適喘樂® 舒沛噴®吸入劑 2.5 微公克
SPIRIVA® RESPIMAT® 2.5mcg, Solution for Inhalation

衛署藥輸字第 025033 號

成分

每噴一次(puff)含 tiotropium 2.5 mcg，相當於 tiotropium bromide monohydrate (= tiotropium bromide) 3.124 mcg
噴二次為一個劑量(INN = tiotropium bromide)
賦形劑：
benzalkonium chloride、disodium edetate、純水、用以調整酸鹼值之鹽酸

藥理學性質

藥物類別：抗膽鹼劑（Anticholinergics）
ATC代碼：R03B B04
Tiotropium bromide為長效、專一性的抗毒蕈鹼藥物(臨床醫學上常稱為抗膽鹼劑)，對各種接受體亞型（M_1至M_5）均有相似的親和力。在呼吸道中，抑制平滑肌的M_3接受體，可以使平滑肌放鬆。過去在源自人類和動物的接受體以及體外分離器官中，已證實此拮抗效果具有競爭性及可逆性等性質。在非臨床體外與體內試驗顯示，支氣管保護效果與劑量高低有關，且可持續長達24小時以上。藥效持續時間長可能導因於其自M_3接受體上解離的速度十分緩慢；其解離半衰期顯著長於ipratropium。Tiotropium bromide為四級銨(N-quaternary)之抗膽鹼劑，吸入後可局部選擇性地作用於支氣管，在產生有效治療濃度時仍還不會產生全身性抗膽鹼作用。在體外功能性試驗中，tiotropium與M_2接受體解離的速度較M_3快，因此以動力學的角度而言，對M_3接受體的選擇性高於M_2。
由於tiotropium與接受體作用強且解離速度慢，因此在臨床上治療COPD和氣喘病人時，具有顯著且長效的支氣管擴張作用。吸入tiotropium後產生的支氣管擴張作用主要是一種局部（針對呼吸道的）而非全身性效果。

慢性阻塞性肺疾（COPD）

針對COPD的第三期臨床試驗計畫包括2個為期一年、2個為期12週與2個為期4週的隨機分組、雙盲研究，共收錄2901名COPD病人(其中1038人使用5μg tiotropium)。為期一年的研究計畫包括2個以安慰劑為對照組的試驗。2個為期12週的試驗則以活性藥物(ipratropium)與安慰劑為對照組。6個臨床試驗均納入肺功能評量，此外，2個為期一年的研究中亦評量呼吸困難、健康相關生活品質與對病情惡化之影響等健康結果指標。

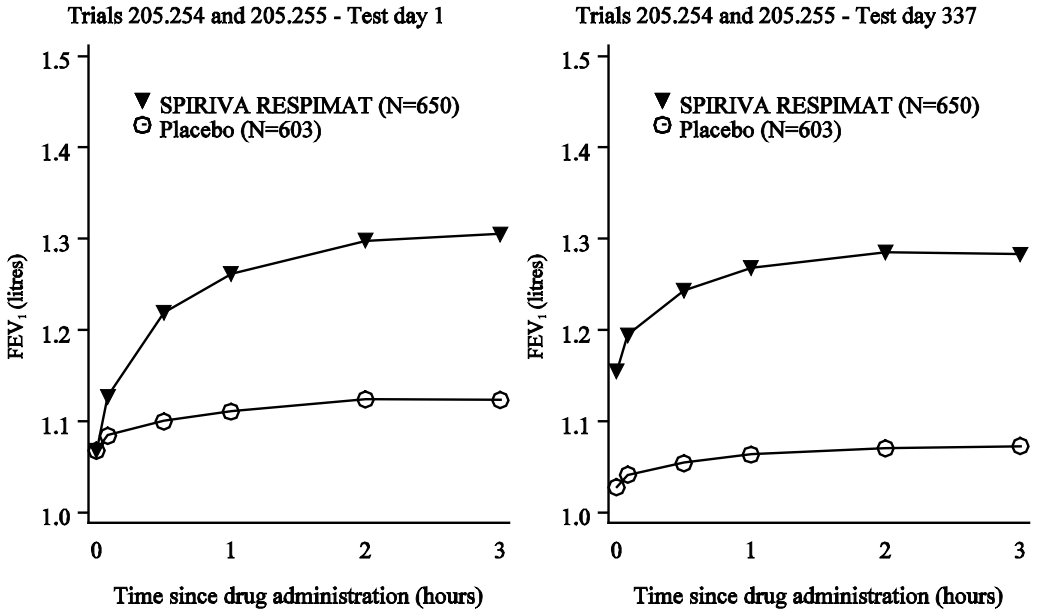
以安慰劑為對照組的試驗

<u>肺功能</u>

相較於安慰劑，每天使用一次 SPIRIVA RESPIMAT，在使用第一次劑量後 30 分鐘內可使肺功能(第一秒吐氣量 FEV_1與用力肺活量 FVC)明顯改善。肺功能改善效果在穩定狀態時可持續 24 小時（FEV_1平均改善：0.122 公升；95% CI：0.106 至 0.138 公升，$p<0.0001$）。藥效可於

一週內達到穩定狀態。
依據病人每日之紀錄， SPIRIVA RESPIMAT相較於安慰劑可顯著改善早晨與晚上的最高吐氣流速（peak expiratory flow rate，PEFR）。相較於安慰劑，使用SPIRIVA RESPIMAT可降低使用急救用支氣管擴張劑的使用次數。
SPIRIVA RESPIMAT的支氣管擴張作用在48週使用期間均能持續維持，且不會產生耐藥性。

圖1：第1天和第337天時，各時間點下(施用試驗藥物之前與之後)的平均FEV_1（公升）（數據由兩項為期1年的平行組試驗彙整而成）*



*平均值已中心化處理、是否抽菸及基期效果等因子校正。SPIVIRA RESPIMAT組和安慰劑組分別共有545人和434人完成第337天的測試。其餘受試者的數據是以最後觀察值或最差觀察值推估法插補而得。

在為期一年的長期研究中，可顯現以下健康結果指標療效：

(a) 相較於安慰劑，SPIRIVA RESPIMAT可顯著改善呼吸困難症狀（以Transition Dyspnoea Index評估）（平均改善1.05單位，95% CI：0.73至1.38單位，p<0.0001）。於整個治療期間均可有效維持改善效果。

(b) 在2個為期一年的研究結束時，相較於安慰劑組，SPIRIVA RESPIMAT組病人對其生活品質的評估結果（以聖喬治呼吸問卷[St. George's Respiratory Questionnaire]評量）的總分平均改善3.5單位(95% CI：2.1至4.9，p<0.0001)。降低4單位可視為具臨床意義。

(c) COPD惡化

在三項為期一年、隨機分組、雙盲、以安慰劑為對照組的臨床試驗中，SPIRIVA RESPIMAT的治療可使COPD惡化的風險較安慰劑組顯著降低。COPD惡化的定義為「出現至少兩項持續三天（含）以上的呼吸系統事件或症狀、且需要改變治療（處方抗生素和/或全身性皮質類固醇，及/或原本處方的呼吸系統用藥有重大改變）」。SPIRIVA RESPIMAT的治療亦可降低因COPD惡化而住院的風險（在檢定力充足的大型COPD惡化試驗中達到顯著意義）。

針對兩項第三期試驗所進行的整合分析以及另一項COPD惡化試驗所進行的獨立分析，其結果呈現於**表1**。試驗期間，受試者可併用除了抗膽鹼藥物及長效型β-促效劑以外的任何呼吸系統用藥（亦即速效型β-促效劑、吸入性皮質類固醇和黃嘌呤類藥物）。另一項COPD惡化試驗還額外允許受試者併用長效型β-促效劑。

表1：於中度至極重度COPD病人，COPD惡化事件與COPD惡化而住院事件之統計分析

試驗（SPIRIVA組人數，安慰劑組人數）	評估指標	SPIRIVA RESPIMAT	安慰劑	風險下降百分比 (95% CI)[a]	p值
為期一年之第III期試驗，整合分析[d] (670, 653)	首次出現COPD惡化的時間(天數)	160[a]	86[a]	29 (16至40)[b]	<0.0001[b]
	平均惡化發生率(人年)	0.78[c]	1.00[c]	22 (8至33)[c]	0.002[c]
	首次出現COPD惡化而住院的時間	NA[e]	NA[e]	25 (-16至51)[b]	0.20[b]
	惡化而住院之平均發生率(人年)	0.09[c]	0.11[c]	20 (-4至38)[c]	0.096[c]
為期一年之第IIIb期惡化試驗 (1939, 1953)	首次出現COPD惡化的時間(天數)	169[a]	119[a]	31 (23至37)[b]	<0.0001[b]
	平均惡化發生率(人年)	0.69[c]	0.87[c]	21 (13至28)[c]	<0.0001[c]
	首次出現COPD惡化而住院的時間	NA[e]	NA[e]	27 (10至41)[b]	0.003[b]
	惡化而住院之平均發生率(人年)	0.12[c]	0.15[c]	19 (7至30)[c]	0.004[c]

[a] 首次事件發生的時間：當25%病人發生至少一件COPD惡化事件/COPD惡化而住院事件的天數。於試驗A，安慰劑組25%病人發生一件惡化事件的時間是在第112天，而SPIRIVA RESPIMAT組則是在第173天(p=0.09)；於試驗B，安慰劑組25%病人發生一件惡化事件的時間是在第74天，而SPIRIVA RESPIMAT組則是在第149天(p<0.0001)。

[b] 危險比（hazard ratio）係以Cox比例危險模型(Cox proportional hazard model)估算而得。風險下降百分比為100(1 - 危險比)。

[c] 採用Poisson迴歸。風險下降百分比為100(1 - 發生率比率)。

[d] 試驗設計時即已明定數據的整合方式。兩項為期一年之試驗的個別分析結果顯示，惡化評估指標獲得顯著改善。

[e]發生COPD惡化而住院的受試者比例未達25%。

探討tiotropium並以活性藥物為對照組的長期試驗

一項長期、大規模、隨機分組、雙盲、以活性藥物為對照組且觀察期最長為3年的試驗，比較SPIRIVA RESPIMAT和SPIRIVA HANDIHALER的療效與安全性（5,711名受試者使用SPIRIVA RESPIMAT 5微公克；5,694名受試者使用SPIRIVA HANDIHALER 18微公克）。主要療效及安全性評估指標為首次出現COPD惡化的時間，以及任何原因死亡的時間；在一項子試驗中（納入906人），評估指標為低谷FEV_1。

結果顯示，首次出現COPD惡化的時間在SPIRIVA RESPIMAT組相較於SPIRIVA HANDIHALER組的危險比為0.98 (95% CI為0.93至1.03)，其差異未達統計顯著。

首次出現COPD惡化的時間的中位數，在SPIRIVA RESPIMAT組為756天，在SPIRIVA HANDIHALER組則為719天。

子試驗顯示SPIRIVA RESPIMAT組的低谷FEV_1與SPIRIVA HANDIHALER組相近。SPIRIVA RESPIMAT在低谷FEV_1上與SPIRIVA HANDIHALER之間的平均差異為-0.010公升(95% CI：-0.038至0.018)。

試驗期間任何原因死亡率在SPIRIVA RESPIMAT組和SPIRIVA HANDIHALER組相近，SPIRIVA RESPIMAT相較於SPIRIVA HANDIHALER的危險比為0.96 (95% CI為0.84至1.09）。

氣喘

成人病人

治療氣喘的臨床療效及安全性

針對持續性氣喘所設計的第三期臨床試驗計畫，包括兩項為期一年的隨機分組、雙盲、安慰劑對照試驗，共收錄 907 名正併用吸入性皮質類固醇(ICS)(每日使用≧800μg budesonide 或等效藥物)和長效型 β-促效劑 (LABA) 仍有症狀的重度持續性氣喘病人 (其中 453 人使用 SPIRIVA RESPIMAT)。病人在過去一年有至少一次氣喘惡化的病史。前述試驗均納入肺功能評量、包含惡化程度的症狀評估及嚴重惡化健康相關生活品質評量。

PrimoTinA-asthma 試驗

在兩項為期一年的試驗中(受試者在至少接受 ICS + LABA 的維持療法時，仍有氣喘症狀)，在背景治療外加上 SPIRIVA RESPIMAT 時，肺功能表現優於安慰劑組、且具臨床意義的改善。

第 24 週時，最高和最低 FEV_1 的平均改善量分別為 0.110 公升 (95% CI：0.063 至 0.158 公升，p<0.0001) 和 0.093 公升 (95% CI：0.050 至 0.137 公升，p<0.0001)。相較於安慰劑，改善肺功能的效果持續了 24 小時。

PrimoTinA-asthma 試驗中，相較於接受 ICS+LABA+安慰劑(N=454)治療組別，有症狀的氣喘病人(N=453)接受 ICS+ LABA+tiotropium 治療後，嚴重氣喘惡化(severe asthma

exacerbation)風險減低 21%。每年每位病人嚴重氣喘惡化風險的平均降幅為 20%。
氣喘惡化風險下降 31%，且每年每位病人氣喘惡化風險的平均降幅為 24% (參見表 2)。

表 2：接受 ICS (每日使用≧800μg budesonide 或等效藥物) + LABA 治療時仍有症狀的病人所經歷的氣喘惡化(PrimoTinA-asthma 試驗)

試驗	評估指標	於至少含 ICS[a]/LABA 的背景治療中加入 SPIRIVA® RESPIMAT® (N=453)	於至少含 ICS[a]/LABA 的背景治療中加入安慰劑 (N=454)	風險下降百分比 (95% CI) [a]	p 值
兩項為期一年的第三期試驗，合併分析	首次嚴重氣喘惡化前所經天數	282[c]	226[c]	21(0, 38)	0.0343
	每人每年嚴重氣喘惡化的平均次數	0.530	0.663	20(0, 36)	0.0458
	首次氣喘惡化前所經天數	315[c]	181[c]	31(18, 42)	<0.0001
	每人每年氣喘惡化的平均次數	2.145	2.835	24(9, 37)	0.0031

[a]每日使用≧800μg budesonide 或等效藥物

[b]危險比、信賴區間和 p 值，均以僅用治療作為效果的 Cox 比例危險模型算出。風險下降百分比為 100 (1–危險比)。

[c]首次事件發生前所經時間：經歷至少一件嚴重氣喘急性發作≠惡化事件的受試者比例達到 25%/50% 時的治療天數。

兒童病人

針對患有持續性氣喘兒童(1-17歲)所設計的第三期臨床試驗計畫包括：
•青少年(12-17歲)：一項為期12週隨機分組、雙盲、安慰劑對照試驗，收錄392名氣喘病人(其中130名使用SPIRIVA RESPIMAT)
•兒童(6-11歲)：一項為期12週隨機分組、雙盲、安慰劑對照試驗，收錄401名氣喘病人(其中130名使用SPIRIVA RESPIMAT)

在這些試驗中，病人已經穩定使用高劑量ICS合併至少一種控制型藥物治療；或是穩定使用

中劑量ICS合併至少兩種控制型藥物治療。

在為期 12 週的 PensieTinA-asthma 試驗中(受試者在併用至少中等劑量以上的 ICS 和一種或一種以上藥物的維持療法時，仍有氣喘症狀)，在背景治療外加上 SPIRIVA RESPIMAT 時，肺功能表現優於安慰劑組，然而在最高和最低 FEV_1變化上沒有統計學意義。

- 第 12 週時，最高和最低 FEV_1的平均改善量分別為 0.090 公升(95% CI: -0.019 至 0.198 公升，p=0.1039)和 0.054 公升(95% CI：-0.061 至 0.168 公升，p=0.3605)
- 第 12 週時，SPIRIVA RESPIMAT 可顯著改善早晨與晚上的最高吐氣流(peak expiratory flow，PEF) (早晨 17.4 公升/分鐘；95% CI：5.1 至 29.6 公升/分鐘；晚上 17.6 公升/分鐘；95% CI：5.9 至 29.6 公升/分鐘)。

兒童(6-11歲)

在為期 12 週的 VivaTinA-asthm 試驗中(受試者在併用至少中等劑量以上的 ICS 和一種或一種以上藥物的維持療法時，仍有氣喘症狀)，在背景治療外加上 SPIRIVA RESPIMAT 時，肺功能表現顯著優於安慰劑組。

- 第 12 週時，最高和最低 FEV_1的平均改善量分別為 0.139 公升(95% CI：0.075 至 0.203 公升，p<0.0001)和 0.087 公升(95% CI：0.019 至 0.154 公升，p=0.0117)

藥物動力學性質

Tiotropium bromide為一種非旋光活性 (non-chiral)的四級銨化合物，略溶於水，現有的吸入液係以Respimat吸入器投藥。吸入的藥物約有40%進入於目標器官肺部，其餘的量則進入於腸胃道。下述藥物動力學數據有些是使用比建議劑量高的劑量。

吸收：

年輕健康自願者吸入之後，其從尿液排除的數據顯示，吸入的藥物約有33%到達全身循環。Tiotropium bromide口服溶液的絕對生體可用率為2-3%。也因此預期食物不會影響tiotropium的吸收。在吸入後5-7分鐘時可觀察到tiotropium的最高血中濃度。在穩定狀態下，COPD病人身上可達到10.5 pg/ml的tiotropium最高血中濃度，接著以多室（multi-compartmental）方式快速下降。穩定狀態下之最低血中濃度為1.60 pg/ml。

氣喘病人施用相同劑量後 5 分鐘時，可達到 5.15 pg/mL 的穩定態 tiotropium 最高血中濃度。

分佈：

此藥物與血中蛋白質的結合率為 72%，分佈體積（volume of distribution）為 32 L/kg。無法得知肺部的局部濃度，但此種給藥方式顯示在肺部應該有更高的濃度。在大鼠的實驗顯示，tiotropium bromide 無法穿透血腦屏障。

生物轉化（Biotransformation）：

Tiotropium bromide 的生物轉化率極低，其證據來自年輕健康自願者以靜脈注射後，有 74%藥物以原型經由尿液排除。

Tiotropium bromide 為一酯類，可不經由酵素而切斷為醇類 N-methylscopine 與 dithienylglycolic acid，兩者皆不會與毒蕈鹼接受體結合。

在人類肝臟微粒體(microsomes)與人類肝細胞的體外實驗中，顯示有一些藥物(小於 20%之靜脈注射劑量)被細胞色素 P450 (cytochrome P450，CYP）以氧化方式代謝，接著與麩胺基硫(glutathione)結合成第二階段代謝物（phase II-metabolites）。肝臟微粒體的體外研究顯示，此酵素代謝途徑會被 CYP 2D6（及 3A4）抑制劑（如 quinidine、ketoconazole 與 gestodene）所抑制，顯示 CYP 2D6 及 3A4 與其代謝途徑有關，這些酵素負責小部分藥物的排除。即使超過治療劑量的 tiotropium bromide，亦不會抑制人類肝臟微粒體之 CYP 1A1、1A2、2B6、2C9、2C19、2D6、2E1 或 3A。

清除：

經 COPD 病人吸入後，tiotropium 的有效半衰期為 27 至 45 小時。

於氣喘病人中，有效半衰期為 34 小時。

年輕健康自願者以靜脈注射後之總清除率為 880 ml/min。靜脈注射的 tiotropium bromide 主要以原型經尿液排除（74%）。COPD 病人以溶液形式吸入時，有 18.6%（0.93 μg）的劑量經尿液排除，其餘大部分未被腸道吸收的藥物則經由糞便排除。

於氣喘病人中，穩定狀態下給藥後 24 小時內，會有 11.9%（0.595 μg）的劑量以原型經由尿液排除。

Tiotropium 之腎臟清除率超過肌酸酐（creatinine）之清除率，表示它會經由主動分泌排泄到尿液中。長期以每日一次的頻率吸入藥物後，第 7 天時即已達到藥物動力學上的穩定狀態，其後體內不再累積藥物。

線性/非線性：Tiotropium 在治療範圍內，無論採用何種劑型，其藥物動力學均呈線性關係。

老年病人：

與其他主要由腎臟排除之藥物相同，可以預期在年紀較大之病人中 tiotropium 的腎臟清除率較低（小於 65 歲之 COPD 病人的清除率為 347 mL/min，而大於/等於 65 歲之 COPD 病人則為 275 mL/min）。這並未導致 $AUC_{0-6,ss}$ 或 $C_{max,ss}$ 數值出現顯著上升。於氣喘病人中，並未發現 tiotropium 的暴露量隨年齡變化的現象。

兒童病人：

在兒童 (6-17 歲)和成人氣喘病人中，tiotropium 的最高和總暴露量沒有不同。1~5 歲氣喘病人的 $fe_{0-3h,ss}$(以尿液評估)，較 6 歲以上和成人氣喘病人低 52 至 60%；以身體表面積調整後的 $fe_{0-3h,ss}$ 數據，在所有年齡組別是相當的。試驗中的 1 至 5 歲病人是以面罩使用 SPIRIVA® RESPIMAT®。

腎功能不全病人：

輕度腎功能**不全**（CL_{CR} 50-80 ml/min）的 COPD 病人持續每日吸入一次 tiotropium 而達到穩定狀態後，$AUC_{0-6,ss}$ 會稍高於腎功能正常（CL_{CR} >80 ml/min）的病人（增幅為 1.8%至 30%），而 $C_{max,ss}$ 則相近。在中度或重度腎功能不全（CL_{CR} ＜50 ml/min）之 COPD 病人，靜脈注射 tiotropium bromide 會使總暴露量增加為腎功能正常之 COPD 病人的兩倍（AUC_{0-4h} 高出 82%而 C_{max} 高出 52%），以乾粉吸入之後的血中濃度亦有同樣情形。

在輕度腎功能受損（CL_{CR} 50-80 ml/min）的氣喘病人中，吸入 tiotropium 不會使暴露量相較於腎功能正常者出現有意義的上升現象。

肝功能不全病人：

肝功能不全對於 tiotropium 之藥物動力學應不會有影響。Tiotropium 主要是經由腎臟排除（在

年輕健康自願者佔 74%）以及藉著簡單的非酵素性酯斷裂形成無藥物活性的代謝物。

適應症

慢性阻塞性肺疾(包括慢性支氣管炎及肺氣腫)之維持治療及降低惡化。
適用於已接受吸入性皮質類固醇合併其他控制型藥物仍未控制症狀之 6 歲及以上的嚴重持續性氣喘病人，作為維持性支氣管擴張劑附加治療。

用法用量

本藥須由醫師處方使用
SPIRIVA® RESPIMAT®推薦劑量為每日一次，每次定時按二次噴藥，相當於 tiotropium 每日 5 微公克(請參見「使用說明」使用本藥)。
治療氣喘時，須使用數個劑量 SPIRIVA RESPIMAT 之後才會顯現完整治療效益。
特殊族群：
年老者可依推薦劑量使用。
腎功能受損病人可依推薦劑量使用。但是與其他主要經由腎臟排泄之藥物相同，當使用於中度到嚴重腎功能受損病人時，需嚴密監控病情。
肝功能受損病人可依推薦劑量使用。
兒童族群：
COPD 通常不會發生於兒童。在氣喘病人中，SPIRIVA RESPIMAT 在 6~17 歲病人的建議劑量是定時每日一次，每次按二次噴藥(請參見「使用說明」使用本藥)。
SPIRIVA RESPIMAT 尚無小於 6 歲氣喘病人之安全性及療效資料。

禁忌

SPIRIVA RESPIMAT 不可用於對阿托品及其衍生物（如 ipratropium、oxitropium）或本藥之任一成分有過敏史之病人。

特殊警語及注意事項

SPIRIVA RESPIMAT 為每日一次的維持性支氣管擴張劑，不可用於急性支氣管痙攣的最初治療，亦即不可用於急救治療，亦不得用以緩解急性症狀。若遭遇急性發作，應使用速效型 β-2-促效劑(short-acting beta-2-agonist)。
治療氣喘時，SPIRIVA RESPIMAT 不可作為第一線療法或單獨療法使用。應建議氣喘病人在開始使用 SPIRIVA RESPIMAT 之後，仍應繼續接受吸入性皮質類固醇之抗發炎療法即使其症狀獲得改善。
在吸入 SPIRIVA RESPIMAT 後，有可能會發生立即的過敏反應。
與其它抗膽鹼性劑相同，狹角性青光眼、攝護腺肥大、或膀胱頸阻塞之病人應小心使用本藥。
吸入性藥物可能會因吸入方式而引發支氣管痙攣(inhalation-induced bronchospasm)，若發生，應立即停用 SPIRIVA RESPIMAT。

與其他主要經由腎臟排除的藥物相同，當 SPIRIVA RESPIMAT 用於中度至嚴重腎功能受損（肌酐酸清除率小於或等於每分鐘 50 毫升）之病人時，應密切監測。
應指導病人正確使用 SPIRIVA RESPIMAT 的方法。必須小心不可讓藥液或噴霧進入眼睛；眼睛疼痛或眼睛不舒服、視線模糊、與充血性結膜炎所造成的紅眼有關之視覺上有光影或多彩影像、及角膜水腫可能是急性狹角性青光眼的症狀。若合併發生以上症狀，應立刻請教醫師。
使用縮瞳眼用滴劑並非有效的治療方法。

使用 SPIRIVA RESPIMAT 每日不可超過一次。
SPIRIVA 藥罐(cartridge)只可以用 RESPIMAT 吸入器來使用。
賦形劑
Spiriva Respimat 含氯化苯二甲羥胺(Benzalkonium chloride).
本藥每噴含有氯化苯二甲羥胺(benzalkonium chloride) 0.0011mg。
氯化苯二甲羥胺(Benzalkonium chloride)可能會造成喘息(wheezing)和呼吸困難。氣喘病人發生這些不良事件的風險增加。

藥物交互作用

雖然尚未完成藥物交互作用之正式研究，臨床上 tiotropium bromide 曾與若干常用於治療 COPD 和氣喘之藥物（包括擬交感神經支氣管擴張劑、methylxanthines、口服及吸入性類固醇、抗組織胺、化痰劑、白三烯調節劑、cromone 類藥物，以及抗 IgE 療法）併用，並無證據顯示會發生藥物交互作用。
過去並未發現 COPD 病人經常併用的藥物（長效型 β-促效劑、吸入性皮質類固醇，及兩者之組合）會影響 tiotropium 的暴露量。
由於 tiotropium bromide 與其他含抗膽鹼性藥物長期併用的影響尚未經研究，故不建議 SPIRIVA RESPIMAT 與其他含抗膽鹼性藥物長期併用。

生育能力、懷孕與哺乳

懷孕與哺乳

目前沒有關於 SPIRIVA 使用於孕婦之臨床報告。臨床前試驗並未顯示 SPIRIVA 對於懷孕、胚胎/胎兒發育、分娩或出生後發育，可能造成直接或間接的傷害。

懷孕

關於 tiotropium 於孕婦中的使用經驗，目前相關資料十分有限。臨床前試驗並未顯示 tiotropium 在臨床相關的劑量下，可能具有生殖毒性而造成直接或間接的傷害。
作為防範措施，建議懷孕期間應避免使用 SPIRIVA RESPIMAT。

哺乳

目前沒有關於 tiotropium 使用於授乳婦女之臨床報告。而齧齒類動物之乳汁研究發現，少量的 tiotropium 會分泌至乳汁。
因此，SPIRIVA RESPIMAT 不應使用於懷孕或授乳婦女，除非所預期的利益超過可能發生於未出生的孩子或嬰兒的風險。

生育能力

目前沒有關於 tiotropium 對生育能力之影響的臨床報告。一項使用 tiotropium 進行的臨床前試驗並未顯示本藥對生育能力有任何不良影響之跡象。

對駕駛和操作機器的影響

尚未有本藥對影響駕駛和操作機器的研究。若發生眩暈或視力模糊，可能會影響駕駛和操作機器的能力。

副作用

下列副作用中，許多可被歸因於 SPIRIVA RESPIMAT 的抗膽鹼作用性質。
藥物不良反應，是由臨床試驗所得之資料及上市後藥品處方經驗中的自發性通報資料所發現。
COPD 的臨床試驗資料包括 7 個為期 4 週至 1 年以安慰劑為對照組之臨床試驗，共有 3,282 名 SPIRIVA RESPIMAT 組受試者，共計 2,440 人次年的使用經驗。
氣喘的臨床試驗資料包括 12 個為期 12 週至 1 年以安慰劑為對照組之臨床試驗，共有 1,930

名 tiotropium 組受試者，共計 1,128 人次年的 tiotropium 使用經驗。

代謝與營養異常：

- 脫水

神經系統失調：

- 暈眩
- 失眠

眼睛失調：

- 青光眼
- 眼球內壓上升
- 視力模糊

心臟失調：

- 心房顫動
- 心悸
- 上心室性心搏過速
- 心搏過快

呼吸、胸腔及縱隔腔不適：

- 咳嗽
- 鼻出血
- 咽頭炎
- 發聲困難
- 支氣管痙攣
- 喉炎
- 竇炎

胃腸失調：

- 口乾，通常輕微
- 便秘
- 口咽念珠菌感染
- 吞嚥困難
- 胃食道逆流疾病
- 牙齦炎
- 舌炎
- 口腔炎
- 腸阻塞包括麻痺性腸阻塞

皮膚與皮下組織失調，免疫系統失調：

- 皮疹
- 癢
- 血管神經性水腫
- 蕁麻疹
- 皮膚感染與皮膚潰瘍
- 皮膚乾燥
- 其他過敏反應(包括立即性的反應)

肌肉骨骼與結締組織異常：

- 關節腫大

腎臟與泌尿失調：
- 尿液滯留(易發生於有潛在病因的男性)
- 排尿困難
- 尿道感染

兒童族群：
兒童族群發生不良反應的頻率、類型和嚴重程度與成人族群類似。

過量
高劑量的 SPIRIVA RESPIMAT 可能導致抗膽鹼性徵兆及症狀發生。
健康自願者每天接受 tiotropium 吸入液 40 微公克(µg)，持續 14 天後，除了與劑量相關〔每日劑量 10 - 40 微公克(µg)〕的口乾/喉嚨乾及鼻黏膜乾燥副作用及自第七天起唾液明顯減少外，並無其他副作用。六個長期研究以慢性阻塞性肺疾(COPD)病人為對象，每日接受 tiotropium 吸入液 10 微公克(µg)為期 4 - 48 週，未觀察到具統計意義之副作用。

毒理學
小鼠、大鼠及狗之吸入及口服產生急性毒性較低，因此，人類藥物過量時，未必會產生急性毒性作用。單一劑量安全性之藥理研究顯示，會出現所預期的抗膽鹼性藥物作用，包括瞳孔放大、心跳速率增加及延長胃腸排空時間。
在小鼠、大鼠及狗之重複劑量試驗，發生與 tiotropium bromide 之抗膽鹼性相關的副作用，包括瞳孔放大、心跳速率增加、便秘、體重增加率減少、唾液及淚腺的分泌減少。其他相關的改變包括：在大鼠造成上呼吸道輕微的刺激，可由鼻炎、鼻腔及喉嚨上皮的改變而得到證實；在公鼠身上造成前列腺炎並伴隨膀胱內出現蛋白質狀沉積及膀胱結石；增加大鼠肺臟重量以及降低狗的心臟重量。
以兔子及大鼠進行生殖毒性試驗發現，在使母體產生毒性的劑量下，才會對於懷孕、胚胎/胎兒發育、分娩以及產後嬰兒的發育具有傷害性。一項於大鼠身上進行的一般繁殖及生育能力試驗發現：在任何試驗劑量下，均無跡象顯示藥物對接受治療之親代或其子代的生育或交配能力有任何不良影響。
在出生後第 7 天至性成熟的青年大鼠之試驗，觀察到與重複劑量毒性試驗相同的直接和間接藥理變化以及鼻炎。沒有觀察到全身性毒性，並且在關鍵發育參數、氣管或關鍵器官發育上沒有觀察到毒理學相關的影響。
進行一系列體內及體外的突變性試驗，發現 tiotropium bromide 並不會造成原核生物及真核生物基因突變、染色體傷害或是原發性 DNA 損傷。

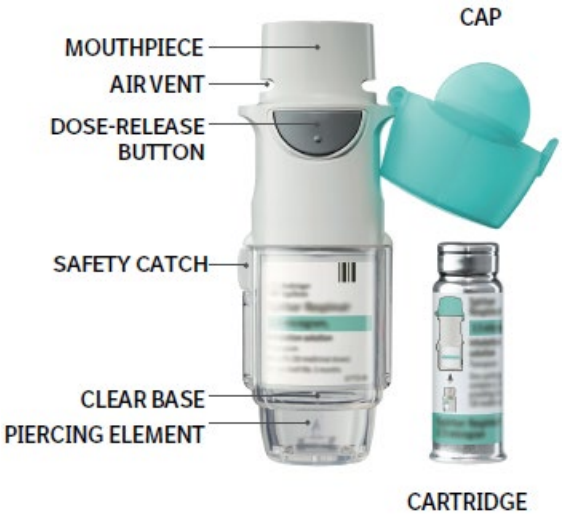
貯存
請勿冷凍!
請存放於兒童伸手不及處！
請存放於 30°C 以下!

包裝
一罐 4.0 毫升鋁罐附一個舒沛噴吸入器。
保存期限：標示於外盒、瓶身及吸入器。

使用說明

請詳閱並仔細遵守下列指示。

兒童使用 SPIRIVA RESPIMAT 須有成人協助。



CAP 蓋子　　MOUTHPICE 口含器　　AIR VENT 通氣孔

DOSE-RELEASE BUTTON 給藥按鈕　　SAFETY CATCH 安全扣

CLEAR BASE 透明底座　　PIERCING ELEMENT 穿刺裝置　　CARTRIDGE 藥罐

拋棄式 RESPIMAT 是一種吸入裝置，可產生慢速移動的氣霧供病人吸入

拋棄式 RESPIMAT 是供單一病人多次使用的裝置。

- 如果您的SPIRIVA RESPIMAT吸入器已超過7天未使用，請先朝向地面噴1次。
- 如果您的SPIRIVA RESPIMAT吸入器已超過21天未使用，請依據「初次使用」步驟4至6操作直到出現霧狀藥液後，再重複步驟4至6的操作3次。

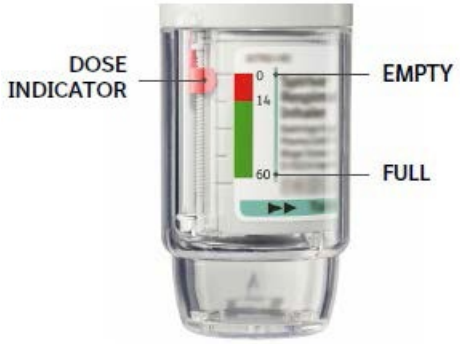
SPIRIVA RESPIMAT 吸入器與 SPIRIVA RESPIMAT 藥罐

如何保養您的 SPIRIVA RESPIMAT

用濕布或濕紙巾清潔口含器及口含器內的金屬部份，每週至少擦拭一次。

口含器如出現輕微褪色，不會影響 SPIRIVA RESPIMAT 吸入器功能。

如何使用新的 SPIRIVA RESPIMAT 吸入劑



DOSE INDICATOR 劑量顯示器

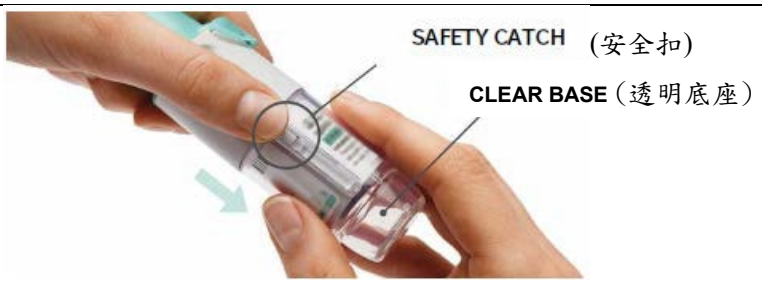
EMPTY 空的

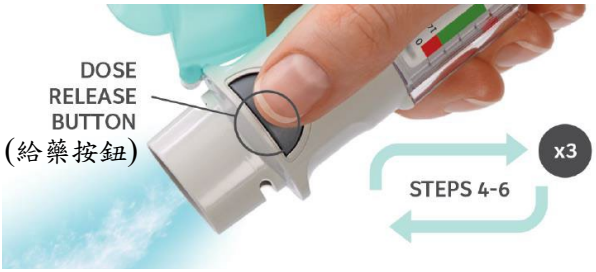
FULL 滿的

依照下方指示使用(2噴/一天一次)，本藥可提供 60噴(30個劑量)。

- 劑量顯示器可顯示大約還剩多少藥。
- 當指針進入刻度上的紅色區域時，代表大約還剩 7 天(14 噴)的藥量。此時你應請醫師開立新的處方，取得新的 SPIRIVA RESPIMAT 吸入劑。
- 一旦劑量顯示器達到紅色刻度的頂端(亦即 30 個劑量已全部用完)，表示 SPIRIVA RESPIMAT 吸入劑已空了並會自動鎖住，此時，透明底座將無法再被旋轉。
- SPIRIVA RESPIMAT 吸入劑從初次使用算起，最多只能用 3 個月，即使藥液尚未用完，也應該將 SPIRIVA RESPIMAT 吸入劑丟棄，不可再使用。
-

初次使用 SPIRIVA RESPIMAT 吸入劑的準備步驟

1. <u>移除透明底座</u> • 蓋子必須蓋緊 • 按壓住安全扣並用另一隻手拔下透明底座。	
2. <u>插入藥罐</u> • 將藥罐的窄端推向吸入器，直到發出「卡嗒」聲。 • 將吸入器放在堅固表面上，並扎實地下壓，將藥罐推入吸入器(直到發出「卡嗒」聲)，以確保藥罐已完全裝入吸入器。	

3. <u>裝回透明底座</u> • 裝回透明底座，直至發出卡嗒聲。	
4. <u>旋轉</u> • 確保蓋子蓋緊。 • 將透明底座依標籤上之箭頭方向旋轉，直到聽到「卡嗒」聲(約轉半圈)。	
5. <u>打開</u> • 打開蓋子直到完全打開。	
6. <u>按壓</u> • 將SPIRIVA RESPIMAT 吸入器朝向地面。 • 按壓給藥按鈕。 • 蓋上蓋子。 • 重覆步驟4、5、6，直到出現霧狀的藥液。 • 在出現霧狀的藥液後，再重複步驟4、5、6三次。 現在你的 SPIRIVA RESPIMAT 吸入劑已備妥可供使用。	

如何每日使用 SPIRIVA RESPIMAT 吸入劑
您每天只需要使用此吸入器一次。
每一次使用吸入器時請噴兩下。

旋轉 • 確保蓋子蓋緊。 • 將透明底座依標籤上之箭頭方向旋轉，直到**聽到「卡嗒」聲**(約轉半圈)。	
打開 • 打開蓋子直到完全打開。	
按壓 • 慢慢地將肺中空氣完全呼出。 • 緊閉雙唇含住口含器但勿遮住通氣孔。 • 通過口腔緩慢深呼吸時，按下給藥按鈕並繼續呼吸。 • 屏住呼吸10秒或儘可能地延長舒適的屏氣時間。 • 重複旋轉，打開，按壓步驟共2次。 • 蓋緊蓋子直到下次再使用SPIRIVA RESPIMAT吸入劑。	 （通氣孔）

嚴重事件

如果您出現與本裝置有關的任何嚴重事件，請告知您的醫師或藥師。您也可以直接向百靈佳殷格翰公司通報嚴重事件，或透過食品藥物管理署藥物食品化妝品上市後品質管理系統(https://qms.fda.gov.tw/)通報。藉由通報嚴重事件，您能幫助提供更多與此裝置有關的安全性資訊。

製造廠/廠址

Boehringer Ingelheim Pharma GmbH & Co. KG

Binger Strasse 173,
55216 Ingelheim am Rhein
Germany
國外許可證持有者
Boehringer Ingelheim International GmbH
Ingelheim am Rhein, Germany

藥商：台灣百靈佳殷格翰股份有限公司
地址：台北市民生東路三段 2 號 12 樓

19 MAR 2021

修訂日期：2021 年 07 月
核定日期 :2021 年 09 月

常見問題

無法將藥罐夠深地插入。

插入藥罐之前，您是否不慎轉動了透明底座？ 請打開蓋子，按壓給藥按鈕，再插入藥罐。
您是否用藥罐較寬的一端插入？ 請以藥罐較窄的一端插入。

我無法按下給藥按鈕。

你是否有轉動透明底座？ 如果沒有，請轉動透明底座，直到聽到咔嗒聲（半圈）。
RESPIMAT上的劑量顯示計是否指向0？ RESPIMAT吸入器會在噴60次之後自動鎖住。請組裝並使用新的RESPIMAT吸入器。

我無法轉動透明底座。

你是否已轉動透明底座？ 如果透明底座已經轉動，請依照「每日使用步驟」所述的「打開」和「按壓」步驟用藥。
RESPIMAT上的劑量顯示計是否指向0？ RESPIMAT吸入器會在噴60次之後自動鎖住。請使用新的RESPIMAT吸入器。

RESPIMAT上的劑量顯示計太早達到0。

您是否依照指示來使用RESPIMAT（每日一次，每次噴兩下）？ 如果每日使用一次，每次噴兩下，RESPIMAT可持續使用30天。
插入藥罐之前，您是否轉動透明底座？ 無論是否插入藥罐，透明底座每轉動一圈，劑量顯示計都會計數。
您是否經常為了檢查RESPIMAT是否正常運作而向空中噴藥？ 在您準備好RESPIMAT之後，如果每天使用，就不需要進行噴藥檢測。
您是否將藥罐插入使用過的 RESPIMAT 中？ 新的藥罐必須插入新的RESPIMAT。

我的RESPIMAT會自動噴藥。

在您轉動透明底座時，蓋子是否已經打開？ 請蓋上蓋子，然後轉動透明底座。
在您轉動透明底座時，是否按下給藥按鈕？ 請蓋上蓋子，蓋住給藥按鈕，然後轉動透明底座。
轉動透明底座時，您是否在聽到咔嗒聲之前就停止轉動？ 請轉動透明底座，一直到聽見咔

嗒聲（半圈）。

我的RESPIMAT無法噴藥。

您有插入藥罐嗎？ 如果沒有，請插入藥罐。

*插入藥罐之後，您重複**轉動**、**打開**、**按壓**步驟的次數是否少於3次？* 如「初次使用的準備步驟」中第4至6步驟所示，插入藥罐之後，請重複**轉動**、**打開**、**按壓**步驟三次。

RESPIMAT上的劑量顯示計是否指向0？ 如果劑量顯示計指向0，表示您已用完所有的藥物，吸入器已被鎖住。

組裝好 RESPIMAT 之後，請勿取下透明底座或藥罐。

新的藥罐必須插入新的 RESPIMAT。

如果您有任何其他問題，請向您的醫師或藥師詢問。

CE 0123

SPIRIVA® RESPIMAT® 2.5mcg, Solution for Inhalation

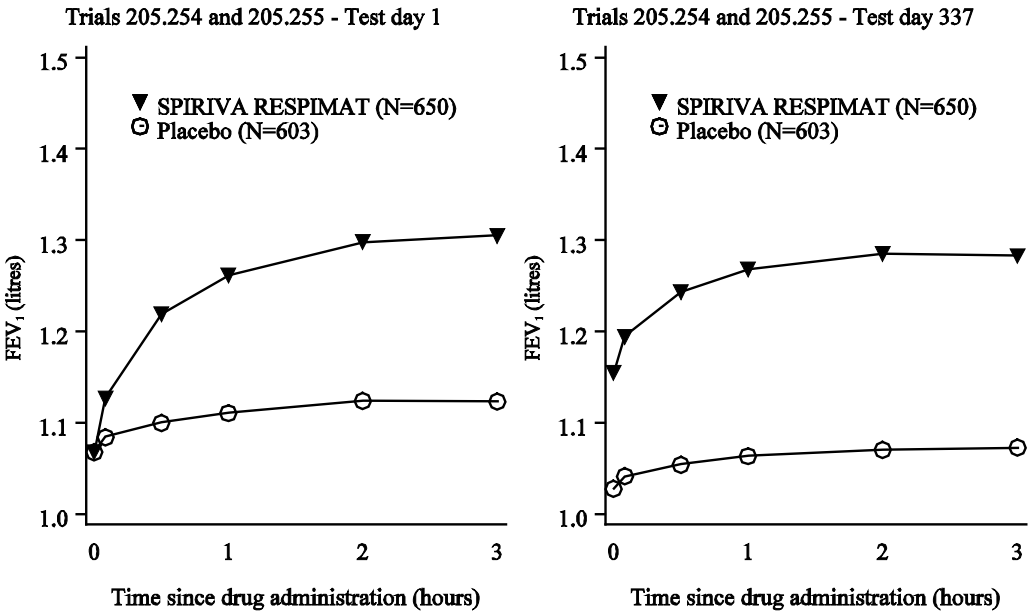
Composition

The delivered dose is 2.5 µg tiotropium per puff (2 puffs per dose).
2.5 µg tiotropium is equivalent to 3.124 µg tiotropium bromide monohydrate
(INN = tiotropium bromide)
Excipients:
benzalkonium chloride, disodium edetate, water, purified, hydrochloric acid for pH adjustment

Pharmacological properties

Pharmacotherapeutic group: Anticholinergics
ATC code: R03B B04
Tiotropium bromide is a long-acting, specific antimuscarinic agent in clinical medicine often called an anticholinergic. It has similar affinity to the subtypes, M_1 to M_5. In the airways, inhibition of M_3-receptors at the smooth muscle results in relaxation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations.
In non-clinical *in vitro* as well as *in vivo* studies bronchoprotective effects were dose dependent and lasted longer than 24h. The long duration of effect is likely to be due to its very slow dissociation from M_3-receptors, exhibiting a significantly longer dissociation half-life than that seen with ipratropium. As an N-quaternary anticholinergic, tiotropium bromide is topically (broncho-) selective when administered by inhalation, demonstrating an acceptable therapeutic range before giving rise to systemic anticholinergic effects.
Dissociation from M_2-receptors is faster than from M_3, which in functional in vitro studies, elicited (kinetically controlled) receptor subtype selectivity of M_3 over M_2.
The high potency and slow receptor dissociation found its clinical correlate in significant and long-acting bronchodilation in patients with COPD and asthma. The bronchodilation following inhalation of tiotropium is primarily a local effect (on the airways) not a systemic one.
COPD
The clinical Phase III programme development for COPD included two 1-year, two 12-weeks and two 4-weeks randomised, double-blind studies in 2901 COPD patients (1038 receiving the 5 µg tiotropium dose). The 1-year programme consisted of two placebo-controlled trials. The two 12-week trials were both active (ipratropium) - and placebo-controlled. All six studies included lung function measurements. In addition, the two 1-year studies included health outcome measures of dyspnoea, health-related quality of life and effect on exacerbations.
Placebo-controlled studies
Lung function
SPIRIVA RESPIMAT, administered once daily, provided significant improvement in lung function (forced expiratory volume in one second and forced vital capacity) within 30 minutes following the first dose, compared to placebo. Improvement of lung function was maintained for 24 hours at steady state (FEV_1 mean improvement: 0.122 litres; 95% CI: 0.106 to 0.138 litres, $p< 0.0001$). Pharmacodynamic steady state was reached within one week.
SPIRIVA RESPIMAT significantly improved morning and evening PEFR (peak expiratory flow rate) as measured by patient's daily recordings-compared to placebo. The use of SPIRIVA RESPIMAT resulted in a reduction of rescue bronchodilator use compared to placebo.
The bronchodilator effects of SPIRIVA RESPIMAT were maintained throughout the 48 weeks period of administration with no evidence of tolerance.

Figure 1: Mean FEV_1 (litres) at each time point (prior to and after administration of study drug) on Days 1 and 337 respectively (combined data from two 1-year, parallel-group trials)*



*Means adjusted for center, smoking status and baseline effect. A total of 545 and 434 patients in the SPIRIVA RESPIMAT and placebo groups, respectively completed test day 337. The data for the remaining patients were imputed using last observation or least favourable observation carried forward.

The following health outcome effects were demonstrated in the long term 1-year trials:
(a) SPIRIVA RESPIMAT significantly improved dyspnoea (as evaluated using the Transition Dyspnoea Index) compared to placebo (mean improvement 1.05 units; 95% CI: 0.73 to 1.38 units, $p<0.0001$). An improvement was maintained throughout the treatment period.
(b) Patients' evaluation of their Quality of Life (as measured using the St. George's Respiratory Questionnaire) between Spiriva Respimat versus placebo at the end of the two 1-year studies was 3.5 units (95% CI: 2.1 to 4.9, $p<0.0001$). A 4-unit decrease is considered clinically relevant.
(c) COPD Exacerbations
In three one-year, randomised, double-blind, placebo-controlled clinical trials SPIRIVA RESPIMAT treatment resulted in a significantly reduced risk of a COPD exacerbation in comparison to placebo. Exacerbations of COPD were defined as "a complex of at least two respiratory events/symptoms with a duration of three days or more requiring a change in treatment (prescription of antibiotics and/or systemic corticosteroids and/or a significant change of the prescribed respiratory medication)". SPIRIVA RESPIMAT treatment resulted in a reduced risk of a hospitalisation due to a COPD exacerbation (significant in the appropriately powered large exacerbation trial)
The pooled analysis of two Phase III trials and separate analysis of an additional exacerbation trial is displayed in **Table 1.** All respiratory medications except anticholinergics and long-acting beta-agonists were allowed as concomitant treatment, i.e. rapidly acting beta-agonists, inhaled corticosteroids and xanthines. Long-acting beta-agonists were allowed in addition in the exacerbation trial.

Table 1: Statistical Analysis of Exacerbations of COPD and Hospitalized COPD Exacerbations in Patients with Moderate to Very Severe COPD

Study ($N_{Spiriva}$, $N_{placebo}$)	Endpoint	Spiriva Respimat	Placebo	% Risk Reduction (95% CI)[a]	p-value
1-year Ph III studies, pooled analysis[d] (670, 653)	Days to first COPD exacerbation	160[a]	86[a]	29 (16 to 40)[b]	<0.0001[b]
	Mean exacerbation incidence rate per patient year	0.78[c]	1.00[c]	22 (8 to 33)[c]	0.002[c]
	Time to first hospitalised COPD exacerbation	NA[e]	NA[e]	25 (-16 to 51)[b]	0.20[b]
	Mean hospitalised exacerbation incidence rate per patient year	0.09[c]	0.11[c]	20 (-4 to 38)[c]	0.096[c]
1-year Ph IIIb exacerbation study (1939, 1953)	Days to first COPD exacerbation	169[a]	119[a]	31 (23 to 37)[b]	<0.0001[b]
	Mean exacerbation incidence rate per patient year	0.69[c]	0.87c	21 (13 to 28)c	<0.0001c
	Time to first hospitalised COPD exacerbation	NA[e]	NA[e]	27 (10 to 41)[b]	0.003[b]
	Mean hospitalised exacerbation incidence rate per patient year	0.12[c]	0.15[c]	19 (7 to 30)[c]	0.004[c]

[a] Time to first event: days on treatment by when 25% of patients had at least one exacerbation of COPD / hospitalized COPD exacerbation. In study A 25% of placebo patients had an exacerbation by day 112, whereas for Spiriva Respimat 25% had an exacerbation by day 173 (p=0.09);in study B 25% of placebo patients had an exacerbation by day 74, whereas for Spiriva Respimat 25% had an exacerbation by day 149 (p<0.0001).
b Hazard ratios were estimated from a Cox proportional hazard model. The percentage risk reduction is 100(1 - hazard ratio).
c) Poisson regression. Risk reduction is 100(1 - rate ratio).
d) Pooling was specified when the studies were designed. The exacerbation endpoints were significantly improved in individual analyses of the two one year studies.
eLess than 25% of patients had a COPD exacerbation leading to hospitalisation

Long-term tiotropium active- controlled study

A long term, large scale, randomised, double-blind, active-controlled study with a treatment period up to 3 years has been performed to compare the efficacy and safety of SPIRIVA RESPIMAT and SPIRIVA HANDIHALER(5,711 patients receiving SPIRIVA RESPIMAT 2.5 microgram (5 microgram medicinal dose); 5,694 patients receiving SPIRIVA HANDIHALER). The primary endpoints were time to first COPD exacerbation, time to all-cause mortality and in a sub-study (906 patients) trough FEV_1 (pre-dose).

The time to first COPD exacerbation was similar during the study with SPIRIVA RESPIMAT and SPIRIVA HANDIHALER (hazard ratio (SPIRIVA RESPIMAT / SPIRIVA HANDIHALER) 0.98 with a 95% CI of 0.93 to 1.03).

The median number of days to the first COPD exacerbation was 756 days for SPIRIVA RESPIMAT and 719 days for SPIRIVA HANDIHALER.

The bronchodilator effect of SPIRIVA RESPIMAT was similar to SPIRIVA HANDIHALER. The mean difference in trough FEV_1 for SPIRIVA RESPIMAT versus SPIRIVA HANDIHALER was -0.010 L (95% CI -0.038 to 0.018 mL).

All-cause mortality was similar during the study with SPIRIVA RESPIMAT and SPIRIVA HANDIHALER (hazard ratio (SPIRIVA RESPIMAT / SPIRIVA HANDIHALER) 0.96 with a 95% CI of 0.84 to 1.09).

Asthma

Adult patients

Clinical efficacy and safety in asthma

The clinical Phase III programme for persistent asthma included two 1-year, randomised, double-blind, placebo-controlled studies in a total of 907 asthma patients (453 receiving Spiriva Respimat) on a combination of ICS (≧800µg budesonide/day or equivalent) of ICS with a LABA. The studies included lung function measurements and the measurements symptoms of severe exacerbations and assessments of health-related quality of life.

PrimoTinA-asthma studies

In the two 1-year studies in patients who were symptomatic on maintenance treatment of at least ICS plus LABA, Spiriva Respimat showed clinically relevant improvements in lung function over placebo when used as add-on to background treatment.

At week 24, mean improvements in peak and trough FEV_1 were 0.110 litres (95% CI: 0.063 to 0.158 litres, p<0.0001) and 0.093 litres (95% CI: 0.050 to 0.137 litres, p<0.0001), respectively. The improvement of lung function compared to placebo was maintained for 24 hours.

In the PrimoTinA-asthma studies, treatment of symptomatic patients (N=453) with ICS plus LABA plus tiotropium reduced the risk of severe asthma exacerbations by 21% as compared to treatment of symptomatic patients (N=454) with ICS plus LABA plus placebo. The risk reduction in the mean number of severe asthma exacerbations/patient year was 20%.

This was supported by a reduction of 31% in risk for asthma worsening and 24% risk reduction in the mean number of asthma worsenings/patient year (see Table 2).

Table 2: Exacerbations in Patients Symptomatic on ICS(≧800µg budesonide/day or equivalent) plus LABA (PrimoTinA-asthma studies)

Study	Endpoint	Spiriva Respimat, added-on to at least ICS[a]/LABA (N=453)	Placebo, added-on to at least ICS[a]/LABA (N=454)	% Risk Reduction (95% CI)[a]	p-value
Two 1-year Phase III studies, pooled analysis	Days to 1st severe asthma exacerbation	282[c]	226[c]	21(0, 38)	0.0343
	Mean number of severe asthma exacerbations/ patient year	0.530	0.663	20(0, 36)	0.0458
	Days to 1st worsening of asthma	315[c]	181[c]	31(18, 42)	<0.0001
	Mean number of asthma worsenings/ patient year	2.145	2.835	24 (9, 37)	0.0031

[a] (≧800µg budesonide/day or equivalent)

[b] Hazard ratio, confidence interval and p-value obtained from a Cox proportional hazards model with only treatment as effect. The percentage risk reduction is 100(1 - hazard ratio).

[c] Time to first event: days on treatment by when 25%/50% of patients had at least one severe asthma exacerbation/worsening of asthma

Paediatric Patients
The clinical Phase III program for persistent asthma in paediatric patients (1-17 years) included:
- Adolescents (12-17 years): one 12-week randomised, double-blind, placebo-controlled studies in a total of 392 asthma patients (130 receiving SPIRIVA RESPIMAT)
- Children (6-11 years): one 12-week randomised, double-blind, placebo-controlled studies in a total of 401 asthma patients (130 receiving SPIRIVA RESPIMAT)

In these studies, patients were on background treatment of high dose ICS in combination with at least one controller medication or use of medium dose ICS in combination with at least controller medication.

In the 12-week PensieTinA-asthma study in patients who were symptomatic on maintenance treatment of at least above medium dose ICS in combination with 1 or more controller medication, SPIRIVA RESPIMAT showed improvements in lung function over placebo when used as add-on to background treatment, however, the differences in peak and trough FEV1 were not statistically significant.
- At week 12, mean improvements in peak and trough FEV1 were 0.090 litres (95% CI: -0.019 to 0.198 litres, p=0.1039) and 0.054 litres (95% CI: -0.061 to 0.168 litres, p=0.3605), respectively.
- At week 12, SPIRIVA RESPIMAT significantly improved morning and evening PEF (morning 17.4 L/min; 95% CI: 5.1 to 29.6 L/min; evening 17.6 L/min; 95% CI: 5.9 to 29.6 L/min).

Children (6-11 years)
In the 12-week VivaTinA-asthma study in patients who were symptomatic on maintenance treatment of at least above medium dose ICS in combination with 1 or more controller medication, SPIRIVA® RESPIMAT® showed significant improvements in lung function over placebo when used as add-on to background treatment.
- At week 12, mean improvements in peak and trough FEV1 were 0.139 litres (95% CI: 0.075 to 0.203 litres, p<0.0001) and 0.087 litres (95% CI: 0.019 to 0.154 litres, p=0.0117), respectively.

Pharmacokinetic properties
Tiotropium bromide is a non-chiral quaternary ammonium compound and is sparingly soluble in water. Tiotropium bromide is available as solution administered by the Respimat inhaler. Approximately 40% of the inhaled dose is deposited in the lungs, the target organ, the remaining amount being deposited in the gastrointestinal tract. Some of the pharmacokinetic data described below were obtained with higher doses than recommended for therapy.
Absorption:
Following inhalation by young healthy volunteers, urinary excretion data suggest that approximately 33% of the inhaled dose reaches the systemic circulation. Oral solutions of tiotropium bromide have an absolute bioavailability of 2-3%. Food is not expected to influence the absorption of tiotropium for the same reason.
Maximum tiotropium plasma concentrations were observed 5-7 minutes after inhalation. At steady state, peak tiotropium plasma concentrations of 10.5 pg/mL were achieved in COPD patients and decreased rapidly in a multi-compartmental manner. Steady state trough plasma concentrations were 1.60 pg/ml.
A steady-state tiotropium peak plasma concentration of 5.15 pg/mL was attained 5 minutes after the administration of the same dose to patients with asthma.

Distribution:
The drug has a plasma protein binding of 72% and shows a volume of distribution of 32 L/kg
The drug is bound by 72% to plasma proteins and shows a volume of distribution of 32 l/kg. Local concentrations in the lung are not known, but the mode of administration suggests substantially higher concentrations in the lung. Studies in rats have shown that tiotropium bromide does not penetrate the blood-brain barrier to any relevant extent.

Biotransformation:
The extent of biotransformation is small. This is evident from a urinary excretion of 74% of unchanged substance after an intravenous dose to young healthy volunteers.
Tiotropium bromide, an ester, is nonenzymatically cleaved to the alcohol N-methylscopine and dithienylglycolic acid, both not binding to muscarinic receptors.
In-vitro experiments with human liver microsomes and human hepatocytes suggest that some further drug (< 20% of dose after intravenous administration) is metabolised by cytochrome P450 (CYP) dependent oxidation and subsequent glutathion conjugation to a variety of Phase II-metabolites.In vitro studies in liver microsomes reveal that the enzymatic pathway can be inhibited by the CYP 2D6 (and 3A4) inhibitors, quinidine, ketoconazole and gestodene. Thus CYP 2D6 and 3A4 are involved in metabolic pathway that is responsible for the elimination of a smaller part of the dose.Tiotropium bromide even in supra-therapeutic concentrations does not inhibit CYP 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1 or 3A in human liver microsomes.

Elimination:
The effective half-life of tiotropium ~~is~~ ranges between 27 to 45 h following inhalation by COPD patients.
The effective half-life was 34 hours in patients with asthma.
Total clearance was 880 mL/min after an intravenous dose in young healthy volunteers.
Intravenously administered tiotropium bromide is mainly excreted unchanged in urine (74%).
After inhalation of the inhalation solution by COPD patients urinary excretion is 18.6% (0.93 µg) of the dose, the remainder being mainly non-absorbed drug in gut that is eliminated via the faeces.
In patients with asthma, 11.9% (0.595 µg) of the dose is excreted unchanged in the urine over 24 hours post dose at steady state.
The renal clearance of tiotropium exceeds the creatinine clearance, indicating secretion into the urine. After chronic once daily inhalation, pharmacokinetic steady state was reached by day 7 with no accumulation thereafter.
Linearity/nonlinearity: Tiotropium demonstrates linear pharmacokinetics in the therapeutic range independent of the formulation.

Elderly Patients:
As expected for all predominantly renally excreted drugs, advancing age was associated with a decrease of tiotropium renal clearance from 347 mL/min in COPD patients < 65 years to 275 mL/min in COPD patients ≥ 65 years. This did not result in a corresponding increase in $AUC_{0-6,ss}$ or $C_{max,ss}$ values.
Exposure to tiotropium found not to differ with age in patients with asthma.

Paediatric Patients:
The peak and total exposure to tiotropium was not found to differ between paediatric patients (aged 6 to 17 years) and adults with asthma. In patients 1 to 5 years old with asthma, the $Fe_{0-3h,ss}$ as measured by urinary excretion was 52 to 60% lower than that observed in patients 6 years and older with asthma; the $Fe_{0-3h,ss}$ when adjusted for body surface area were found to be comparable in all age groups. SPIRIVA RESPIMAT was administered with a valved holding chamber with facemask in patients 1 to 5 years of age.

Renally Impaired Patients:
Following once daily inhaled administration of tiotropium to steady-state in COPD patients with mild renal impairment (CL_{CR} 50-80 mL/min) resulted in slightly higher $AUC_{0-6,ss}$(between 1.8 to 30% higher) and similar $C_{max,ss}$ compared to patients with normal renal function (CLcr > 80 mL/min). In COPD patients with moderate to severe renal impairment (CL_{CR} <50 ml/min) the intravenous administration of tiotropium bromide resulted in doubling of the total exposure (82%

higher AUC_{0-4h}) and 52% higher C_{max}.) compared to COPD patients with normal renal function, which was confirmed by plasma concentrations after dry powder inhalation.
In asthma patients with mild renal impairment (CL_{CR} 50-80 mL/min) inhaled tiotropium did not result in relevant increases in exposure compared to patients with normal renal function.
Hepatically Impaired Patients:
Liver insufficiency is not expected to have any relevant influence on tiotropium pharmacokinetics. Tiotropium is predominantly cleared by renal elimination (74% in young healthy volunteers) and simple non-enzymatic ester cleavage to pharmacologically inactive products.

Indications
Maintenance treatment of patients with COPD (including chronic bronchitis and emphysema) and reduction of exacerbations.
As an add-on maintenance bronchodilator treatment in patients aged 6 year and older with severe asthma who remain symptomatic on treatments that include an inhaled corticosteroid in a combination with other controller medication.

Dosage and administration
The product should be used by physician prescription.
The recommended dosage of SPIRIVA RESPIMAT is inhalation of the spray of two puffs once daily from the RESPIMAT inhaler, at the same time of day (see Instructions for use).
In the treatment of asthma, the full benefits will be apparent after several doses of SPIRIVA RESPIMAT
Special populations:
Elderly patients can use SPIRIVA RESPIMAT at the recommended dose.
Renally impaired patients can use SPIRIVA RESPIMAT at the recommended dose. However, as with all predominantly renally excreted drugs, SPIRIVA RESPIMAT use should be monitored closely in patients with moderate to severe renal impairment.
Hepatically impaired patients can use SPIRIVA RESPIMAT at the recommended dose.
Paediatric population:
COPD does not normally occur in children.
In asthma, the recommended dosage of SPIRIVA RESPIMAT in patients 6 to 17 years of age is inhalation of the spray of two puffs once daily from the RESPIMAT inhaler, at the same time of day (see Instructions for use).
The efficacy and safety of SPIRIVA RESPIMAT in paediatric patients below 6 year of age with asthma has not yet been established.

Contraindications
SPIRIVA RESPIMAT is contraindicated in patients with a history of hypersensitivity to atropine or its derivatives, e.g. ipratropium or oxitropium or to any component of this product.

Special warnings and precautions
SPIRIVA RESPIMAT, as a once daily maintenance bronchodilator, should not be used for the initial treatment of acute episodes of bronchospasm, ie rescue therapy or for the relief of acute symptoms. In the event of an acute attack, a rapid-acting beta-2-agonist should be used.
SPIRIVA RESPIMAT should not be used as a first-line treatment for asthma. Asthma patients must be advised to continue taking anti-inflammatory therapy, i.e. inhaled corticosteroids, unchanged after the introduction of SPIRIVA RESPIMAT, even when their symptoms improve.
Immediate hypersensitivity reactions may occur after administration of SPIRIVA RESPIMAT inhalation solution
As with other anticholinergic drugs, SPIRIVA RESPIMAT should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction.
Inhaled medicines may cause inhalation-induced bronchospasm.

As with all predominantly renally excreted drugs, SPIRIVA use should be monitored closely in patients with moderate to severe renal impairment (creatinine clearance of ≤ 50 ml/min).
Patients must be instructed in the correct administration of SPIRIVARESPIMAT. Care must be taken not to allow the solution or mist to enter into 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 specialist advice should be sought immediately.
Miotic eye drops are not considered to be effective treatment.
SPIRIVA RESPIMAT should not be used more frequently than once daily.
SPIRIVA cartridges are to be used only with the RESPIMAT inhaler.
Excipients
Spiriva Respimat contains Benzalkonium chloride.
This medicine contains 0.0011 mg benzalkonium chloride in each actuation.
Benzalkonium chloride may cause wheezing and breathing difficulties. Patients with asthma are at an increased risk for these adverse events.

Interactions
Although no formal drug interaction studies have been performed, tiotropium bromide has been used concomitantly with other drugs commonly used in the treatment of COPD and asthma, including sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids, antihistamines, mucolytics, leucotriene modifiers, cromones and anti-IgE treatment without clinical evidence of drug interactions
Common concomitant medications (LABA, ICS and their combinations) used by patients with COPD were not found to alter the exposure to tiotropium.
The chronic co-administration of tiotropium bromide with other anticholinergic drugs has not been studied. Therefore, the chronic co-administration of other anticholinergic drugs with SPIRIVA RESPIMAT is not recommended.

Fertility, pregnancy and lactation
Pregnancy and lactation
For SPIRIVA, no clinical data on exposed pregnancies are available. Preclinical studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/ foetal development, parturition or postnatal development.
Pregnancy
There is a limited amount of data from the use of tiotropium in pregnant women. Preclinical studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant doses.
As a precautionary measure, it is preferable to avoid the use of SPIRIVA RESPIMAT during pregnancy.
Lactation
Clinical data from nursing women exposed to tiotropium are not available. Based on lactating rodent studies, a small amount of tiotropium is excreted into breast milk.
Therefore, SPIRIVA RESPIMAT should not be used in pregnant or nursing women unless the expected benefit outweighs any possible risk to the unborn child or the infant.
Fertility
Clinical data on fertility are not available for tiotropium. A preclinical study performed with tiotropium showed no indication of any adverse effect on fertility.

Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. The occurrence of dizziness or blurred vision may influence the ability to drive and use machinery.

Side effects

Many of the listed undesirable effects can be assigned to the anticholinergic properties of SPIRIVA RESPIMAT.
Adverse drug reactions were identified from data obtained in clinical trials and spontaneous reporting during post approval use of the drug.
The clinical trial database for COPD includes 3,282 SPIRIVA RESPIMAT patients from 7 placebo-controlled clinical trials with treatment periods ranging between four weeks and one year, contributing 2,440 person years of exposure.
The clinical trial database for asthma includes 1,930 tiotropium treated patients from 12 placebo controlled trials with treatment period ranging between twelve weeks and one year, contributing 1,128 person years of exposure to tiotropium.

Metabolism and nutrition disorders:
- dehydration

Nervous system disorders:
- dizziness
- insomnia

Eye disorders:
- glaucoma
- intraocular pressure increased
- vision blurred

Cardiac disorders:
- atrial fibrillation
- palpitations
- supraventricular tachycardia
- tachycardia

Respiratory, thoracic and mediastinal disorders:
- cough
- epistaxis
- pharyngitis
- dysphonia
- bronchospasm
- laryngitis
- sinusitis

Gastrointestinal disorders:
- dry mouth, usually mild
- constipation
- oropharyngaeal candidiasis
- dysphagia
- gastrooesophageal reflux disease
- gingivitis
- glossitis
- stomatitis stomatitis
- intestinal obstruction incl. ileus paralytic

Skin and subcutaneous tissue disorders, Immune system disorders:
- rash
- pruritus
- angioneurotic oedema
- urticaria
- skin infection and skin ulcer
- dry skin
- hypersensitivity (including immediate reactions)

Musculoskeletal and connective tissue disorders:
-joint swelling

Renal and urinary disorders:

-urinary retention (usually in men with predisposing factors)
-dysuria
-urinary tract infection

Paedriatic population:
The frequency, type, and severity of adverse reactions in the paediatric population are similar as in adults.

Overdose
High doses of SPIRIVA RESPIMAT may lead to anticholinergic signs and symptoms.
No relevant adverse events, beyond dry mouth/throat and dry nasal mucosa in a dose-dependent [10 - 40 µg daily] incidence, were observed following 14-day dosing of up to 40 µg tiotropium inhalation solution in healthy subjects with the exception of pronounced reduction in salivary flow from day 7 onwards. No significant undesirable effects have been observed in six long term studies in COPD patients when a daily dose of 10 µg tiotropium inhalation solution was given over 4 - 48 weeks

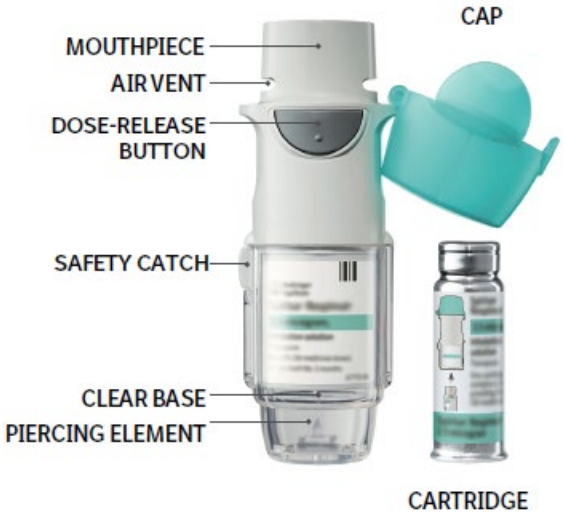
Toxicology
The acute inhalation and oral toxicity in mice, rats, and dogs was low; therefore, toxic effects from acute human drug over-dosage are unlikely The single dose safety pharmacology studies showed the expected effects of an anticholinergic drug including mydriasis, increased heart rate and prolonged gastro-intestinal transit time.
The side effects of the repeat-dose studies in rats, mice and dogs were related to anticholinergic properties of tiotropium bromide including mydriasis, increased heart rate, constipation, decreased body weight gain, reduced salivary and lacrimal gland secretion. Other relevant changes noted were: mild irritancy of the upper respiratory tract in rats evinced by rhinitis and epithelial changes of the nasal cavity and larynx, and prostatitis along with proteinaceous deposits and lithiasis in the bladder of male rats, increased lung weights in rats and decreased heart weights in dogs.
In the reproduction studies in rabbits and rats harmful effects with respect to pregnancy, embryo/foetal development, parturition or postnatal development could only be demonstrated at maternally toxic dose levels. In a general reproduction and fertility study in rats, there was no indication of any adverse effect on fertility or mating performance of either treated parents or their offspring at any dosage.
In juvenile rats exposed from postnatal day 7 to sexual maturity, the same direct and indirect pharmacological changes were observed as in the repeat-dose toxicity studies as well as rhinitis. No systemic toxicity was noted and no toxicologically relevant effects on key developmental parameters, tracheal or key organ development were seen.
In a series of *in vivo* and *in vitro* mutagenicity assays, tiotropium bromide did not cause gene mutations in prokaryotes and in eucaryotes, chromosomal damage *in vitro* and *in vivo* conditions or primary DNA damage.

Storage conditions
Do not freeze.
Store in a safe place out of the reach of children!
Store below 30℃!

Availability
1 cartridge of 4.0 ml + 1 Respimat inhaler
Expiration labelled on folding box, labels

Instructions for Use

Please read and carefully follow these instructions.
Children should use SPIRIVA RESPIMAT with an adult's assistance.



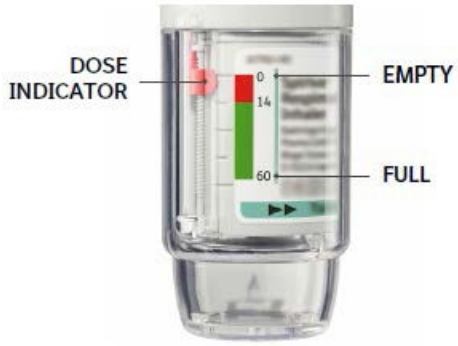
The RESPIMAT disposable is an inhaler device that generates a slow moving mist for inhalation
RESPIMAT disposable is a single patient device intended for multiple use

- If not been used for more than 7 days release one puff towards the ground.
- If not been used for more than 21 days repeat steps 4 to 6 until a cloud is visible. Then repeat steps 4 to 6 three more times.

SPIRIVA RESPIMAT inhaler and SPIRIVA RESPIMAT cartridge

How to care for your SPIRIVA RESPIMAT
Clean the mouthpiece including the metal part inside the mouthpiece with a damp cloth or tissue only, at least once a week.
Any minor discoloration in the mouthpiece does not affect your SPIRIVA® RESPIMAT® inhaler performance.

When to get a new SPIRIVA RESPIMAT



- Your SPIRIVA RESPIMAT inhaler contains 60 puffs (30 doses) if used as indicated (two puffs/Once daily).
- The dose indicator shows approximately how much medication is left.
- When the dose indicator enters the red area of the scale you need to get a new prescription; there is approximately medication for 7 days left (14 puffs).
- Once the dose indicator reaches the end of the red scale, your SPIRIVA® RESPIMAT® locks automatically – no more doses can be released. At this point, the clear base cannot be turned any further.

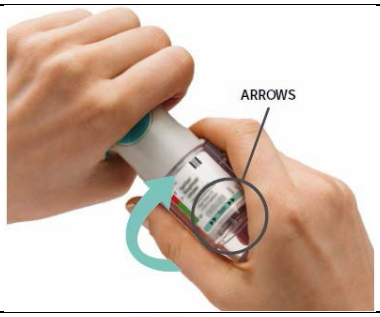
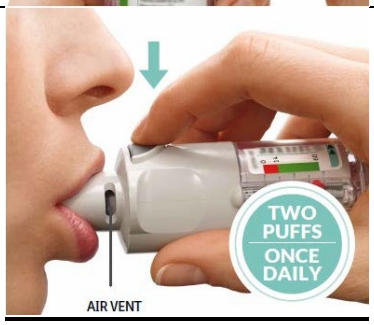
- Three months after first use, the SPIRIVA RESPIMAT should be discarded even if it has not been used.

Prepare for first use

1. Remove clear base • Keep the cap closed. • Press the safety catch while firmly pulling off the clear base with your other hand.	
2. Insert cartridge • Insert the narrow end of the cartridge into the inhaler. • Place the inhaler on a firm surface and push down firmly until it snaps into place.	
3. Replace clear base • Put the clear base back into place until it clicks.	
4. Turn • Keep the cap closed. • Turn the clear base in the direction of the arrows on the label until it clicks (half a turn).	
5. Open • Open the cap until it snaps fully open.	
6. Press • Point the inhaler toward the ground • Press the dose-release button. • Close the cap. • Repeat steps 4-6 until a cloud is visible. • After a cloud is visible, repeat steps 4-6 three more times. Your SPIRIVA RESPIMAT inhaler is now	

ready to use.	

Daily use of your SPIRIVA RESPIMAT inhaler
You will need to use this inhaler ONLY ONCE A DAY.
Each time you use it take TWO PUFFS.

TURN • Keep the cap closed. • TURN the clear base in the direction of the arrows on the label until it clicks (half a turn).	
OPEN • OPEN the cap until it snaps fully open.	
PRESS • Breathe out slowly and fully. • Close your lips around the mouthpiece without covering the air vents. • While taking a slow, deep breath through your mouth, PRESS the dose-release button and continue to breathe in. • Hold your breath for 10 seconds or for as long as comfortable. • Repeat Turn, Open, Press for a total of 2 puffs. Close the cap until you use your inhaler again.	

Serious incidents
If you experience any serious incident in relation to the device, talk to your doctor or pharmacist. You can also report serious incidents directly to Boehringer Ingelheim, or via the TFDA Quality management system website (https://qms.fda.gov.tw/). By reporting serious incidents, you can help provide more information on the safety of this device.

Mfd by
Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Strasse 173
55216 Ingelheim am Rhein, Germany
For
Boehringer Ingelheim International GmbH
Ingelheim am Rhein, Germany

19 MAR 2021

Answers to Common Questions

It is difficult to insert the cartridge deep enough.

Did you accidentally turn the clear base before inserting the cartridge? Open the cap, press the dose-release button, then insert the cartridge.

Did you insert the cartridge with the wide end first? Insert the cartridge with the narrow end first.

I cannot press the dose-release button.

Did you turn the clear base? If not, turn the clear base in a continuous movement until it clicks (half a turn).

Is the dose indicator on the RESPIMAT pointing to zero? The RESPIMAT inhaler is locked after 60 puffs. Prepare and use your new RESPIMAT inhaler.

I cannot turn the clear base.

Did you turn the clear base already? If the clear base has already been turned, follow steps "OPEN" and "PRESS" under "Daily Use" to get your medicine.

Is the dose indicator on the RESPIMAT pointing to zero? The RESPIMAT inhaler is locked after 60 puffs. Prepare and use your new RESPIMAT inhaler.

The dose indicator on the RESPIMAT reaches zero too soon.

Did you use RESPIMAT as indicated (two puffs/once daily)? RESPIMAT will last 30 days if used at two puffs once daily.

Did you turn the clear base before you inserted the cartridge? The dose indicator counts each turn of the clear base regardless whether a cartridge has been inserted or not.

Did you spray in the air often to check whether the RESPIMAT is working? Once you have prepared RESPIMAT, no test-spraying is required if used daily.

Did you insert the cartridge into a used RESPIMAT? Always insert a new cartridge into a NEW RESPIMAT.

My RESPIMAT sprays automatically.

Was the cap open when you turned the clear base? Close the cap, then turn the clear base.

Did you press the dose-release button when turning the clear base? Close the cap, so the dose-release button is covered, then turn the clear base.

Did you stop when turning the clear base before it clicked? Turn the clear base in a continuous movement until it clicks (half a turn).

My RESPIMAT doesn't spray.

Did you insert a cartridge? If not, insert a cartridge.

Did you repeat TURN, OPEN, PRESS less than three times after inserting the cartridge? Repeat TURN, OPEN, PRESS three times after inserting the cartridge as shown in the steps 4 to 6 under "Prepare for first Use".

Is the dose indicator on the RESPIMAT pointing to 0? If the dose indicator points to 0, you have used up all your medication and the inhaler is locked.

Once your RESPIMAT is assembled, do not remove the clear base or the cartridge.

Always insert a new cartridge into a NEW RESPIMAT.

If you have any further questions, ask your doctor or pharmacist.

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