非吸入給藥的非臨床試驗並未發現任何直接或間接的有害影響，除非吸入劑量超過人類每日最高建議劑量(MRHDD)(參見毒物學)。

哺乳

目前並不確知 ipratropium bromide 與 salbutamol sulphate 是否會分泌至乳汁中。一般認為 iprotropium bromide 不會在嬰兒體內到達有意義的濃度，尤其是以吸入方式給藥時。但是哺乳母親使用 COMBIVENT 時，仍須謹慎。

生育力

目前尚無任何探討使用 COMBIVENT 對人類生育力之影響的研究。不管是併用 ipratropium bromide 及 salbutamol sulphate，或是兩種併用成分中的任一種，目前都沒有生育力方面的臨床資料。以 ipratropium bromide 及 salbutamol 所進行的非臨床試驗並未發現任何生育力方面的不良影響(參見毒物學)。

駕駛及操作機械

目前尚未進行過任何探討本品對駕駛和機械操作能力之影響的研究。
不過，應告知病人他們在使用 COMBIVENT 治療期間可能會出現如暈眩、視力調節障礙、瞳孔放大及視覺模糊這類的不良反應。因此，建議在開車或操作機械時應謹慎。如果病人出現上述的不良反應，應避免進行可能有危險的活動，如開車或操作機械。

不良反應

安全性摘要

所列出的不良作用有許多都可歸因於 COMBIVENT 的抗乙醯膽鹼作用及 β_2擬交感神經作用。和所有的吸入治療藥物一樣，COMBIVENT 也可能會引發局部刺激的症狀。
在臨床試驗中最常通報的副作用為頭痛、咽喉刺激感、咳嗽、口乾、胃腸道運動障礙(包括便秘、腹瀉及嘔吐)、噁心、以及暈眩。

不良反應摘要表

下列不良反應皆透過臨床試驗與上市後藥物安全監測中取得。

系統器官類別	**不良反應**
免疫系統異常	過敏性反應 過敏性反應過度
代謝及營養異常	低鉀血症

精神異常	精神緊張 精神障礙
神經系統異常	頭痛 震顫 眩暈
眼睛異常	視力調節障礙 角膜水腫 青光眼 眼內壓上升 散瞳 視力模糊 眼痛 結膜充血 光暈 Ipratropium bromide 噴霧劑，單方或與β_2-交感神經興奮劑合併的複方，若不慎噴入眼睛，都曾有病例發生上述眼睛併發症。
心臟異常	心悸 心跳過快 心律不整 心房纖維顫動 上心室心跳過速 心肌缺血
呼吸、胸及縱膈異常	咳嗽 發聲困難 咽喉乾燥 支氣管痙攣 異常性支氣管痙攣

	喉痙攣 咽部水腫
胃腸異常	口乾 噁心 咽喉刺激感 腹瀉 嘔吐 便秘 胃腸道運動障礙 嘴水腫 口腔炎
皮膚及皮下組織異常	皮膚反應，如 - 發疹 - 搔癢 - 蕁麻疹 血管性水腫 多汗
骨骼肌肉及結締組織異常	肌肉痙攣 肌肉無力 肌痛
腎臟及泌尿異常	尿滯留
一般異常及投與部位的狀況	無力
檢查發現	舒張壓降低 收縮壓上升

過量

症狀

過量主要與 salbutamol 有關。

過量時所產生的症狀即為β-擬交感神經刺激過度時的症狀，最常見的有心跳過速、心悸、震顫、高血壓、低血壓、低血鉀症、脈壓變寬、心絞痛、心律不整與發熱。代謝性酸中毒曾發生於 salbutamol 過量。

Ipratropium bromide 過量時的症狀有口乾、視力調節障礙等，由於其治療

劑量範圍寬，且只有局部使用，因此其症狀輕微且短暫。

治療

應停止 COMBIVENT 治療。應考慮監測酸鹼值及電解質。

可使用鎮定劑，嚴重病例或許需給予加護醫療。

β-受體阻斷劑，特別是選擇性β_1受體阻斷劑，適合為特定的解毒劑，但需考慮其可能增加支氣管阻塞，所以對支氣管氣喘病人，劑量需小心調整。

毒物學

<u>單一劑量毒性</u>

對大鼠與狗投與單一吸入劑量的 COMBIVENT 觀察其急性毒性，技術上所能投與的最高劑量(ipratropium bromide/salbutamol)大鼠為 887/5397 mcg /kg，狗 164/861 mcg /kg，在此最高劑量下並無全身性毒性，且局部耐受性良好。靜脈注射後的大約半數致死量(LD_{50})係依個別成分來計算，視測試動物(小鼠、大鼠、狗)而定，ipratropium bromide 的 LD_{50} 為 12 ~ 20 mg/kg，salbutamol sulphate 的 LD_{50} 為 60 ~ 73 mg/kg。

<u>重複劑量毒性</u>

有兩個為期 13 週，針對大鼠及狗測試 ipratropium bromide 與 salbutamol sulphate 併用時其吸入毒性的研究顯示心臟為標的器官。給予大鼠 ipratropium bromide/salbutamol sulphate 劑量範圍為 34/197 ~ 354.5/2604 mcg /kg/day 時，心臟的重量有增加的現象，但與劑量無關，且沒有任何相關的病理變化。狗的投與劑量則為 ipratropium bromide/salbutamol sulphate 32/198 ~129/790 mcg /kg /day，其心跳速率稍微增加，劑量較高時，可觀察到左心室乳頭肌出現瘢痕及/或纖維化，有時會伴隨有礦質化。

上述試驗中的發現皆為β-擬交感神經劑 (如 salbutamol)的已知作用。

Ipratropium bromide 的毒性也熟知多年，為典型的抗乙醯膽鹼的作用，如：黏膜乾燥、散瞳，在狗則會出現乾性角膜結膜炎(乾眼)，並會減少大鼠胃腸道之張力及抑制胃腸道蠕動。

<u>生殖毒性</u>

曾對 COMBIVENT 個別的主成分研究其生殖毒性，皮下注射高劑量的 salbutamol sulphate (從相當於吸入給藥之 MRHDD 的劑量[以 mg/m^2 為比較基礎]開始)會造成小鼠裂顎畸形，不過，這種情形也出現於投與其他β-擬交感神經興奮劑之後，或被認為由於全身性壓力引起母體的皮質脂酮(corticosterone)濃度上升，與其他動物物種無關。除了上述的發現，這些針對 salbutamol sulphate 及 ipratropium bromide 所做的研究得到的結果不論是對胚胎、胎兒或年幼的哺乳動物，都屬於母體毒性的範圍。Ipratropium bromide 口服劑量高達 50 mg/kg 時(大約是 MRHDD 的 3,400 倍，單位為 mg/m^2)，也不會影響雄性或雌性大鼠的生育力。大鼠使用 salbutamol 的生殖試驗無證據顯示生育力受損。

基因毒性

兩種個別成分都曾進行過多項體內與體外基因毒性試驗。這些試驗均顯示 salbutamole sulphate 與 ipratropoium bromide 沒有致突變性。此外，COMBIVENT 在體外分析中也未呈現任何基因毒性作用。

致癌性

Salbutamol sulphate 與 ipratropium bromide 皆曾個別作過數個致癌性研究。當大鼠口服 salbutamol sulphate 劑量較吸入投予之 MRHDD 高出 20 倍以上時，其卵巢系膜出現平滑肌瘤的機會增加，但此情形未見於小鼠、倉鼠與狗。若同時服用β-拮抗劑可防止平滑肌瘤的生成。上述情形只和生物種類有關，且無臨床相關性，因此，salbutamol sulphate 的臨床使用並不受限制。小鼠與大鼠口服 ipratropium bromide 並無致腫瘤性。

免疫毒性

沒有證據顯示 COMBIVENT 與其個別活性成分會造成免疫毒性。

包裝

單一劑量吸入液小瓶。

100 小瓶以下盒裝。

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Ingelheim am Rhein, Germany

藥商

台灣百靈佳殷格翰股份有限公司
台北市中山區民生東路三段 2 號 12 樓

11 APR 2019

修訂時間: 110 年 5 月

核定時間: 110 年 7 月

Combivent® UDV Inhalation Solution

Composition

1 unit-dose vial (2.5 ml) solution for inhalation contains:

(8r)-3α-hydroxy-8-isopropyl-1αH,5αH-tropanium bromide (±)-tropate monohydrate (= ipratropium bromide) corresponding to 0.5 mg ipratropium bromide anhydrous	0.52 mg
di[(RS)-2-tert-butylamino-1-(4-hydroxy-3-hydroxymethyl-phenyl)ethanol] sulphate (= salbutamol sulphate) corresponding to 2.5 mg salbutamol base	3.01 mg

Excipients

Sodium chloride, hydrochloric acid, purified water

Pharmacological properties

Pharmacotherapeutic group: Adrenergics in combination with anticholinergics for obstructive airway diseases.

ATC code: R03AL02

Mode of action and pharmacodynamics

Ipratropium bromide is a quaternary ammonium compound with anticholinergic (parasympatholytic) properties. In nonclinical studies, it appears to inhibit vagally mediated reflexes by antagonizing 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 ipratropium bromide is primarily local and site specific to the lung and not systemic in nature.

Salbutamol sulphate is a $beta_2$-adrenergic agent which acts on airway smooth muscle resulting in relaxation. Salbutamol relaxes all smooth muscle from the trachea to the terminal bronchioles and protects against all bronchoconstrictor challenges.

COMBIVENT provides the simultaneous release of ipratropium bromide and salbutamol sulphate allowing the additive effect on both muscarinic and $beta_2$-adrenergic receptors in the lung resulting in a bronchodilation which is superior to that provided by each single agent.

Clinical Trials

Controlled studies in patients with reversible bronchospasm have demonstrated that COMBIVENT has a greater bronchodilator effect than either of its components and there was no potentiation of adverse events.

Paediatric population

COMBIVENT has not been studied in the paediatric population.

Pharmacokinetics

Ipratropium

Absorption

Cumulative renal excretion (0-24 hrs) of ipratropium (parent compound) is approximated to 46% of an intravenously administered dose, below 1% of an oral dose and approximately 3-13% 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 9% 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. Preclinical studies with rats and dogs revealed that the quarternary amine ipratropium does not cross the blood-brain barrier.

Biotransformation

The main urinary metabolites bind poorly to the muscarinic receptor and have to be regarded as ineffective. After intravenous administration approximately 60% of a dose is metabolised probably mainly in the liver by oxidation.

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.

Salbutamol

Absorption and Distribution

Salbutamol is rapidly and completely absorbed following oral administration either by the inhaled or gastric route and has an oral bioavailability of approximately 50%. Mean peak plasma salbutamol concentrations of 492 pg/ml occur within three hours after inhalation of COMBIVENT. Kinetic parameters were calculated from plasma concentrations after i.v. administration. The apparent volume of distribution (Vz) is approximately 156 L (≈ 2.5 L/kg). Only 8% of the drug is bound to plasma proteins. Salbutamol will cross the blood brain barrier reaching concentrations amounting to about 5% of the plasma concentrations.

Biotransformation and Elimination

Salbutamol is conjugatively metabolised to salbutamol 4'-O-sulphate. The R(-)-enantiomer of salbutamol (levosalbutamol) is preferentially metabolised and is therefore cleared from the body more rapidly than the S(+)-enantiomer. Following intravenous administration, urinary excretion was complete after approximately 24 hours. The majority of the dose was excreted as parent compound (64.2%) and 12.0% were excreted as sulphate conjugate. After oral administration urinary excretion of unchanged drug and sulphate conjugate were 31.8% and 48.2% of the dose, respectively. Following this single inhaled administration, approximately 27% of the estimated mouthpiece dose is excreted unchanged in the 24-hour urine. The mean terminal half-life is approximately 4 hours with a mean total clearance of 480 mL/min and a mean renal clearance of 291 mL/min.

Co- administration of ipratropium bromide and salbutamol sulphate does not potentiate the systemic absorption of either component and therefore the additive activity of COMBIVENT is due to the combined local effect on the lung following inhalation.

Indications

COMBIVENT unit dose vials are indicated for the management of reversible bronchospasm associated with obstructive airway diseases in patients who require more than a single bronchodilator.

Dosage and administration

The product should be used by physician prescription

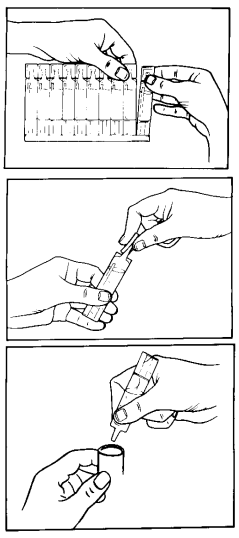
Patients should be advised to consult a physician or the nearest hospital immediately in the case of acute or rapidly worsening dyspnoea if additional inhalations of COMBIVENT do not produce an adequate improvement.

If higher than recommended doses of COMBIVENT are required to control symptoms, the patient's therapy plan should be reviewed by a doctor.

In asthma, concomitant anti-inflammatory therapy should be considered.
The following doses of COMBIVENT are recommended for adults (including elderly patients):
COMBIVENT inhalation solution in unit dose vials may be administered from a suitable nebuliser or an intermittent positive pressure ventilator.
Treatment should be initiated and administered under medical supervision, e.g. in the hospital setting. Home based treatment can be recommended in exceptional cases (severe symptoms or experienced patients requiring higher doses) when a low dose rapid acting beta-agonist bronchodilator has been insufficient in providing relief after consultation with an experienced physician.
The treatment with the nebuliser solution in UDVs should always be started with the lowest recommended dose (1 UDV). In very severe cases two unit dose vials may be required for symptom relief. Administration should be stopped when sufficient symptom relief is achieved.
Treatment of acute attacks:
1 unit dose vial is sufficient for prompt symptom relief in many cases.
In severe cases if an attack has not been relieved by one unit dose vial, the administration of a second unit dose vials may be required. Patients should be advised to consult the physician or the nearest hospital immediately in these cases.
Maintenance treatment:
1 unit dose vial three or four times daily.

Special populations
Patients with hepatic or renal impairment
COMBIVENT has not been studied in patients with hepatic or renal insufficiency. It should be used with caution in those patient populations.
Paediatric population
Because of insufficient information in children COMBIVENT is not indicated for pediatric patients.

Instructions for use
The unit dose vials are intended only for inhalation with suitable nebulising devices and must not be taken orally or administered parenterally.
The content of the unit dose vials does not need to be diluted for nebulization.



1. Prepare the nebuliser for filling, according to the instructions provided by the manufacturer or physician.
2. Open the pouch foil and 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. Assemble the nebuliser and use as directed.
6. After use throw away any solution left in the reservoir and clean the nebuliser, following the manufacturer's instructions.

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.

It is strongly recommended not to mix COMBIVENT solution for inhalation with other drugs in the same nebuliser.

Contraindications
COMBIVENT is contraindicated in:
- Patients with hypertrophic obstructive cardiomyopathy or tachyarrhythmia
- Patients with known hypersensitivity to atropine or its derivatives or to any other component of the product

Special warnings and precautions
Hypersensitivity
Immediate hypersensitivity reactions may occur after administration of COMBIVENT, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm and oropharyngeal oedema.
Paradoxical bronchospasm
As with other inhaled medicines COMBIVENT may result in paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs COMBIVENT should be discontinued immediately and substituted with an alternative therapy.
Ocular complications
There have been isolated cases 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 in contact with the eyes.
Eye pain or discomfort, blurred vision, visual halos or colored 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 sought immediately.
Patients must be instructed in the correct administration of COMBIVENT. Care must be taken not to allow the solution or mist to enter into the eyes. Patients who may be predisposed to glaucoma should be warned specifically to protect their eyes.
It is recommended that COMBIVENT nebuliser solution in unit dose vials (UDV) be administered via a mouth piece. If this is not available and a nebuliser mask is used, it must fit properly.
Systemic effects
In the following conditions COMBIVENT should only be used after careful risk/benefit assessment, especially when doses higher than recommended are used:
insufficiently controlled diabetes mellitus, recent myocardial infarction, severe organic heart or vascular disorders, hyperthyroidism, phaeochromocytoma, risk of narrow-angle glaucoma, prostatic hypertrophy or bladder-neck obstruction.
Cardiovascular effects
Cardiovascular effects may be seen with sympathomimetic drugs, including COMBIVENT. There is some evidence from post-marketing data and published literature of rare occurrences of myocardial ischaemia associated with salbutamol. Patients with underlying severe heart disease (e.g.ischaemic heart disease, tachyarrhythmia or severe heart failure) who are receiving salbutamol for respiratory disease, should be warned to seek medical advice if they experience chest pain or other symptoms of worsening heart disease. Attention should be paid to assessment of symptoms as dyspnoea and chest pain, as they may be of either respiratory or cardiac origin.
Hypokalaemia
Potentially serious hypokalaemia may result from beta$_2$-agonist therapy. Additionally, hypoxia may aggravate the effects of hypokalaemia on cardiac rhythm. In such situations, monitoring of serum potassium levels is recommended.
Gastro-intestinal motility disturbances
Patients with cystic fibrosis may be more prone to gastro-intestinal motility disturbances.
Dyspnoea

In the case of acute, rapidly worsening dyspnoea patients should be advised to consult a physician immediately.
Interference with laboratory tests or other diagnostic measures
The use of COMBIVENT may lead to positive results with regards to salbutamol in tests for nonclinical substance abuse, e.g. in the context of athletic performance enhancement (doping)
Lactic acidosis
Lactic acidosis has been reported in association with high therapeutic doses of intravenous and nebulised short-acting beta-agonist therapy, mainly in patients being treated for an acute exacerbation of bronchospasm in severe asthma or chronic obstructive pulmonary disease. Increase in lactate levels may lead to dyspnoea and compensatory hyperventilation, which could be misinterpreted as a sign of asthma treatment failure and lead to inappropriate intensification of short-acting beta-agonist treatment. It is therefore recommended that patients are monitored for the development of elevated serum lactate and consequent metabolic acidosis in this setting.

Interactions
The chronic co-administration of COMBIVENT with other anticholinergic drugs has not been studied. Therefore, the chronic co-administration of COMBIVENT with other anticholinergic drugs is not recommended.
The concurrent administration of xanthine derivatives as well as other beta-adrenergics and anticholinergics may increase the side effects.
Beta$_2$-agonist induced hypokalaemia may be increased by concomitant treatment with xanthine derivatives, glucocorticosteroids and diuretics. This should be taken into account particularly in patients with severe airway obstruction.
Hypokalaemia may result in an increased susceptibility to arrhythmias in patients receiving digoxin. It is recommended that serum potassium levels are monitored in such situations.
A potentially serious reduction in bronchodilator effect may occur during concurrent administration of beta-blockers.
Beta$_2$-adrenergic agonists should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, since the action of beta-adrenergic agonists may be enhanced.
Inhalation of halogenated hydrocarbon anaesthetics such as halothane, trichloroethylene and enflurane may increase the susceptibility to the cardiovascular effects of beta-agonists.

Fertility, pregnancy and lactation
Pregnancy
The safety of COMBIVENT during human pregnancy ~~is~~ has not been established. The inhibitory effect of COMBIVENT on uterine contraction should be taken into account. The benefits of using COMBIVENT during a confirmed or suspected pregnancy must be weighed against possible hazards to the unborn child. The usual precautions regarding the use of drugs in pregnancy, especially during the first trimester, should be observed.
For ipratropium bromide, nonclinical studies have shown no embryotoxic or teratogenic effects following inhalation or intranasal application at doses considerably higher than those recommended in man. For salbutamol sulphate, non-inhalation nonclinical studies did not indicate direct or indirect harmful effects unless the inhalation Maximum Recommended Human Daily Dose (MRHDD) was exceeded (see section Toxicology)
Lactation
It is not known whether ipratropium bromide and salbutamol sulphate are excreted in breast milk. It is considered unlikely that ipratropium bromide would reach the infant to an important extent, especially when administered by inhalation. However, caution should be exercised when COMBIVENT is administered to nursing mothers.
Fertility

No studies on the effect on human fertility have been conducted for COMBIVENT. Clinical data on fertility are neither available for the combination of ipratropium bromide and salbutamol sulphate nor for each of the two components of the combination.
Nonclinical studies performed with ipratropium bromide and salbutamol showed no adverse effect on fertility (see section Toxicology).

Driving and Using 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 COMBIVENT. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience the above mentioned side effects they should avoid potentially hazardous tasks such as driving or operating machinery.

Adverse Reactions
Summary of the safety profile
Many of the listed undesirable effects can be assigned to the anticholinergic and beta2-sympathomimetic properties of COMBIVENT. As with all inhalation therapy COMBIVENT may show symptoms of local irritation.
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.
Tabulated summary of adverse reactions
The following adverse reactions have been reported during use of COMBIVENT in clinical trials and during the post-marketing experience.

System Organ Class	**COMBIVENT adverse reactions**
Immune system disorders	Anaphylactic reaction Hypersensitivity
Metabolsim and nutrition disorders	Hypokalaemia
Psychiatric disorders	Nervousness Mental disorder
Nervous system disorders	Headache Tremor Dizziness
Eye disorders	Accommodation disorder Corneal oedema Glaucoma Intraocular pressure increased Mydriasis Vision blurred Eye pain Conjunctival hyperaemia Halo vision There have been isolated reports of ocular complications with symptoms mentioned above when aerosolised ipratropium bromide either alone or in combination with an adrenergic $beta_2$-agonist, has escaped into the eyes
Cardiac disorders	Palpitations Tachycardia Arrhythmia

	Atrial fibrillation Supraventricular tachycardia Myocardial ischaemia-
Respiratroy, thoracic and mediastinal disorders	Cough Dysphonia Dry throat Bronchospasm Bronchospasm paradoxical Laryngospasm Pharyngeal oedema
Gatrointestinal disorders	Dry mouth Nausea Throat irritation Diarrhoea Vomiting Constipation Gastrointestinal motility disorder Oedema mouth Stomatitis
Skin and subcutaneous tissue disorders	Skin reactions such as - Rash - Pruritus - Urticaria Angioedema Hyperhidrosis
Musculoskeletal and connective tissue disorders	Muscle spasms Muscular weakness Myalgia
Renal and urinary disorders	Urinary retention
General disorders and administration site conditions	Asthenia
Investigations	Blood pressure diastolic decreased Blood pressure systolic increased

Overdose

Symptoms

The effects of overdosage are expected to be primarily related to salbutamol.

The expected symptoms with overdosage are those of excessive beta-adrenergic-stimulation, the most prominent being tachycardia, palpitation, tremor, hypertension, hypotension, hypokalaemia, widening of the pulse pressure, anginal pain, arrhythmias, and flushing. Metabolic acidosis has also been observed with overdosage of salbutamol.

Expected symptoms of overdosage with ipratropium bromide (such as dry mouth, visual accomodation disorders) are mild and transient in nature in view of the wide therapeutic range and topical administration.

Therapy

Treatment with COMBIVENT should be discontinued. Acid base and electrolyte monitoring should be considered.

Administration of sedatives and, in severe cases intensive therapy may be needed.

Beta-receptor blockers, preferably $beta_1$-selective, are suitable as specific antidotes; however, a possible increase in bronchial obstruction must be taken into account and the dose should be adjusted carefully in patients suffering from bronchial asthma.

Toxicology

Single dose toxicity

The acute toxicity of COMBIVENT after single inhalation administration was tested in rats and dogs. Up to the highest technically feasible dose (rat: 887/5397mcg/kg ipratropium bromide/salbutamol, dog: 164/861mcg/kg ipratropium bromide/salbutamol) there were no indications of systemic toxic effects, the combination was locally well tolerated. The approximate LD_{50} after intravenous administration was calculated for the individual substances to be between 12 and 20 mg/kg for ipratropium bromide and between 60 and 73 mg/kg for salbutamol sulphate depending on the species tested (mouse, rat, dog).

Repeat-dose toxicity

Two 13-week inhalation toxicity studies in rats and dogs, have been performed with the combination of ipratropium bromide and salbutamol sulphate. In these studies, the heart proved to be the target organ. In the rat at dosages of 34/197 to 354.5/2604 mcg/kg/day ipratropium bromide/salbutamol sulphate, a nondose dependent increase in heart weights was present, however without any histopathological correlate. In the dog at doses of 32/198 to 129/790 mcg /kg/day ipratropium bromide/salbutamol sulphate, slightly increased heart rate and, at higher dosages, histopathologically detectable scars and/or fibrosis in the papillary muscle of the left ventricle, sometimes accompanied with mineralisation, were observed.

The cardiovascular findings obtained in the above mentioned studies must be regarded as well known effects of beta-adrenergics such as salbutamol. The toxicological profile of ipratropium bromide is also well known for many years and characterised by typical anticholinergic effects as dryness of the mucosal membranes of the head, mydriasis, keratoconjunctivitis sicca (dry eye) in dogs only, reduction in tone and inhibition of motility in the gastrointestinal tract (rat).

Reproduction toxicity

Reproduction toxicity studies are available for the two individual components of COMBIVENT. Salbutamol sulphate caused cleft palates at high subcutaneous dosages in mice, starting at dosages in the range of the inhalation MRHDD (based on mg/m^2). However this phenomenon is well known and occurs also after the administration of other beta-adrenergic compounds. Today it is assumed that this effect is caused by an increase in the maternal corticosterone level and might be regarded as a result of general stress not relevant for other species. Apart from these findings, the studies performed with salbutamol sulphate and with ipratropium bromide revealed only marginal effects, if any, on embryos, foetuses and pups and these only in the range of maternal toxicity. Ipratropium bromide did not affect fertility of male or female rats at oral doses up to 50 mg/kg (approximately 3,400 times the MRHDD on a mg/m^2 basis). Reproduction studies in rats with salbutamol revealed no evidence of impaired fertility.

Genotoxicity

Both individual substances were tested in numerous *in-vivo* and *in-vitro* genotoxicity tests. Neither salbutamol sulphate nor ipratropium bromide showed any evidence of mutagenic properties. In addition COMBIVENT did not show genotoxic activity in *in vitro* assays.

Carcinogenicity

Salbutamol sulphate and ipratropium bromide were tested individually for neoplastic properties in several carcinogenicity studies. After oral administration of salbutamol sulphate in rats, but not in mice, hamsters and dogs, an increased incidence of leiomyomas of the mesovarium was observed at dosages about ≥ 20-fold higher than inhalation MRHDD. The development of the leiomyomas was found to be preventable by simultaneous administration of beta-blockers. These findings were assessed to be species specific and therefore without clinical relevance, consequently not leading to any restriction of the clinical use of salbutamol sulphate.

Ipratropium bromide revealed no carcinogenic potential when tested orally in mice and rats.

Immunogenicity

No evidence was found of any immunotoxicological effect caused by COMBIVENT or its individual active ingredients.

Availability
Solution for inhalation in unit dose vials: below 100 unit dose vials in paper box.

Storage Store in a safe place out of the reach of children!
Store below 30°C!
Protect from light!

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