適倍樂 ® 舒沛噴 ® 吸入劑
Spiolto® Respimat® , Solution for Inhalation

衛部藥輸字第 026735 號

1 藥品名稱
適倍樂舒沛噴吸入劑
SPIOLTO RESPIMAT Solution for Inhalation

2 定性與定量成分
每噴一次含 tiotropium 2.5mcg 和 olodaterol 2.5mcg，相當於 tiotropium bromide monohydrate 3.124mcg 和 olodaterol hydrochloride 2.736 mcg。

投予的實際劑量為病人使用吸入器吸入後的劑量。

具有已知作用的賦形劑: 本藥品每噴含有氯化苯二甲羥胺(benzalkonium chloride) 0.0011mg。
完整的賦形劑清單請見第6.1節。

3 劑型
吸入性溶液
澄清、無色之吸入劑溶液

4 臨床性質
4.1 適應症
適用於慢性阻塞性肺疾(包括慢性支氣管炎及肺氣腫)之長期維持治療法。

4.2 用法用量
本藥須由醫師使用
劑量學
本藥品僅供吸入使用。藥罐僅限插入 RESPIMAT 吸入器中使用。

每劑藥物為按壓 RESPIMAT 吸入器二次噴藥。

成人
建議劑量為 5mcg tiotropium 和 5mcg olodaterol，每日同一時間以 RESPIMAT 吸入器用藥一次，每次按壓二次噴藥。

用量不可超過建議劑量。

老年族群
老年病人可依建議劑量使用 SPIOLTO RESPIMAT。

肝功能不全與腎功能不全病人
SPIOLTO RESPIMAT 中的 tiotropium 主要是經由腎臟排泄，而 olodaterol 主要經由肝臟代謝。

肝功能不全病人
輕度與中度肝功能不全病人可依建議劑量使用 SPIOLTO RESPIMAT。

目前尚無 olodaterol 用於重度肝功能不全病人的相關數據。

腎功能不全病人
腎功能不全病人可依建議劑量使用 SPIOLTO RESPIMAT。
對於中度至重度腎功能不全(肌酸酐清除率 ≤ 50 ml/min)的病人，請見第 4.4 與 5.2 節。SPIOLTO RESPIMAT 含有 olodaterol。在重度腎功能不全病人使用 olodaterol 的經驗極有限。

兒童族群
兒童病人 (18 歲以下)通常不會使用 SPIOLTO RESPIMAT。

用法
為確保正確使用本藥品，醫生或其他醫護人員應為病人示範如何使用吸入器。

4.3 禁忌
對其活性物質或列於第 6.1 節之任何賦形劑過敏。

曾經對 atropine 或其衍生物(如 ipratropium 或 oxitropium)過敏。

4.4 特殊警語與注意事項
氣喘
SPIOLTO RESPIMAT 不可用於氣喘病人。尚無研究探討 SPIOLTO RESPIMAT 用於氣喘病人的療效及安全性。

不可作為急救使用
SPIOLTO RESPIMAT 不適用於急性支氣管痙攣的治療(亦即做為救援療法)。

反常性支氣管痙攣(Paradoxical bronchospasm)
一如其他吸入性藥物，SPIOLTO RESPIMAT 可造成可能致命的反常性支氣管痙攣。若發生反常性支氣管痙攣，應立即停用 SPIOLTO RESPIMAT，而以其他療法取代。

與tiotropium相關的抗膽鹼作用

狹角性青光眼、攝護腺肥大或膀胱頸阻塞
由於 tiotropium 具有抗膽鹼活性，狹角性青光眼、攝護腺肥大或膀胱頸阻塞的病人應小心使用 SPIOLTO RESPIMAT。

眼睛症狀
病人應小心避免讓噴霧進入眼睛。應告知病人這樣可能導致藥物沉積或青光眼惡化，眼睛疼痛或眼睛不舒服、暫時性視線模糊、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。若合併發生任何以上眼睛症狀，應立刻停止使用 SPIOLTO RESPIMAT 並請教專科醫生。

蛀牙
抗膽鹼治療時曾觀察到口乾現象，而長期口乾可能與蛀牙有關。

腎功能不全病人
由於中至重度腎功能不全病人(肌酸酐清除率 ≤ 50 mL/min)血漿中的 tiotropium 濃度隨腎功能下降而增高，因此僅在預期益處超過潛在風險時方可使用 SPIOLTO RESPIMAT。目前尚無在重度腎功能不全病患長期使用的經驗(請見第 5.2 節)。

心血管作用
SPIOLTO RESPIMAT 在前一年期間曾有心肌梗塞病史、有不穩定型或危及性命之心律不整、前一年期間因心臟衰竭住院或有陣發性心搏過速(>100 下／分鐘)診斷之病人的使用經驗極有限，因為臨床試驗中皆排除這些病人。在這些病人族群使用 SPIOLTO RESPIMAT 時應特別謹慎。

一如其他的 $ß_2$-腎上腺素受體促效劑，olodaterol 可在某些病人身上產生臨床上顯著的心血管作用，此可由脈搏速率、血壓及/或症狀量值升高得知。若發生此類作用，可能必須中斷治療。此外，過去曾有通報，ß-腎上腺素受體促效劑可使病人的心電圖(ECG)產生變化，例如 T 波變平以及 ST 段下降，但這些發現的臨床重要性仍不明。

長效型 $ß_2$-腎上腺素受體促效劑用於以下病人時，應特別謹慎：心血管疾病(尤其缺血性心臟疾病、重度心臟代償失調、心律不整、肥厚性阻塞型心肌病變、高血壓及動脈瘤)病人、癲癇症或甲狀腺毒症(thyrotoxicosis)病人、已知或疑似 QT 間隔延長(例如 QT> 0.44 秒)的病人、以及對擬交感胺類(sympathomimetic amines)有異常反應的病人。

低血鉀症(Hypokalaemia)
$ß_2$-腎上腺素受體促效劑可能在某些病人身上引發顯著的低血鉀症，可能進而導致不良的心血管作用。血清中鉀減少的現象通常屬於暫時性，無須進行補充。在重度 COPD 病人，低血鉀症可能因缺氧與併用療法(請見第 4.5 節)而惡化，而這可能增加心律不整的發生機會。

高血糖(Hyperglycaemia)
吸入高劑量 $ß_2$-腎上腺素受體促效劑可能導致血糖增高。

麻醉
若計畫進行手術而使用鹵化碳氫化合物(halogenated hydrocarbon)類麻醉劑，因為對$ß_2$-腎上腺素受體促效劑類支氣管擴張劑產生不良心臟作用的可能性增加，因此必須特別謹慎。

SPIOLTO RESPIMAT 不可與任何其他含有長效性 $ß_2$-腎上腺素受體促效劑的藥物併用。對於已在規律(例如，一天四次)使用吸入性短效型 $ß_2$-腎上腺素受體促效劑的病人，務必請他們僅在發生急性呼吸症狀時，才可使用此類藥物進行症狀紓解。

SPIOLTO RESPIMAT 的使用頻率不可超過一天一次。

過敏
一如所有的藥物，在使用 SPIOLTO RESPIMAT 後，有可能會發生立即性的過敏反應。

賦形劑

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。

4.5 與其他藥品之交互作用以及其他形式之交互作用

雖然尚未針對SPIOLTO RESPIMAT與其他藥物之間的體內藥物交互作用進行正式的研究，但吸入性SPIOLTO RESPIMAT曾與其他COPD藥品(包括短效性擬交感神經性支氣管擴張劑與吸入性皮質類固醇) 同時使用，且無藥物交互作用的臨床證據。

抗膽鹼藥物

尚未針對 SPIOLTO RESPIMAT 的成分 tiotropium bromide 與其他含抗膽鹼劑藥物的併用狀況進行研究，因此不建議其併用。

腎上腺素性藥(Adrenergic agents)

同時使用其他腎上腺素性藥 (單獨使用或作為合併療法的一部分使用)可能增加 SPIOLTO RESPIMAT 的不良作用。

Xanthine 衍生物、類固醇或利尿劑

與 Xanthine 衍生物、類固醇或非留鉀類利尿劑併用可能增加腎上腺素受體促效劑之任何低鉀血症作用的風險(請見第 4.4 節)。

ß-阻斷劑

ß-腎上腺素受體阻斷劑可能減弱或拮抗 olodaterol 的作用。可考慮具有心臟選擇性的 ß-阻斷劑，但使用時應謹慎。

MAO 抑制劑與三環抗憂鬱藥物，QTc 延長藥物

單胺氧化酶抑制劑或三環抗憂鬱藥物或其他已知可延長 QTc 間隔的藥物皆有增加 SPIOLTO RESPIMAT 之心血管系統作用的風險。

藥物動力學之藥物交互作用

在與 fluconazole (作為 CYP2C9 抑制劑的代表)併用的藥物交互作用研究中，未觀察到其對 olodaterol 的全身性暴露量有相關作用。

併用強效的 P-gp 與 CYP3A4 抑制劑 ketoconazole 時，olodaterol 的全身性暴露量會增加約 70%。無須調整 SPIOLTO RESPIMAT 的劑量。

*體外*研究顯示，在臨床使用時可達到的血漿濃度下，olodaterol 不會抑制 CYP 酵素或藥物轉運蛋白。

4.6 生育力、懷孕與哺乳

懷孕

Tiotropium

關於 tiotropium 於孕婦的使用經驗，目前相關資料十分有限。臨床前研究並未顯示 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(請見第 5.3 節)。

Olodaterol

目前尚無 olodaterol 在孕婦中使用的相關臨床資料。Olodaterol 的臨床前資料顯示，在較治療劑量高出多倍的劑量下，會出現 ß-腎上腺素受體促效劑的典型作用(請見第 5.3 節)。

作為防範措施，建議懷孕期間應避免使用 SPIOLTO RESPIMAT。

如同其他 $ß_2$-腎上腺素受體促效劑，SPIOLTO RESPIMAT 所含成分 olodaterol 對子宮平滑肌具有鬆弛作用，因此可能對分娩過程具抑制作用。

哺乳
目前尚無 tiotropium 及/或 olodaterol 在授乳婦女使用的相關臨床資料。

Tiotropium 和 olodaterol 的動物實驗發現，在泌乳大鼠的乳汁中可偵測到本藥物及/或其代謝產物，但不清楚 tiotropium 及/或 olodaterol 是否可分泌至人乳。

在決定是否繼續/停止哺乳或繼續/停止 SPIOLTO RESPIMAT 治療時，應考量哺乳對嬰兒的益處與 SPIOLTO RESPIMAT 治療對婦女的益處。

生育力
目前尚無 tiotropium 和 olodaterol 或兩成分併用對生育力之影響的相關臨床資料。以個別成分 tiotropium 和 olodaterol 進行的臨床前研究顯示，其對生育力無不良作用（請見第 5.3 節）。

4.7 對駕駛和操作機器能力之影響
尚無本藥對駕駛和操作機器能力之影響的研究。

然而，應告知病人，SPIOLTO RESPIMAT 的使用經驗中曾有病人出現眩暈和視力模糊的報告。因此，在開車或操作機器時，應特別謹慎。若病人發生上述症狀，應即避免從事可能具危險性的工作，例如駕駛或操作機器。

4.8 不良作用
a. 安全性摘要

所列之不良作用有許多可歸因於 SPIOLTO RESPIMAT 之成分 tiotropium bromide 的抗膽鹼性質或 olodaterol 的 $ß_2$-腎上腺素性質。

b. 不良反應摘要表

下列不良作用之發生頻率係根據 8 項針對 COPD 患者所進行之活性劑或安慰劑對照、平行組別之臨床試驗(治療期 4 至 52 週不等)中，在 tiotropium 5 mcg/olodaterol 5mcg 劑量組(5646 位受試者)所觀察到的不良藥物反應(亦即可歸因於 SPIOLTO RESPIMAT 的事件)之粗估發生率。

下表為所有 SPIOLTO RESPIMAT 臨床試驗中所通報之依據系統器官類別分列的不良反應。

這也包括先前單獨使用其任一個別成分時所通報的所有不良反應。

發生頻率係以下列慣用定義：

極常見 (≥1/10)；常見(≥1/100 至<1/10)；不常見 (≥1/1,000 至<1/100)；罕見(≥1/10,000 至<1/1,000)；極罕見(<1/10,000)；未知(無法從現有資料估計)

系統器官類別	不良反應	發生頻率
感染與寄生蟲感染	鼻咽炎	未知
代謝與營養方面異常	脫水	未知
神經系統異常	眩暈	不常見
	失眠	罕見
	頭痛	不常見
眼睛視力方面異常	視力模糊	罕見
	青光眼	未知
	眼內壓上升	未知
心臟方面異常	心房顫動	罕見
	心悸	罕見
	心搏過速	不常見
	上心室性心搏過速	罕見
血管異常	高血壓	罕見
呼吸道、胸腔及縱隔腔異常	咳嗽	不常見
	發聲困難	不常見
	鼻出血	罕見
	喉炎	罕見
	咽頭炎	罕見
	支氣管痙攣	罕見
	鼻竇炎	未知
胃腸消化系統異常	口乾	不常見
	便秘	罕見
	牙齦炎	罕見
	噁心	罕見
	口咽念珠菌感染	罕見
	腸阻塞 麻痺性腸阻塞	未知
	蛀牙	未知
	吞嚥困難	未知
	胃食道逆流疾病	未知
	舌炎	未知

	口腔炎	罕見
皮膚與皮下組織異常、免疫系統異常	血管性水腫	罕見
	蕁麻疹	罕見
	過敏	罕見
	搔癢	罕見
	全身性過敏性反應	未知
	皮疹	罕見
	皮膚乾燥	未知
	皮膚感染與皮膚潰瘍	未知
肌肉骨骼與結締組織異常	背痛[1]	罕見
	關節痛	罕見
	關節腫大	罕見
腎臟與泌尿系統異常	尿液滯留	罕見
	排尿疼痛	罕見
	泌尿道感染	罕見

[1]使用 SPIOLTO RESPIMAT 時曾通報、但使用個別成分時並未通報的不良作用

c. 重要不良反應說明

SPIOLTO RESPIMAT 的性質為其 tiotropium 與 olodaterol 成分之抗膽鹼與 $ß_2$-腎上腺素能性質的結合。

抗膽鹼藥物之不良反應狀況

在為期 52 週的長期 SPIOLTO RESPIMAT 臨床試驗中，最常觀察到的抗膽鹼不良作用為口乾，其在 SPIOLTO RESPIMAT 治療組的發生率約 1.3%，在 tiotropium 5 mcg 組與 olodaterol 5 mcg 組則分別為 1.7%與 1%。SPIOLTO RESPIMAT 治療組有 2／4,968 (0.04 %)受試者因口乾而停止用藥。

與抗膽鹼作用相關的嚴重不良作用包括青光眼、便秘、腸阻塞(包括麻痺性腸阻塞)與尿滯留。

ß-腎上腺素藥物之不良反應狀況

SPIOLTO RESPIMAT的成分olodaterol屬於長效型$ß_2$-腎上腺素受體促效劑藥物。因此亦應注意與ß-腎上腺素受體促效劑藥物有關之其他不良作用(未列於上者)的發生風險，例如心律不整、心肌梗塞、心絞痛、低血壓、顫抖、緊張不安、肌肉痙攣、疲勞、身體不適、低血鉀症、高血糖與代謝性酸中毒。

d. 其他特殊族群

抗膽鹼作用可能隨年齡增加而增強。

疑似不良反應之通報

使用藥品後的疑似不良反應通報非常重要，可藉以繼續監測藥品的益處／風險平衡。醫護人員請透過http://adr.fda.gov.tw網站通報任何疑似的不良反應。

4.9 用藥過量

與 SPIOLTO RESPIMAT 用藥過量相關的資訊極有限。SPIOLTO RESPIMAT 曾針對 COPD 病人進行高達 5mcg / 10mcg(tiotropium/olodaterol)的研究，亦曾針對健康受試者進行高達 10mcg/ 40mcg(tiotropium/olodaterol)的研究；皆未觀察到具有臨床重要性的作用。用藥過量可能導致 tiotropium 的抗蕈毒鹼作用加重，與／或 olodaterol 的 β_2 促效劑作用加重。

症狀

抗膽鹼劑tiotropium之用藥過量

高劑量的 tiotropium 可能導致抗膽鹼性徵兆及症狀發生。

不過，健康自願受試者在吸入單劑高達 340mcg 的 tiotropium bromide 之後，未發生全身性抗膽鹼性不良作用。此外，健康自願受試者在使用高達 40mcg 的 tiotropium 吸入劑 14 天之後，除了口腔／喉嚨乾燥與鼻黏膜乾燥以外，未觀察到相關不良事件，唯一的例外為從第 7 天開始唾液量明顯減少。

β_2-促效劑olodaterol之用藥過量

Olodaterol用藥過量可能導致β_2 腎上腺受體促效劑的典型作用加重，例如心肌缺血、高血壓或低血壓、心搏過速、心律不整、心悸、暈眩、緊張不安、失眠、焦慮、頭痛、顫抖、口乾、肌肉痙攣、噁心、疲勞、身體不適、低血鉀症、高血糖與代謝性酸中毒。

用藥過量之治療

應立即中斷 SPIOLTO RESPIMAT 治療，並給予支持性治療與症狀治療。嚴重的病例應住院接受治療。可考慮使用心臟選擇性 ß-阻斷劑，但務必非常謹慎，因為使用 ß-腎上腺素阻斷劑藥物可能引發支氣管痙攣。

5 藥理學性質

5.1 藥效學性質

藥物類別：

阻塞性呼吸道疾病治療用藥，含腎上腺素性藥物及抗膽鹼劑。

ATC 代碼：R03AL06

作用機轉

SPIOLTO RESPIMAT

SPIOLTO RESPIMAT 為含有 tiotropium(一種長效型蕈毒鹼受體拮抗劑)和 olodaterol(一種長效型 β_2-腎上腺素受體促效劑)(LAMA/LABA)的固定劑量複合吸入性溶液，以 SPIOLTO RESPIMAT soft mist 吸入器投藥。

此兩種活性成分由於具有不同的作用機轉，因此可帶來加成性支氣管擴張效果。因為中央呼吸道有較多蕈毒鹼受體，而 ß2-腎上腺素受體則在周邊呼吸道表現較多，因此併用 tiotropium 與 olodaterol 應可在肺臟的所有部位提供最理想的支氣管擴張作用。

Tiotropium

Tiotropium bromide 為毒蕈鹼受體之長效專一性拮抗劑，對 M1 至 M5 亞型均有相似的親和力。在呼吸道中，tiotropium bromide 可與支氣管平滑肌中的 M3 受體以競爭性及可逆性的方式結合，透過拮抗乙醯膽鹼的膽鹼作用(支氣管收縮)，因而使支氣管平滑肌

放鬆。此拮抗效果具有劑量相關性，且可持續長達 24 小時以上。由於 tiotropium bromide 為四級銨(N-quaternary)之抗膽鹼劑，吸入後可選擇性地局部作用於支氣管，因此在產生有效治療濃度時仍不致產生全身性抗膽鹼作用。

Olodaterol
Olodaterol 對人類 $ß_2$-腎上腺素受體具有高親和力及高選擇性。體外研究顯示，olodaterol 對 $ß_2$-腎上腺素受體的促效活性，是對 $ß_1$-腎上腺素受體的 241 倍，也是對 $ß_3$-腎上腺素受體的 2299 倍。在以吸入方式局部投藥後，本化合物可藉由與 $ß_2$-腎上腺素受體結合，將其活化而產生藥效。
此類呼吸道內的受體受到活化時，會導致細胞內的腺苷酸環化酶(adenyl cyclase)受到刺激；此為調控環腺苷單磷酸(cyclic-3',5' adenosine monophosphate，簡稱 cAMP)合成的酵素。cAMP 濃度升高可使呼吸道的平滑肌細胞鬆弛，因而促使支氣管擴張。
臨床前研究顯示，olodaterol 為長效型選擇性 $ß_2$-腎上腺素受體促效劑(long-acting selective $beta_2$-adrenoceptor agonist，簡稱 LABA)，可快速產生藥效，且藥效可持續至少 24 小時。
ß-腎上腺素受體可分為三個亞型：$ß_1$-腎上腺素受體主要存在心肌上、$ß_2$-腎上腺素受體主要存在呼吸道平滑肌上、$ß_3$-腎上腺素受體則主要存在脂肪組織上。$ß_2$-腎上腺素受體促效劑可引發支氣管擴張。$ß_2$-腎上腺素受體雖為呼吸道平滑肌上的主要腎上腺素受體，但亦存在各種其他細胞的表面，包括肺臟上皮與內皮細胞，以及心臟內。$ß_2$-腎上腺素受體在心臟內的確切功能尚不明，但其存在表示即使具高度選擇性的 $ß_2$-腎上腺素受體促效劑亦可能對心臟具有影響。

對心臟電生理學性質的影響
Tiotropium
在 53 名健康自願受試者針對 QT 進行的試驗中，使用 tiotropium 吸入性粉末 18mcg 與 54mcg(亦即治療劑量的 3 倍)治療 12 天期間，心電圖上的 QT 間隔未顯著延長。

Olodaterol
Olodaterol 對心電圖 QT/QTc 間隔的影響，已在一項針對 24 名健康男性及女性自願受試者所進行的雙盲、隨機分組、以安慰劑及活性劑(moxifloxacin)對照的試驗中進行研究。研究顯示，相較於安慰劑，使用單劑 10、20、30 及 50 mcg olodaterol 之後，20 分鐘至 2 小時之間的 QT 間隔與基準點的平均差異具有劑量相關性，數值可從 1.6(10 mcg olodaterol)增至 6.5 ms(50 mcg olodaterol)，且對於個別矯正的 QT (QTcI)，在所有的劑量下，QTc1 雙尾 90%信賴區間的上限值皆低於 10 ms。

5 mcg及10 mcg olodaterol對心跳速率及節律的影響，已針對一項為期48週、以安慰劑對照之第三期試驗的772名受試者子群，使用連續24小時心電圖記錄(Holter監測)進行評估。在心跳速率或早期收縮(premature beats)的平均變化幅度方面，並未觀察到劑量相關性或時間相關性的趨勢或模式存在。在基準點至治療結束時的早期收縮變化上，olodaterol 5 mcg 、10 mcg與安慰劑之間並無具臨床意義的差異存在。

SPIOLTO RESPIMAT
兩項使用 SPIOLTO RESPIMAT 的 52 週、隨機分組、雙盲試驗中納入 5162 名 COPD 病人。在統合分析中，第 85、169 與 365 天給藥後 40 分鐘時，校正後之 QTcF (Fridericia 校正)間隔相較於基準值的變化>30 ms 的受試者比例，在 SPIOLTO RESPIMAT 組內分別為 3.1%、4.7%與 3.6%，在 olodaterol 5 mcg 組內分別為 4.1%、4.4%與 3.6%，而在 tiotropium 5 mcg 組內則分別為 3.4%、2.3%與 4.6%。

臨床功效與安全性

SPIOLTO RESPIMAT 的第三期臨床開發計畫包括三項隨機分組、雙盲試驗：

(i) 以 SPIOLTO RESPIMAT 與 tiotropium 5 mcg 和 olodaterol 5 mcg 比較、平行組別、為期 52 週的 2 項重複試驗(1029 人使用 SPIOLTO RESPIMAT)[試驗 1 與 2]

(ii) 以 SPIOLTO RESPIMAT 與 tiotropium 5 mcg 和 olodaterol 5 mcg 和安慰劑比較、交叉用藥、為期 6 週的 1 項試驗(139 人使用 SPIOLTO RESPIMAT)[試驗 3]

在這些試驗中，tiotropium 5 mcg、olodaterol 5 mcg 和安慰劑等對照藥品都是經由 Respimat 吸入器給藥。

受試者特徵

全球性的 52 週試驗 [試驗 1 與 2] 所收錄的 5162 名受試者，大多數為男性(73%)、白種人(71%)或亞洲裔(25%)，平均年齡 64.0 歲。使用支氣管擴張劑後的 FEV_1 平均值為 1.37 L(GOLD 2 [50%]、GOLD 3 [39%]、GOLD 4 [11%])。$ß_2$-促效劑反應平均值為基準值的 16.6%(0.171 L)。允許併用的肺部用藥包括吸入性類固醇 [47%]和 xanthines [10%]）。

為期 6 週的試驗 [試驗 3] 是在歐洲與北美進行。其所收錄的 219 名受試者大部分為男性(59%)與白種人(99%)，平均年齡 61.1 歲。使用支氣管擴張劑後的 FEV_1 平均值為 1.55 L(GOLD 2 [64%]、GOLD 3 [34%]、GOLD 4 [2%])。$ß_2$-促效劑反應平均為基準值的 15.9%(0.193 L)。允許併用的肺部用藥包括吸入性類固醇[41%]、xanthines [4%]。

對肺功能之作用

在為期 52 週的試驗中，SPIOLTO RESPIMAT(每日一次於上午使用)可於使用第一劑之後 5 分鐘內相較於 tiotropium 5 mcg 明顯改善肺功能(的 FEV_1 平均增加 0.137 L，tiotropium 5 mcg 平均增加 0.058 L [p<0.0001]，而 olodaterol 5 mcg 平均增加 0.125 L [p=0.16])。在兩項研究中，24 週後的 FEV_1 AUC_{0-3h}反應和谷底期 FEV_1反應(肺功能主要評估指標)都是以 SPIOLTO RESPIMAT 顯著優於 tiotropium 5 mcg 和 olodaterol 5 mcg(表 1)。

表1 24週後，SPIOLTO RESPIMAT組在FEV_1 AUC_{0-3h} 反應和谷底期 FEV_1 反應上相較於tiotropium 5 mcg組和olodaterol 5 mcg組的差異(試驗1與試驗2)

	FEV_1 AUC_{0-3h} 反應				**谷底期 FEV_1 反應**			
	試驗 1		**試驗 2**		**試驗 1**		**試驗 2**	
	n	**平均**	**n**	**平均**	**n**	**平均**	**n**	**平均**
SPIOLTO RESPIMAT 比上	522	--	502	--	521	--	497	--
Tiotropium 5 mcg	526	0.117 L	500	0.103 L	520	0.071 L	498	0.050 L
Olodaterol 5 mcg	525	0.123 L	507	0.132 L	519	0.082 L	503	0.088 L

治療前基準點 FEV_1 = 1.16 L(試驗 1)與 1.15 L(試驗 2）

所有比較的 p 值均≤0.0001

n=受試者人數。

與基期時可逆性程度較低的病人相較，基期時可逆性程度較高的病人對 SPIOLTO RESPIMAT 通常有較高的支氣管擴張反應。

SPIOLTO RESPIMAT 組支氣管擴張效果高於 tiotropium 5 mcg 組和 olodaterol 5 mcg 組的現象，在整個 52 週治療期內皆持續存在。根據病人的每日記錄結果，SPIOLTO RESPIMAT 組的晨間和夜間尖峰呼氣流速(PEFR)也優於 tiotropium 5 mcg 組和 olodaterol 5 mcg 組。

在為期 6 週的試驗中，於 24 小時的用藥間隔全程內，SPIOLTO RESPIMAT 組的 FEV_1 反應均顯著高於 tiotropium 5 mcg 組、olodaterol 5 mcg 組和安慰劑組(表 2)。

表2　6週後，SPIOLTO RESPIMAT組相較於tiotropium 5 mcg組、olodaterol 5 mcg組與安慰劑組，在3小時、12小時與24小時之FEV1 (L)平均值上的差異以及在谷底期FEV1 (L)上的差異 (試驗3)。

	n	3 小時平均	n	12 小時平均	24 小時平均 [1]	谷底期
SPIOLTO RESPIMAT 比上	138		138			
Tiotropium 5 mcg	137	0.109	135	0.119	0.110	0.079
Olodaterol 5 mcg	138	0.109	136	0.126	0.115	0.092
安慰劑	135	0.325	132	0.319	0.280	0.207

治療前基準點FEV_1 = 1.30 L
[1] 主要評估指標
所有比較的p值均<0.0001
n=受試者人數。

呼吸困難
在 24 週之後[試驗 1 與試驗 2]，SPIOLTO RESPIMAT 組的 TDI 總分(focal score)平均值為 1.98 單位，較 tiotropium 5 mcg 組(平均值差異為 0.36，p=0.008)和 olodaterol 5 mcg 組(平均值差異為 0.42，p=0.002)顯著改善(表 3)。

SPIOLTO RESPIMAT 組內，TDI 總分改善幅度高於最小臨床重要差異值(MCID，定義為至少達 1 單位的數值)的受試者多於 tiotropium 5 mcg 組(54.9%相較於 50.6%，p=0.0546）和 olodaterol 5 mcg 組(54.9%相較於 48.2%，p=0.0026)。

表3 在24週治療後的TDI總分[試驗1與試驗2**]**

	n	治療平均值	與SPIOLTO RESPIMAT組的差異
			平均值(p-值)
SPIOLTO RESPIMAT	992	1.98	
Tiotropium 5 mcg	978	1.63	0.36 (p=0.008)
Olodaterol 5 mcg	984	1.56	0.42 (p=0.002)

救援藥物使用

接受 SPIOLTO RESPIMAT 治療者的日間及夜間救援藥物 salbutamol 使用量較 tiotropium 5 mcg 組和 olodaterol 5 mcg 組少(SPIOLTO RESPIMAT 組的日間救援藥物使用次數平均為 0.76 次／天，tiotropium 5 mcg 組為 0.97 次／天，olodaterol 5 mcg 組為 0.87 次／天，p<0.0001；夜間救援藥物使用次數平均為 1.24 次／天，tiotropium 5 mcg 組為 1.69 次／天，olodaterol 5 mcg 組為 1.52 次／天，p<0.0001) [試驗 1 與試驗 2]。

病人全面評比

以病人全面評比(Patient´s Global Rating，簡稱 PGR)量表進行評估時，相較於 tiotropium 5 mcg 組和 olodaterol 5 mcg 組，SPIOLTO RESPIMAT 組受試者感受其呼吸狀況獲得較大幅度的改善[試驗 1 與試驗 2]。

急性惡化

過往研究已證實 tiotropium 5 mcg 的 COPD 急性惡化在統計上顯著低於安慰劑。為期 52 週的樞紐試驗(試驗 1 和試驗 2)將 COPD 急性惡化納為一項額外的評估指標。在合併資料中，經歷至少一次中度/重度 COPD 急性惡化的病人比例在 SPIOLTO RESPIMAT 組內為 27.7%，在 tiotropium 5 mcg 組內則為 28.8% (p=0.39)。這些試驗並非專門設計用於評估療法對於 COPD 急性惡化的影響。

在一項為期一年隨機、雙盲、活性對照、平行組別的臨床試驗(試驗9)中，比較SPIOLTO RESPIMAT和tiotropium 5 mcg對COPD急性惡化的作用。除了抗膽鹼藥物、長效β-促效劑及其複方外，其他的呼吸道藥物均可作為併用治療，亦即速效β-促效劑、吸入皮質類固醇和xanthines。主要療效指標是全年中度至重度COPD惡化率(接受SPIOLTO RESPIMAT和tiotropium 5 mcg治療分別為3939例及3941例)。

大部分病人是男性(71.4%)和白種人(79.3%)。平均年齡為 66.4 歲，使用支氣管擴張劑後的 FEV1 平均值為 1.187 L(SD 0.381)，29.4%的病人具有臨床重大的心血管病史。

COPD 的中度至重度急性惡化定義為「與潛在疾病 COPD 相關之下呼吸道事件/症狀(增加或新發生)，需持續三天以上，需要投予抗生素和/或全身性類固醇和/或住院」。

SPIOLTO RESPIMAT 在全年中度至重度 COPD 急性惡化率相較於 tiotropium 5 mcg 治療降低了 7%。本試驗主要療效指標全年中度至重度 COPD 惡化率，事先設定之顯著水準為 p< 0.01，結果顯示 SPIOLTO RESPIMAT 治療在統計上未達顯著優於 tiotropium 5 mcg 吸入噴霧劑(RR 0.93，99%信賴區間(CI)，0.85-1.02，p =0.0498)。

健康相關生活品質

聖喬治呼吸問卷(SGRQ)總分降低，顯示出SPIOLTO RESPIMAT可改善健康相關生活品質。在24週之後[試驗1與試驗2]，相較於tiotropium 5 mcg和olodaterol 5 mcg，SPIOLTO RESPIMAT組的SGRQ總分的平均值獲得統計上顯著的改善(表4)；且於全部的SGRQ面向中皆可看到改善效果。SPIOLTO RESPIMAT組內，SGRQ總分改善幅度高於最小臨床重要差異值(MCID，定義為自基準點至少下降4個單位)的受試者多於tiotropium 5 mcg組(57.5%相較於48.7%，p=0.0001)和olodaterol 5 mcg組(57.5%相較於44.8%，p<0.0001)。

表 4：治療 24 週之後的 SGRQ 總分(試驗 1 與試驗 2)

		n	治療平均值（與基準值的差異）	與 SPIOLTO® RESPIMAT®組的差異
				平均值(p-值)
總分	基準點		43.5	
	SPIOLTO RESPIMAT	979	36.7 (-6.8)	
	Tiotropium 5 mcg	954	37.9 (-5.6)	-1.23 (p=0.025)
	Olodaterol 5 mcg	954	38.4 (-5.1)	-1.69 (p=0.002)

n=受試者人數。

吸氣容量、呼吸不適以及運動耐力

SPIOLTO RESPIMAT 在 COPD 病人中對吸氣容量、呼吸不適及受症狀限制之運動耐力的影響，已在隨機分組、雙盲的 2 項試驗中進行研究：

(i) 於固定功率單車騎乘過程中，以 SPIOLTO RESPIMAT 與 tiotropium 5 mcg、olodaterol 5 mcg 和安慰劑比較、交叉用藥、為期 6 週的 2 項重複試驗(450 人使用 SPIOLTO RESPIMAT)[試驗 4 與 5]

(ii) 於固定功率單車騎乘(139 人使用 SPIOLTO RESPIMAT)和固定速率行走(一部分受試者)過程中，以 SPIOLTO RESPIMAT 與安慰劑比較、平行組別、為期 12 週的 1 項試驗 [試驗 6]

在 6 週之後， SPIOLTO RESPIMAT 組用藥後 2 小時之休息時呼氣容量顯著優於 tiotropium 5 mcg (0.114 L，p<0.0001；試驗 4，0.088 L，p=0.0005；試驗 5)、olodaterol 5 mcg (0.119 L，p<0.0001；試驗 4，0.080 L，p=0.0015；試驗)和安慰劑(0.244 L，p<0.0001；試驗 4，0.265 L，p<0.0001；試驗 5)。

在 6 週之後，在試驗 4 和試驗 5 中，相較於安慰劑，SPIOLTO RESPIMAT 可使固定功率單車騎乘的耐久時間顯著改善(試驗 4：SPIOLTO RESPIMAT 組的耐久時間幾何平均值為 454 秒，安慰組為 375 秒，改善 20.9%，p<0.0001；試驗 5：SPIOLTO RESPIMAT 組的耐久時間幾何平均值為 466 秒，安慰組為 411 秒，改善 13.4%，p<0.0001)。

在試驗 6 中，12 週之後，SPIOLTO RESPIMAT 可使固定功率單車騎乘的耐久時間較安慰劑組顯著改善(SPIOLTO RESPIMAT 組的耐久時間幾何平均值為 528 秒，安慰劑組為 464 秒，改善 13.8%，p=0.021)。

兒童族群

依據藥物類別豁免規定，歐洲藥品局已豁免藥廠提交針對慢性阻塞性肺疾(COPD)兒童病人族群之所有子群所進行的 SPIOLTO RESPIMAT 試驗結果(在兒童使用之相關資訊詳見第 4.2 節)。

5.2 藥物動力學性質

a. 序言

以吸入途徑同時投予 tiotropium 和 olodaterol 時，各成分的藥物動力學參數係與各活性成分分開投予時的觀察值相近。

Tiotropium 和 olodaterol 在治療濃度下的藥物動力學呈線性關係。在重複每日一次吸入 tiotropium 時，可於第 7 天達到穩定狀態。在每日一次吸入 olodaterol 時，可於 8 天後達到穩定狀態，而累積暴露量較單劑時最高增至 1.8 倍。

b. 藥品使用後之活性物質的一般特性

吸收

Tiotropium：年輕健康自願者的尿液排泄資料顯示，經由 RESPIMAT 吸入器吸入的劑量約有 33%可進入體循環。研究發現以口服液劑型投藥時，絕對生體可用率為 2-3%。透過 RESPIMAT 吸入藥物後，可於吸入後 5-7 分鐘觀察到最高 tiotropium 血漿濃度。

Olodaterol：健康自願者於吸入 olodaterol 之後，絕對生體可用率估計約為 30%，但以口服液劑型投藥時，絕對生體可用率低於 1%。透過 RESPIMAT 吸入藥物後，通常可於吸入後 10 至 20 分鐘內達到最高 olodaterol 血漿濃度。

分佈

Tiotropium 與血漿蛋白的結合率為 72%，而分佈體積為 32 L/kg。大鼠研究已證實，tiotropium 穿透血腦障壁的能力並未達到具有任何意義的程度。

Olodaterol 與血漿蛋白的結合率約為 60%，而分佈體積為 1110 L。Olodaterol 為 P-gp、OAT1、OAT3 與 OCT1 轉運蛋白的受質。Olodaterol 不屬於以下轉運蛋白的受質：BCRP、MRP、OATP2、OATP8、OATP-B、OCT2 與 OCT3。

生物轉化

Tiotropium：此藥受到代謝的比例甚低，這可由「經靜脈投予之劑量有 74%以原型藥物的型態經由尿中排出」得證。Tiotropium 為一酯類，可經由非酵素途徑分解成醇類和酸類成分(分別為 N-methylscopine 和 dithienylglycolic acid)，兩者都不會與蕈毒鹼受體結合。在人類肝臟微粒體和人類肝細胞中進行的體內實驗顯示，還會有一部分藥物(佔經靜脈投予劑量的<20%)經由細胞色素 P450(CYP)2D6 和 3A4 依賴型氧化作用及後續的麩胱甘肽(glutathion)共軛結合作用代謝成多種第二階段代謝產物。

Olodaterol 可經由直接葡萄糖醛酸化作用(direct glucuronidation)以及甲氧基(methoxy)部分的 O-脫甲基作用(O-demethylation)而被大量代謝，接著即進行共軛結合作用(conjugation)。在找到的 6 種代謝產物中，僅有非共軛結合態的脫甲基產物可與 $ß_2$-受體結合；但在長期吸入建議治療劑量、或最高為其 4 倍的劑量時，血漿中仍偵測不到此代謝產物。細胞色素 P450 同功酶 CYP2C9 及 CYP2C8(CYP3A4 的貢獻極微）皆參與 olodaterol 的脫甲基作用，而尿苷雙磷酸葡萄糖醛酸基轉移酶(uridine diphosphate glycosyl transferase)同功酶 UGT2B7、UGT1A1、1A7 及 1A9 則參與 olodaterol 葡萄糖醛酸苷(olodaterol glucuronides)的形成過程。

清除

Tiotropium：在健康自願者的總清除率為 880 mL/min。經靜脈投予的 tiotropium 主要皆以原型藥物的型態由尿中排出(74%)。在穩定狀態下由 COPD 病人吸入時，尿中排泄量為劑量的 18.6%，其餘則主要是腸道中未被吸收、即將由糞便排除的藥物。Tiotropium

的腎臟清除率超過腎絲球過濾率，代表腎臟會將藥物主動分泌至尿中。經 COPD 病人吸入後，tiotropium 的有效半衰期為 27 到 45 小時之間。

Olodaterol：Olodaterol 在健康自願者的總清除率為 872 ml/min，腎臟清除率為 173 mL/min。在靜脈注射[^{14}C]-olodaterol 後，38%的放射活性劑量可從尿液回收，53%由糞便回收。靜脈注射後從尿液回收的原型 olodaterol 約佔 19%。口服後從尿液回收的放射活性僅 9% (0.7%為未改變的 olodaterol)，大部分從糞便回收(84%)。在靜脈注射與口服之後，超過 90%的劑量分別於 6 天與 5 天內排除。在穩定狀態下，健康自願者吸入 olodaterol 之後，在用藥間隔期間內，原型 olodaterol 從尿液排泄的總量佔該劑量的 5-7%。吸入後血漿中的 olodaterol 濃度以雙相方式下降，終端半衰期約為 45 小時。

c. 在病人中的特性

Tiotropium：如同針對所有主要由腎臟排除的藥物所預期之狀況，tiotropium 的腎臟清除率會隨著年齡增長而下降：在<65 歲的 COPD 病人中為 347 mL/min，在≥65 歲的 COPD 病人中則為 275 mL/min。這並未導致 $AUC_{0-6,ss}$ 或 $C_{max,ss}$ 數值相對應地上升。

Olodaterol：使用 2 項有對照之臨床試驗(共納入 405 名 COPD 病人與 296 名氣喘病人)的資料所進行的一項藥物動力學綜合分析顯示，根據年齡、性別及體重對 olodaterol 全身性暴露量的影響，無須針對上述因子進行劑量調整。

人種

Olodaterol：針對藥物動力學資料所進行的研究內及研究間比較顯示，日本人及其他亞洲人的全身性暴露量有高於白種人的趨勢。

在一些針對白種人及亞洲人的臨床試驗中，以最高劑量為建議治療劑量兩倍的 Olodaterol Respimat 治療最長一年時，未發現任何安全上的顧慮。

腎功能不全

Tiotropium：輕度腎功能不全(CL_{CR} 50-80 mL/min)的 COPD 病人每日吸入一次 tiotropium 直到穩定狀態後，$AUC_{0-6,ss}$(高出 1.8 到 30%)會稍高於腎功能正常者(CL_{CR} >80 mL/min），而 $C_{max,ss}$ 則相近。中至重度腎功能不全(CL_{CR} <50 mL/min)的受試者經靜脈施用 tiotropium 後，總暴露量會是腎功能正常者的兩倍(AUC_{0-4h} 高出 82%，C_{max} 高出 52%)；吸入乾粉後的觀察可驗證上述結果。

Olodaterol: 腎功能不全病人的全身性暴露量未出現具臨床重要性的增加。

肝功能不全

Tiotropium：肝功能不全不預期會對 tiotropium 的藥物動力學特性帶來任何有意義的影響。Tiotropium 的主要清除方式，是腎臟的排除作用(在年輕健康自願者中佔 74%)，以及酯類單純經由非酵素途徑分解成無藥理活性之產物的作用。

Olodaterol：在輕度至中度肝功能不全的受試者，其 olodaterol 之清除率以及與蛋白質之結合狀況皆與健康的對照組無差異。尚未針對重度肝功能不全的病人進行研究。

5.3 臨床前安全性資料

Tiotropium + olodaterol

在併用 tiotropium/olodaterol 的非臨床試驗中，僅在暴露量遠超過人體最大暴露量(亦即不太可能在臨床使用的劑量)時才觀察到影響。

Tiotropium
基因毒性與致癌性研究顯示其對人體無特別危險性。
對於懷孕、胚胎／胎兒發育、分娩或出生後之發育的有害作用僅在對母體具毒性的劑量下才會出現。Tiotropium bromide 在大鼠或兔子不具致畸胎性。在局部或全身性暴露量超過治療暴露量 5 倍時可觀察到呼吸(刺激)及泌尿生殖系統(攝護腺炎)的變化與生殖毒性。

Olodaterol
基因毒性與致癌性研究顯示其對人體無特別危險性。
觀察到大鼠 mesovarian leiomyoma 與小鼠子宮 leiomyoma 及 leiomyosarcoma 的發生率皆增高。此為在嚙齒類動物長期暴露於高劑量 β2-促效劑之後觀察到的一種類別效應。目前為止尚未發現 β2-促效劑與癌症有關。

大鼠中，在 1054 mcg/kg/天的吸入劑量(為 5 mcg 劑量下人體暴露量[$AUC_{(0-24h)}$]的>2600 倍)下，未發生致畸胎作用。懷孕的 NZW 兔子中，在 2489 µg/kg/天的吸入劑量(依據 $AUC_{(0-24h)}$，約為 5 mcg 劑量下人體暴露量的 7130 倍)下，olodaterol 會引發 ß-腎上腺素受體刺激作用所造成的特有胎兒毒性，包括補綴性成骨作用(patchy ossifications)、骨骼較短或彎曲、眼睛張開不完全、顎裂、心血管異常。在 974 µg/kg／天的吸入劑量(依據 $AUC_{(0-24h)}$計算，約為 5 mcg 劑量的 1353 倍)下，無顯著的影響。

6 製藥學特性

6.1 賦形劑清單
氯化苯二甲羥胺(benzalkonium chloride)、依地酸二鈉(disodium edetate)、純水、用以調整酸鹼值之鹽酸。

6.2 不相容性
不適用

6.3 使用期限
請在外包裝標示之使用期限內使用。
本產品在藥罐插放入吸入器之後，僅能使用 3 個月。

6.4 儲存時之特殊注意事項
請勿冷凍!
請存放於兒童無法取得之處！
請存放於 30°C 以下!

6.5 容器之性質與容量
與本藥品接觸之容器的種類與材質：
藥液裝於聚乙烯/聚丙烯材質之藥罐，使用有矽膠密封圈的聚丙烯材質蓋子。藥罐包裹在鋁製圓筒內。
每個藥罐裝有 4 毫升吸入劑溶液。

包裝：
100 毫升以下鋁罐附舒沛噴吸入器。
供應的包裝大小與裝置：
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。

6.6 丟棄處置之特殊注意事項

任何未使用的藥品或廢棄物皆應根據當地法規要求丟棄處置。

病人之使用與操作說明

在開始使用 SPIOLTO RESPIMAT 前請閱讀使用與操作說明。

您每天只需使用此吸入器一次。每一次使用吸入器時請噴 2 下。

(A) 蓋子 (B)口含器 (C)通氣孔 (D)給藥按鈕
(E) 安全扣 (F)透明底座 (G) 穿刺裝置 (H)藥罐

SPIOLTO RESPIMAT 吸入器與 SPIOLTO RESPIMAT 藥罐

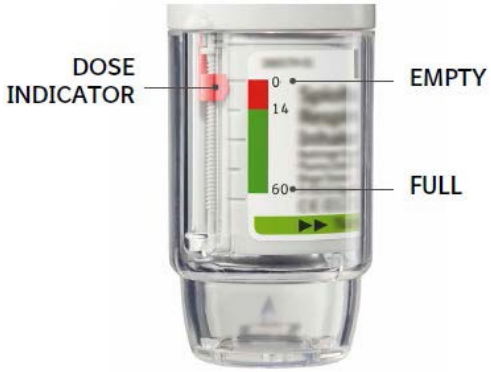
拋棄式 RESPIMAT 是一種吸入裝置，可產生慢速移動的氣霧供病人吸入
拋棄式 RESPIMAT 是供單一病人多次使用的裝置。

- 如果您的 SPIOLTO 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 SPIOLTO 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。
- 請勿觸摸透明底座內的穿刺裝置。

如何保養您的 SPIOLTO 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 SPIOLTO RESPIMAT 吸入器的功能。
必要時，可用濕布擦拭 SPIOLTO RESPIMAT 吸入器的外面。

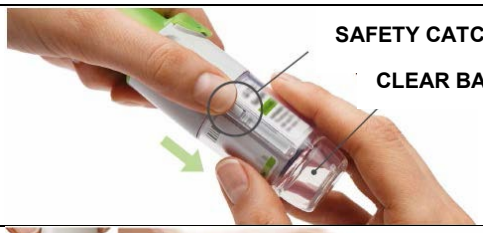
如何使用新的 SPIOLTO RESPIMAT 吸入劑



- **SPIOLTO RESPIMAT 吸入劑可提供 30 個劑量(60 噴)(2 噴/一天一次)。**
- **劑量顯示計(DOSE INDICATOR)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 SPIOLTO RESPIMAT 吸入劑。**
- **一旦劑量顯示計到達刻度上紅色區域的頂端(亦即 30 個劑量已全部用完)，表示 SPIOLTO RESPIMAT 吸入器會自動鎖住，無法再噴出藥物；此時，透明底座將無法再被旋轉。**
- **SPIOLTO 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 SPIOLTO RESPIMAT 吸入劑丟棄，不可再使用。**

<u>初次使用</u>

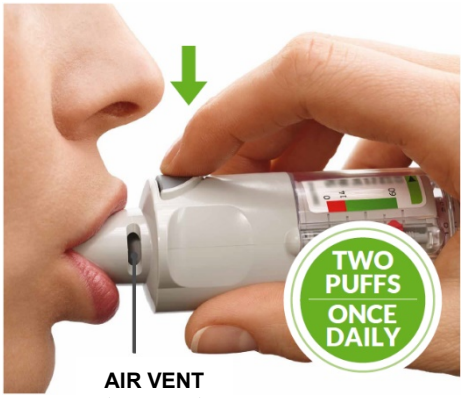
在第一次使用前，請務必執行步驟 1 至 6：

1. 移除透明底座 • 蓋子(A)必須蓋緊 • 按壓住安全扣(E)並用另一隻手拔下透明底座(F)。	
2. 插入藥罐 • 將藥罐(H)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. 裝回透明底座(F) • 裝回透明底座，直至發出卡嗒聲。	
4. 旋轉 • 確保蓋子蓋緊(A)。 • 將透明底座(F)依標籤上之箭頭方向旋轉，直到聽到「卡嗒」聲(約轉半圈)。	

5. 打開 打開蓋子(A)直到完全打開。	
6. 按壓 • 將SPIOLTO RESPIMAT 吸入器朝向地面。 • 按壓給藥按鈕(D)。 • 蓋上蓋子(A)。 • 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。 這些步驟不會影響可供使用的劑量數。在備妥 SPIOLTO RESPIMAT 吸入器後，本藥可提供 30 個劑量(噴 60 次）。	

<u>SPIOLTO® RESPIMAT®吸入器的每日使用步驟</u>

旋轉 • 確保蓋子蓋緊(A)。 • 將透明底座(F)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(A)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(C)。 • 通過口腔緩慢深呼吸時，按下給藥按鈕(D)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。 • 重複步驟旋轉、打開、按壓共2次。 • 蓋上蓋子直到下次再使用SPIOLTO RESPIMAT吸入劑。	 AIR VENT （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，請告知您的醫生或藥師。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

R1g/UK/SPC/a 16/06/2015

19 MAR 2021

修訂時間：2021 年 07 月

核定時間：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，請向您的醫生或藥師詢問。

CE 0123

Spiolto® Respimat®, Solution for Inhalation

1 NAME OF THE MEDICINAL PRODUCT

SPIOLTO RESPIMAT, Solution for Inhalation

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The delivered dose is 2.5 microgram tiotropium and 2.5 microgram olodaterol per puff (2 puffs comprise one medicinal dose) and is equivalent to 3.124 microgram tiotropium bromide monohydrate and 2.736 microgram olodaterol hydrochloride.

The delivered dose is the dose which is available for the patient after passing the mouthpiece.

Excipient with known effect: This medicine contains 0.0011 mg benzalkonium chloride in each actuation.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Inhalation solution
Clear, colourless, inhalation solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

SPIOLTO RESPIMAT is indicated as a long term maintenance treatment of patients with Chronic Obstructive Pulmonary Disease (including chronic bronchitis and emphysema).

4.2 Posology and method of administration

The product should be used by physicians.
Posology
The medicinal product is intended for inhalation use only. The cartridge can only be inserted and used in the Respimat inhaler.

Two puffs from the Respimat inhaler comprise one medicinal dose.

Adults
The recommended dose is 5 microgram tiotropium and 5 microgram olodaterol given as two puffs from the Respimat inhaler once daily, at the same time of the day.

The recommended dose should not be exceeded.

Elderly population
Elderly patients can use SPIOLTO RESPIMAT at the recommended dose.

Hepatic impairment and Renal impairment
SPIOLTO RESPIMAT contains tiotropium which is a predominantly renally excreted drug and olodaterol, which is predominantly metabolized in the liver.

Hepatic impairment
Patients with mild and moderate hepatic impairment can use SPIOLTO RESPIMAT at the recommended dose.

There are no data available for use of olodaterol in patients with severe hepatic impairment.

Renal impairment
Renally impaired patients can use SPIOLTO RESPIMAT at the recommended dose.
For patients with moderate to severe impairment (creatinine clearance ≤ 50 ml/min) see 4.4 and 5.2.

SPIOLTO RESPIMAT contains olodaterol. There is limited experience with the use of olodaterol in patients with severe renal impairment.

Paediatric population
There is no relevant use of SPIOLTO RESPIMAT in the paediatric population (under 18 years).

Method of administration
To ensure proper administration of the medicinal product, the patient should be shown how to use the inhaler by a physician or other health care professionals.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

History of hypersensitivity to atropine or its derivatives, e.g. ipratropium or oxitropium.

4.4 Special warnings and precautions for use

Asthma
SPIOLTO RESPIMAT should not be used in asthma. The efficacy and safety of SPIOLTO RESPIMAT in asthma have not been studied.

Not for acute use
SPIOLTO RESPIMAT is not indicated for the treatment of acute episodes of bronchospasm, i.e. as rescue therapy.

Paradoxical bronchospasm
As with other inhaled medicines SPIOLTO RESPIMAT may result in paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs SPIOLTO RESPIMAT should be discontinued immediately and alternative therapy substituted.

Anticholinergic effects related to tiotropium

Narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction
Consistent with the anticholinergic activity of tiotropium, SPIOLTO RESPIMAT should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction.

Eye symptoms
Patients should be cautioned to avoid getting the spray into their eyes. They should be advised that this may result in precipitation or worsening of narrow-angle glaucoma, eye pain or discomfort, temporary blurring of vision, visual halos or coloured images in association with red eyes from conjunctival congestion and corneal oedema. Should any combination of these eye symptoms develop, patients should stop using SPIOLTO RESPIMAT and consult a specialist immediately.

Dental caries
Dry mouth, which has been observed with anti-cholinergic treatment, may in the long term be associated with dental caries.

Patients with renal impairment
As plasma concentration of tiotropium increases with decreased renal function in patients with moderate to severe renal impairment (creatinine clearance ≤ 50 ml/min) SPIOLTO RESPIMAT should be used only if the expected benefit outweighs the potential risk. There is no long term experience in patients with severe renal impairment (see 5.2).

Cardiovascular effects
The experience with SPIOLTO RESPIMAT is limited in patients with a history of myocardial infarction during the previous year, unstable or life-threatening cardiac arrhythmia, hospitalized for heart failure during the previous year or with a diagnosis of paroxysmal tachycardia (>100 beats per minute) because these patients were excluded from the clinical trials. SPIOLTO RESPIMAT should be used with caution in these patient groups.

Like other beta$_2$-adrenergic agonists, olodaterol may produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms. In case such effects occur, treatment may need to be discontinued. In addition, beta-adrenergic agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave and ST segment depression, although the clinical significance of these observations is unknown.

Long acting beta$_2$-adrenergic agonists should be administered with caution in patients with cardiovascular disorders, especially ischaemic heart disease, severe cardiac decompensation, cardiac arrhythmias, hypertrophic obstructive cardiomyopathy**,** hypertension, and aneurysm, in patients with convulsive disorders or thyrotoxicosis, in patients with known or suspected prolongation of the QT interval (e.g. QT> 0.44 s), and in patients who are unusually responsive to sympathomimetic amines.

Hypokalaemia
Beta$_2$-adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. In patients with severe COPD, hypokalaemia may be potentiated by hypoxia and concomitant treatment (see section 4.5), which may increase the susceptibility to cardiac arrhythmias.

Hyperglycaemia
Inhalation of high doses of beta$_2$-adrenergic agonists may produce increases in plasma glucose.

Anaesthesia

Caution needs to be taken in case of a planned operation with halogenated hydrocarbon anaesthetics due to an increased susceptibility to the adverse cardiac effects of beta agonist bronchodilators.

SPIOLTO RESPIMAT should not be used in conjunction with any other medications containing long-acting beta$_2$-adrenergic agonists.
Patients who have been taking inhaled, short-acting beta$_2$-adrenergic agonists on a regular basis (e.g. four times a day) should be instructed to use them only for symptomatic relief of acute respiratory symptoms.

SPIOLTO RESPIMAT should not be used more frequently than once daily.

Hypersensitivity
As with all medications, immediate hypersensitivity reactions may occur after administration of SPIOLTO RESPIMAT.

Excipients
Benzalkonium chloride may cause wheezing and breathing difficulties. Patients with asthma are at an increased risk for these adverse events.

4.5 Interaction with other medicinal products and other forms of interaction

Although no formal *in vivo* drug interaction studies have been performed between SPIOLTO RESPIMAT and other drugs, inhaled SPIOLTO RESPIMAT has been used concomitantly with other COPD medicinal products, including short acting sympathomimetic bronchodilators and inhaled corticosteroids without clinical evidence of drug interactions.

Anticholinergic agents
The co-administration of tiotropium bromide, one component of SPIOLTO RESPIMAT, with other anticholinergic containing drugs has not been studied and therefore is not recommended.

Adrenergic agents
Concomitant administration of other adrenergic agents (alone or as part of combination therapy) may potentiate the undesirable effects of SPIOLTO RESPIMAT.

Xanthine derivatives, steroids or diuretics
Concomitant treatment with xanthine derivatives, steroids, or non-potassium sparing diuretics may potentiate any hypokalaemic effect of adrenergic agonists (see section 4.4).

Beta-blockers
Beta-adrenergic blockers may weaken or antagonise the effect of olodaterol. Cardioselective beta-blockers could be considered, although they should be administered with caution.

MAO inhibitors and tricyclic antidepressants, QTc Prolonging drugs
Monamine oxidase inhibitors or tricyclic antidepressants or other drugs known to prolong the QTc interval may potentiate the action of SPIOLTO RESPIMAT on the cardiovascular system.

Pharmacokinetic Drug Drug interactions
No relevant effect on systemic exposure to olodaterol has been observed in drug-drug interaction studies with co-administration of fluconazole, used as model inhibitor of CYP2C9.

Co-administration of ketoconazole as potent P-gp and CYP3A4 inhibitor increased systemic exposure to olodaterol by approximately 70%. No dose adjustment of SPIOLTO RESPIMAT is necessary.

In vitro investigations have shown that olodaterol does not inhibit CYP enzymes or drug transporters at the plasma concentrations achieved in clinical practice.

4.6 Fertility, pregnancy and lactation

Pregnancy

Tiotropium
There is a very 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 (see 5.3).

Olodaterol
For olodaterol no clinical data on exposed pregnancies are available. Preclinical data for olodaterol revealed effects typical for beta-adrenergic agonists at high multiples of the therapeutic doses (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of SPIOLTO RESPIMAT during pregnancy.

Like other beta$_2$-adrenergic agonists, olodaterol a component of SPIOLTO RESPIMAT may inhibit labour due to a relaxant effect on uterine smooth muscle.

Breast-feeding
Clinical data from nursing women exposed to tiotropium and/or olodaterol are not available.

In animal studies for both tiotropium and olodaterol the substances and/or their metabolites have been detected in the milk of lactating rats, but it is not known whether tiotropium and/or olodaterol passes into human breast milk.

A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with SPIOLTO RESPIMAT should be made taking into account the benefit of breast-feeding to the child and the benefit of SPIOLTO RESPIMAT therapy to the woman.

Fertility
Clinical data on fertility are not available for tiotropium and olodaterol or the combination of both components. Preclinical studies performed with the individual components tiotropium and olodaterol showed no indication of any adverse effect on fertility (see 5.3).

4.7 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 dizziness and blurred vision have been reported with the use of SPIOLTO RESPIMAT. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience such symptoms, they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

a. Summary of the safety profile

Many of the listed undesirable effects can be assigned to the anticholinergic properties of tiotropium bromide or to the ß$_2$-adrenergic properties of olodaterol, the components of SPIOLTO RESPIMAT.

b. Tabulated summary of adverse reactions

The frequencies assigned to the undesirable effects listed below are based on the crude incidence rates of adverse drug reactions (i.e. events attributed to SPIOLTO RESPIMAT) observed in the tiotropium 5 microgram/olodaterol 5 microgram dose group (5646 patients), pooled from 8 active or placebo-controlled, parallel group clinical trials in COPD patients with treatment periods ranging between 4 and 52 weeks.

Adverse reactions reported in all clinical trials with SPIOLTO RESPIMAT are shown below according to system organ class.
These also include all adverse reactions previously reported with one of the individual components.

Frequency is defined using the following convention:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data)

System Organ Class	Adverse reaction	Frequency
Infections and infestations	Nasopharyngitis	not known
Metabolism and nutrition disorders	Dehydration	not known
Nervous system disorders	Dizziness	uncommon
	Insomnia	rare
	Headache	uncommon
Eye disorders	Vision blurred	rare
	Glaucoma	not known
	Intraocular pressure increased	not known
Cardiac disorders	Atrial fibrillation	rare
	Palpitations	rare
	Tachycardia	uncommon
	Supraventricular tachycardia	rare
Vascular disorders	Hypertension	rare
Respiratory, thoracic and mediastinal disorders	Cough	uncommon
	Dysphonia	uncommon

	Epistaxis	rare
	Laryngitis	rare
	Pharyngitis	rare
	Bronchospasm	rare
	Sinusitis	not known
Gastrointestinal disorders	Dry mouth	uncommon
	Constipation	rare
	Gingivitis	rare
	Nausea	rare
	Oropharyngeal candidiasis	rare
	Intestinal obstruction Ileus paralytic	not known
	Dental caries	not known
	Dysphagia	not known
	Gastrooesophageal reflux disease	not known
	Glossitis	not known
	Stomatitis	rare
Skin and subcutaneous tissue disorders, Immune system disorders	Angioedema	rare
	Urticaria	rare
	Hypersensitivity	rare
	Pruritus	rare
	Anaphylactic reaction	not known
	Rash	rare
	Dry skin	not known
	Skin infection and skin ulcer	not known
Musculoskeletal and connective tissue disorders	Back pain[1]	rare
	Arthralgia	rare
	Joint swelling	rare
Renal and urinary disorders	Urinary retention	rare
	Dysuria	rare
	Urinary tract infection	rare

[1] undesirable effects reported with SPIOLTO® RESPIMAT®, but not with the individual components

c. Description of selected adverse reactions

SPIOLTO RESPIMAT combines anticholinergic and ß$_2$-adrenergic properties due to its components tiotropium and olodaterol.

Anticholinergic adverse reaction profile
In the long term 52-weeks clinical trials with SPIOLTO RESPIMAT, the most frequently observed undesirable anticholinergic effect was dry mouth which occurred in approximately 1.3% of patients treated with SPIOLTO RESPIMAT and in 1.7% and 1% in the tiotropium 5 microgram and olodaterol 5 microgram arms, respectively. Dry mouth led to discontinuation in 2 of 4,968 patients (0.04 %) treated with SPIOLTO RESPIMAT.

Serious undesirable effects consistent with anticholinergic effects include glaucoma, constipation, intestinal obstruction including ileus paralytic and urinary retention.

ß-adrenergic adverse reaction profile

Olodaterol, one component of SPIOLTO RESPIMAT is a member of the therapeutic class of long-acting beta$_2$-adrenergic agonists. Therefore the occurrence of other undesirable effects related to the beta-adrenergic agonist class, which are not listed above, should be taken into consideration, such as, arrhythmia, myocardial ischaemia, angina pectoris, hypotension, tremor, nervousness, muscle spasms, fatigue, malaise, hypokalemia, hyperglycemia, and metabolic acidosis.

d. Other special populations
An increase in anticholinergic effect may occur with increasing age.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://adr.fda.gov.tw.

4.9 Overdose

There is limited information on overdosing with SPIOLTO RESPIMAT. SPIOLTO RESPIMAT has been studied up to 5 microgram / 10 microgram (tiotropium/olodaterol) in COPD patients and up to 10 microgram / 40 microgram (tiotropium/olodaterol) in healthy subjects; no clinically relevant effects were observed. An overdose could lead to exaggerated anti-muscarinic effects of tiotropium and/or exaggerated β_2 agonists effects of olodaterol.

Symptoms
Overdose of anticholinergic tiotropium
High doses of tiotropium may lead to anticholinergic signs and symptoms.

However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 340 microgram tiotropium bromide in healthy volunteers. Additionally, no relevant adverse events, beyond dry mouth/throat and dry nasal mucosa were observed following 14-day dosing of up to 40 microgram tiotropium inhalation solution in healthy volunteers with the exception of pronounced reduction in salivary flow from day 7 onwards.

Overdose of ß$_2$-agonist olodaterol
An overdose of olodaterol is likely to lead to exaggerated effects typical of beta$_2$-adrenergic agonists, e.g. myocardial ischaemia, hypertension or hypotension, tachycardia, arrhythmias,

palpitation, dizziness, nervousness, insomnia, anxiety, headache, tremor, dry mouth, muscle spasms, nausea, fatigue, malaise, hypokalemia, hyperglycemia, and metabolic acidosis.

Treatment of overdose
Treatment with SPIOLTO RESPIMAT should be discontinued. Supportive and symptomatic treatment is indicated. Serious cases should be hospitalised. Use of cardioselective beta-blockers may be considered, but only subject to extreme caution since the use of beta-adrenergic blocker medication may provoke bronchospasm.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Drugs for obstructive airway diseases, adrenergics in combination with anticholinergics
ATC code: R03AL06

Mechanism of action
SPIOLTO RESPIMAT
SPIOLTO RESPIMAT is a fixed dose combination inhalation solution containing a long acting muscarinic receptor antagonist, tiotropium and a long acting beta2-adrenergic agonist, olodaterol (LAMA/LABA) which is delivered via the SPIOLTO RESPIMAT soft mist inhaler device.

The two active ingredients provide additive bronchodilation due to their different mode of action. Since muscarinic receptors appear to be more prominent in the central airways while ß$_2$ adrenoceptors have a higher expression level in the peripheral airways, a combination of tiotropium and olodaterol should provide optimal bronchodilatation in all regions of the lungs.

Tiotropium
Tiotropium bromide is a long-acting, specific antagonist at muscarinic receptors. It has similar affinity to the subtypes, M_1 to M_5. In the airways, tiotropium bromide competitively and reversibly binds to the M_3 receptors in the bronchial smooth musculature, antagonising the cholinergic (bronchoconstrictive) effects of acetylcholine, resulting in bronchial smooth muscle relaxation. The effect was dose dependent and lasted longer than 24h. As an N-quaternary anticholinergic, tiotropium bromide is topically (broncho-) selective when administered by inhalation, demonstrating an acceptable therapeutic range before systemic anticholinergic effects may occur.

Olodaterol
Olodaterol has a high affinity and high selectivity to the human beta$_2$-adrenoceptor.
In vitro studies have shown that olodaterol has 241-fold greater agonist activity at beta$_2$-adrenoceptors compared to beta$_1$-adrenoceptors and 2299-fold greater agonist activity compared to beta$_3$-adrenoceptors.
The compound exerts its pharmacological effects by binding and activation of beta$_2$-adrenoceptors after topical administration by inhalation.
Activation of these receptors in the airways results in a stimulation of intracellular adenyl cyclase, an enzyme that mediates the synthesis of cyclic-3',5' adenosine monophosphate (cAMP). Elevated levels of cAMP induce bronchodilation by relaxation of airway smooth muscle cells.
Olodaterol has the pre-clinical profile of a long-acting selective beta$_2$-adrenoceptor agonist (LABA) with a fast onset of action and a duration of action of at least 24 hours.

Beta-adrenoceptors are divided into three subtypes, $beta_1$-adrenoceptors predominantly expressed on cardiac muscle, $beta_2$-adrenoceptors predominantly expressed on airway smooth muscle and $beta_3$-adrenoceptors predominantly expressed on adipose tissue. $Beta_2$-agonists cause bronchodilation. Although the $beta_2$-adrenoceptor is the predominant adrenergic receptor in the airway smooth muscle it is also present on the surface of a variety of other cells, including lung epithelial and endothelial cells and in the heart. The precise function of $beta_2$-receptors in the heart is not known, but their presence raises the possibility that even highly selective $beta_2$-adrenergic agonists may have cardiac effects.

Effects on cardiac electrophysiology

Tiotropium
In a dedicated QT study involving 53 healthy volunteers, tiotropium inhalation powder 18 microgram and 54 microgram (i.e. three times the therapeutic dose) over 12 days did not significantly prolong QT intervals of the ECG.

Olodaterol
The effect of olodaterol on the QT/QTc interval of the ECG was investigated in 24 healthy male and female volunteers in a double-blind, randomised, placebo- and active (moxifloxacin) controlled study. Olodaterol at single doses of 10, 20, 30 and 50 microgram, demonstrated that compared with placebo, the mean changes from baseline in QT interval over 20 minutes to 2 hours after dosing increased dose-dependently from 1.6 (10 microgram olodaterol) to 6.5 ms (50 microgram olodaterol), with the upper limit of the two-sided 90% confidence intervals being less than 10 ms at all dose levels for individually corrected QT (QTcI).

The effect of 5 microgram and 10 microgram olodaterol on heart rate and rhythm was assessed using continuous 24-hour ECG recording (Holter monitoring) in a subset of 772 patients in the 48-week, placebo-controlled Phase 3 trials. There were no dose- or time-related trends or patterns observed for the magnitudes of mean changes in heart rate or premature beats. Shifts from baseline to the end of treatment in premature beats did not indicate meaningful differences between olodaterol 5 microgram, 10 microgram and placebo.

SPIOLTO RESPIMAT
Two 52-week randomized, double-blind trials using SPIOLTO RESPIMAT enrolled 5162 patients with COPD. In a pooled analysis the number of subjects with changes from baseline-corrected QTcF (Fridericia correction) interval of >30 msec at 40 minutes post-dose on day 85, 169, and 365, ranged from 3.1%, 4.7%, and 3.6% for the SPIOLTO RESPIMAT group compared to 4.1%, 4.4%, and 3.6% for olodaterol 5 microgram and 3.4%, 2.3%, and 4.6% for the tiotropium 5 microgram group, respectively.

Clinical efficacy and safety
The Phase III clinical development program for SPIOLTO RESPIMAT included three randomised, double-blind trials:
(i) two replicate, 52 week parallel group trials comparing SPIOLTO RESPIMAT with tiotropium 5 microgram and olodaterol 5 microgram (1029 received SPIOLTO RESPIMAT) [Trials 1 and 2]
(ii) one 6 week cross-over trial comparing SPIOLTO RESPIMAT with tiotropium 5 microgram and olodaterol 5 microgram and placebo (139 received SPIOLTO RESPIMAT) [Trial 3]

In these trials, the comparator products, tiotropium 5 microgram, olodaterol 5 microgram and placebo were administered via the Respimat inhaler.

Patient characteristics
The majority of the 5162 patients recruited in the global, 52 week trials [Trials 1 and 2] were male (73%), white (71%) or Asian (25%), with a mean age of 64.0 years. Mean post-bronchodilator FEV_1 was 1.37 L (GOLD 2 [50%], GOLD 3 [39%], GOLD 4 [11%]). Mean β_2-agonist responsiveness was 16.6% of baseline (0.171 L). Pulmonary medications allowed as concomitant therapy included inhaled steroids [47%] and xanthines [10%].

The 6 week trial [Trial 3] was conducted in Europe and North America. The majority of the 219 recruited patients were male (59%) and white (99%), with a mean age of 61.1 years. Mean post-bronchodilator FEV_1 was 1.55 L (GOLD 2 [64%], GOLD 3 [34%], GOLD 4 [2%]). Mean β_2-agonist responsiveness was 15.9% of baseline (0.193 L). Pulmonary medications allowed as concomitant therapy included inhaled steroids [41%] and xanthines [4%].

Effects on lung function
In the 52 week trials, SPIOLTO RESPIMAT administered once daily in the morning, provided clear improvement in lung function within 5 minutes after the first dose compared to tiotropium 5 microgram (mean increase in FEV_1 of 0.137 L for SPIOLTO RESPIMAT vs. 0.058 L for tiotropium 5 microgram [$p<0.0001$] and 0.125 L for olodaterol 5 microgram [$p=0.16$]).
In both studies, significant improvements were observed in FEV_1 AUC_{0-3h} response and trough FEV_1 response after 24 weeks (lung function primary endpoints) for SPIOLTO RESPIMAT compared to tiotropium 5 microgram and olodaterol 5 microgram (Table 1).

Table 1 Difference in FEV_1 AUC_{0-3h} and trough FEV_1 response for SPIOLTO® RESPIMAT® compared to tiotropium 5 microgram, olodaterol 5 microgram after 24 weeks (Trials 1 and 2)

	FEV_1 AUC_{0-3h} response				**Trough FEV_1 response**			
	Trial 1		**Trial 2**		**Trial 1**		**Trial 2**	
	n	**Mean**	**n**	**Mean**	n	**Mean**	**n**	**Mean**
SPIOLTO® RESPIMAT® versus	522	--	502	--	521	--	497	--
Tiotropium 5 microgram	526	0.117 L	500	0.103 L	520	0.071 L	498	0.050 L
Olodaterol 5 microgram	525	0.123 L	507	0.132 L	519	0.082 L	503	0.088 L

pre-treatment baseline FEV_1: Trial 1 = 1.16 L; Trial 2 = 1.15 L
$p \leq 0.0001$ for all comparisons
n= number of patients

Patients with a higher degree of reversibility at baseline generally exhibited a higher bronchodilator response with SPIOLTO RESPIMAT than patients with a lower degree of reversibility at baseline.

The increased bronchodilator effects of SPIOLTO RESPIMAT compared to tiotropium 5 microgram and olodaterol 5 microgram were maintained throughout the 52 week treatment period. SPIOLTO RESPIMAT also improved morning and evening PEFR (peak expiratory flow rate) compared to tiotropium 5 microgram and olodaterol 5 microgram as measured by patient's daily recordings.

In the 6 week trial, SPIOLTO RESPIMAT showed a significantly greater FEV_1 response compared to tiotropium 5 microgram, olodaterol 5 microgram and placebo ($p<0.0001$) over the full 24 hour dosing interval (Table 2).

Table 2 Average difference in FEV_1 (L) over 3 hr, 12 hr and 24 hr and difference in trough FEV_1 (L) for SPIOLTO RESPIMAT compared to tiotropium 5 microgram, olodaterol 5 microgram and placebo after 6 weeks (Trial 3)

	n	3 hr average	n	12 hr average	24 hr average[1]	Trough
SPIOLTO RESPIMAT versus	138		138			
Tiotropium 5 microgram	137	0.109	135	0.119	0.110	0.079
Olodaterol 5 microgram	138	0.109	136	0.126	0.115	0.092
Placebo	135	0.325	132	0.319	0.280	0.207

pre-treatment baseline FEV_1 = 1.30 L
[1] primary endpoint
$p<0.0001$ for all comparisons
n= number of patients

Dyspnea
After 24 weeks [Trials 1 and 2], mean TDI focal score was 1.98 units for SPIOLTO RESPIMAT, with a significant improvement compared to tiotropium 5 microgram (mean difference 0.36, p=0.008) and olodaterol 5 microgram (mean difference 0.42 (p=0.002)) (Table 3).

More patients treated with SPIOLTO RESPIMAT had a clinically meaningful improvement in TDI focal score (MCID, defined as a value of at least 1 unit) compared to tiotropium 5 microgram (54.9% vs. 50.6%, p=0.0546) and olodaterol 5 microgram (54.9% vs. 48.2%, p=0.0026).

Table 3: TDI focal score after 24 weeks of treatment [Trials 1 and 2]

	n	Treatment Mean	Difference to SPIOLTO RESPIMAT
			Mean (p-value)
SPIOLTO® RESPIMAT®	992	1.98	
Tiotropium 5 microgram	978	1.63	0.36 (p=0.008)
Olodaterol 5 microgram	984	1.56	0.42 (p=0.002)

Rescue Medication Use
Patients treated with SPIOLTO RESPIMAT used less daytime and nighttime rescue salbutamol compared to patients treated with tiotropium 5 microgram and olodaterol 5 microgram (mean daytime rescue use for SPIOLTO RESPIMAT of 0.76 occasions per day compared to 0.97 occasions per day for tiotropium 5 microgram and 0.87 occasions per day for olodaterol 5 microgram, $p<0.0001$; mean nighttime rescue use for SPIOLTO RESPIMAT of 1.24 occasions per day compared to 1.69 occasions per day for tiotropium 5 microgram and 1.52 occasions per day for olodaterol 5 microgram, $p<0.0001$) [Trials 1 and 2].

Patient Global Rating

Patients treated with SPIOLTO RESPIMAT perceived a greater improvement in their respiratory condition compared to tiotropium 5 microgram and olodaterol 5 microgram, as measured by a Patient´s Global Rating (PGR) scale [Trials 1 and 2].

Exacerbations
Tiotropium 5 microgram has previously demonstrated a statistically significant reduction in risk of a COPD exacerbation compared to placebo. COPD exacerbations was included as an additional endpoint in the 52 week pivotal trials (Trials 1 and 2). In the combined dataset, the proportion of patients experiencing at least one moderate/severe COPD exacerbation was 27.7% for SPIOLTO RESPIMAT and 28.8% for tiotropium 5 microgram (p=0.39). These studies were not specifically designed to evaluate the effect of treatments on COPD exacerbations.

In a one-year, randomised, double-blind, active-controlled parallel group clinical trial (Trial 9) SPIOLTO RESPIMAT was compared with tiotropium 5 microgram on COPD exacerbations. All respiratory medications except anticholinergics, long-acting beta-agonists and combinations thereof were allowed as concomitant treatment, i.e. rapidly acting beta-agonists, inhaled corticosteroids and xanthines. The primary endpoint was the annualised rate of moderate to severe COPD exacerbations (3939 patients received SPIOLTO RESPIMAT and 3941 patients received tiotropium 5 microgram).

The majority of patients were male (71.4%) and Caucasian (79.3%). The mean age was 66.4 years, mean post-bronchodilator FEV1 was 1.187 L (SD 0.381), and 29.4% of patients had a history of clinically important cardiovascular disease.

Exacerbations of COPD were defined as “a complex of lower respiratory events / symptoms (increase or new onset) related to the underlying COPD, with duration of three days or more, requiring a prescription of antibiotics and/or systemic steroids and/or hospitalisation”.

SPIOLTO RESPIMAT treatment resulted in an additional 7% reduction in the annualised rate of moderate to severe COPD exacerbation in comparison to tiotropium 5 microgram (rate ratio (RR) 0.93, 99% Confidence Interval (CI), 0.85-1.02, p=0.0498). SPIOLTO RESPIMAT treatment did not demonstrate superiority to tiotropium 5 microgram for the primary endpoint. The study was designed to reach a significance level of 1%.

Health-related Quality of Life
SPIOLTO RESPIMAT showed improvement in health-related quality of life as indicated by a reduction in St. George Respiratory Questionnaire (SGRQ) total score. After 24 weeks [Trials 1 and 2], there was a statistically significant improvement in mean SGRQ total score for SPIOLTO RESPIMAT compared to tiotropium 5 microgram and olodaterol 5 microgram (Table 4); improvements were seen in all SGRQ domains. More patients treated with SPIOLTO RESPIMAT had a clinically meaningful improvement in SGRQ total score (MCID, defined as a decrease of at least 4 units from baseline) compared to tiotropium 5 microgram (57.5% vs. 48.7%, p=0.0001) and olodaterol 5 microgram (57.5% vs. 44.8%, p<0.0001).

Table 4: SGRQ total score after 24 weeks of treatment [Trials 1 and 2]

		n	Treatment Mean (change from baseline)	Difference to SPIOLTO RESPIMAT
				Mean (p-value)
Total score	**Baseline**		43.5	
	SPIOLTO RESPIMAT	979	36.7 (-6.8)	
	Tiotropium 5 microgram	954	37.9 (-5.6)	-1.23 (p=0.025)
	Olodaterol 5 microgram	954	38.4 (-5.1)	-1.69 (p=0.002)

n= number of patients

Inspiratory capacity, breathing discomfort and exercise endurance

The effect of SPIOLTO RESPIMAT on inspiratory capacity, breathing discomfort and symptom-limited exercise endurance was investigated in three randomised, double-blind trials in COPD patients:

(i) two replicate, 6 week cross-over trials comparing SPIOLTO RESPIMAT with tiotropium 5 microgram, olodaterol 5 microgram and placebo during constant work rate cycling (450 received SPIOLTO RESPIMAT) [Trials 4 and 5]

(ii) one 12 week parallel group trial comparing SPIOLTO RESPIMAT with placebo during constant work rate cycling (139 received SPIOLTO RESPIMAT) and constant speed walking (sub-set of patients) [Trial 6]

SPIOLTO RESPIMAT significantly improved inspiratory capacity at rest two hours post-dose compared to tiotropium 5 microgram (0.114 L, p<0.0001; Trial 4, 0.088 L, p=0.0005; Trial 5), olodaterol 5 microgram (0.119 L, p<0.0001; Trial 4, 0.080 L, p=0.0015; Trial 5) and placebo (0.244 L, p<0.0001; Trial 4, 0.265 L, p<0.0001; Trial 5) after 6 weeks.

In Trials 4 and 5, SPIOLTO RESPIMAT significantly improved endurance time during constant work rate cycling compared to placebo after 6 weeks (Trial 4: geometric mean endurance time of 454s for SPIOLTO RESPIMAT compared to 375 seconds for placebo (20.9% improvement, p<0.0001); Trial 5: geometric mean endurance time of 466 seconds for SPIOLTO RESPIMAT compared to 411 seconds for placebo (13.4% improvement, p<0.0001).
In Trial 6, SPIOLTO RESPIMAT significantly improved endurance time during constant work rate cycling compared to placebo after 12 weeks (geometric endurance time of 528 seconds for SPIOLTO RESPIMAT compared to 464 seconds for placebo (13.8% improvement, p=0.021).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with SPIOLTO RESPIMAT in all subsets of the paediatric population in chronic obstructive pulmonary disease (COPD) as per decision on class waivers (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

a. General Introduction

When tiotropium and olodaterol were administered in combination by the inhaled route, the pharmacokinetic parameters for each component were similar to those observed when each active substance was administered separately.

Tiotropium and olodaterol demonstrate linear pharmacokinetics in the therapeutic range. On repeated once-daily inhalation administration, steady state of tiotropium is reached by day 7. Steady state of olodaterol is achieved after 8 days of once-daily inhalation, and accumulation is up to 1.8-fold as compared to a single dose.

b. General Characteristics of the Active Substance after Administration of the Medicinal Product

Absorption
Tiotropium: Urinary excretion data from young healthy volunteers suggests that approximately 33% of the dose inhaled via the RESPIMAT inhaler reaches the systemic circulation. The absolute bioavailability from an orally administered solution was found to be 2–3%. Maximum tiotropium plasma concentrations are observed 5–7 minutes after the inhalation via RESPIMAT.

Olodaterol: In healthy volunteers the absolute bioavailability of olodaterol following inhalation was estimated to be approximately 30%, whereas the absolute bioavailability was below 1% when given as an oral solution. Maximum olodaterol plasma concentrations generally are reached within 10 to 20 minutes following drug inhalation via RESPIMAT.

Distribution
Tiotropium has a plasma protein binding of 72% and shows a volume of distribution of 32 L/kg. Studies in rats have shown that tiotropium does not penetrate the blood-brain barrier to any relevant extent.

Olodaterol has a plasma protein binding of approximately 60% and shows a volume of distribution of 1110 L. Olodaterol is a substrate for the P-gp, OAT1, OAT3 and OCT1 transporter. Olodaterol is not a substrate for the following transporters: BCRP, MRP, OATP2, OATP8, OATP-B, OCT2 and OCT3.

Biotransformation
Tiotropium: The extent of metabolism is small. This is evident from 74% of an intravenous dose being excreted in the urine as unchanged drug. The ester tiotropium is nonenzymatically cleaved into its alcohol and acid component (N-methylscopine and dithienylglycolic acid, respectively), both not binding to muscarinic receptors. *In vitro* experiments with human liver microsomes and human hepatocytes suggest that some further drug (<20% of the dose after intravenous administration) is metabolised by cytochrome P450 (CYP) 2D6 and 3A4 dependent oxidation and subsequent glutathion conjugation to a variety of Phase II-metabolites.

Olodaterol is substantially metabolized by direct glucuronidation and by O-demethylation at the methoxy moiety followed by conjugation. Of the six metabolites identified, only the unconjugated demethylation product binds to $ß_2$-receptors; this metabolite however is not detectable in plasma after chronic inhalation of the recommended therapeutic dose or doses of up to 4-fold higher. Cytochrome P450 isozymes CYP2C9 and CYP2C8, with negligible contribution of CYP3A4, are involved in the O-demethylation of olodaterol, while uridine diphosphate glycosyl transferase isoforms UGT2B7, UGT1A1, 1A7 and 1A9 were shown to be involved in the formation of olodaterol glucuronides.

Elimination

Tiotropium: The total clearance in healthy volunteers is 880 mL/min. Intravenously administered tiotropium is mainly excreted unchanged in urine (74%). After inhalation by COPD patients to steady-state, urinary excretion is 18.6% of the dose, the remainder being mainly non-absorbed drug in gut that is eliminated via the faeces. The renal clearance of tiotropium exceeds the glomerular filtration rate, indicating active secretion into the urine. The effective half-life of tiotropium following inhalation by COPD patients ranges between 27 and 45 h.

Olodaterol: Total clearance of olodaterol in healthy volunteers is 872 mL/min, and renal clearance is 173 mL/min. Following intravenous administration of [^{14}C]-labelled olodaterol, 38% of the radioactive dose was recovered in the urine and 53% was recovered in faeces. The amount of unchanged olodaterol recovered in the urine after intravenous administration was 19%. Following oral administration, only 9% of the radioactivity (0.7% unchanged olodaterol) was recovered in urine, while the major portion was recovered in faeces (84%). More than 90% of the dose was excreted within 6 and 5 days following intravenous and oral administration, respectively. Following inhalation, excretion of unchanged olodaterol in urine within the dosing interval in healthy volunteers at steady state accounted for 5-7% of the dose. Olodaterol plasma concentrations after inhalation decline in a multiphasic manner with a terminal half-life of approximately 45 hours.

c. Characteristics in Patients

Tiotropium: 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.

Olodaterol: A pharmacokinetic meta-analysis utilizing data from 2 controlled clinical trials that included 405 patients with COPD and 296 patients with asthma showed that no dose adjustment is necessary due to effects of age, gender and weight on systemic exposure to olodaterol.

Race
Olodaterol: Comparison of pharmacokinetic data within and across studies with olodaterol revealed a trend for higher systemic exposure in Japanese and other Asians than in Caucasians. No safety concerns were identified in clinical studies with olodaterol in Caucasians and Asians of up to one year with olodaterol Respimat at doses up to twice the recommended therapeutic dose.

Renal Insufficiency
Tiotropium: 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 subjects with moderate to severe renal impairment (CL_{CR} <50 ml/min) intravenous administration of tiotropium resulted in twofold higher total exposure (82% higher AUC_{0-4h} and 52% higher C_{max}) compared to subjects with normal renal function, which was confirmed by observations after dry powder inhalation.

Olodaterol: There were no clinically relevant increases of systemic exposure in patients with renal impairment.

Hepatic Insufficiency
Tiotropium: 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.

Olodaterol: There was no evidence for differences in elimination of olodaterol, nor did protein binding differ, between subjects with mild or moderate hepatic impairment and their healthy controls. A study in subjects with severe hepatic impairment was not performed.

5.3 Preclinical safety data

Tiotropium + olodaterol
Effects in non-clinical studies with the combination tiotropium/olodaterol were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Tiotropium
Studies on genotoxicity and carcinogenic potential revealed no special hazard for humans. Harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development could only be demonstrated at maternally toxic dose levels. Tiotropium bromide was not teratogenic in rats or rabbits. The respiratory (irritation) and urogenital (prostatitis) changes and reproductive toxicity were observed at local or systemic exposures more than five-fold the therapeutic exposure.

Olodaterol
Studies on genotoxicity and carcinogenic potential revealed no special hazard for humans. Increased incidences were observed of mesovarian leiomyoma in rats and of uterus leiomyoma and leiomyosarcoma in mice. This is considered a class effect which is observed in rodents after long-term exposure to high doses of β_2-agonists. Up to now, β_2-agonists have not been associated with cancer in humans.

In rats, no teratogenic effects occurred after inhalation at doses of 1054 microgram/kg/day (> 2600 times the human exposure ($AUC_{(0-24h)}$) at the dose of 5 mcg). In pregnant NZW rabbits, an inhalation dose of 2489 microgram/kg/day (approximately 7130 times the human exposure at 5 microgram based on $AUC_{(0-24h)}$) of olodaterol exhibited fetal toxicity characteristically resulting from beta-adrenoceptor stimulation; these included patchy ossifications, short/bent bones, partially open eye, cleft palate, cardiovascular abnormalities. No significant effects occurred at an inhalation dose of 974 microgram/kg/day (approximately 1353 times the 5 microgram dose based on $AUC_{(0-24h)}$).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride
Disodium edetate
Water, purified
1M Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please use before the expiry date that label on the folding box, label.
The product only can be used for 3 months after insertion of the cartridge to the inhaler..

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Type and material of the container in contact with the medicinal product:
Solution filled into a polyethylene/polypropylene cartridge with a polypropylene cap with integrated silicone sealing ring. The cartridge is enclosed within an aluminium cylinder.
Each cartridge contains 4 ml inhalation solution.

Pack sizes and devices supplied:
1 cartridge of 4.0 ml + 1 Respimat inhaler
Expiration labelled on folding box, labels

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

<u>Patient's instructions for use and handling</u>

Read these Instructions for Use before you start using SPIOLTO RESPIMAT.

You will need to use this inhaler only ONCE A DAY. Each time you use it take TWO PUFFS.

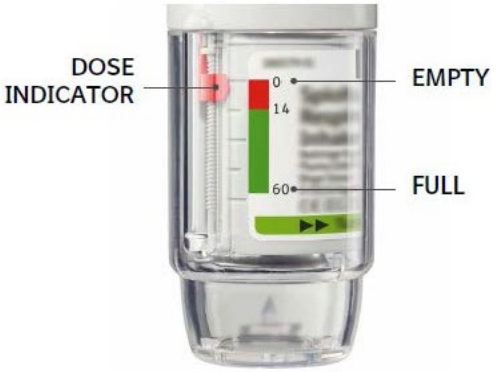
SPIOLTO RESPIMAT inhaler and the SPIOLTO RESPIMAT cartridge

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 under 'Prepare for first use' until a cloud is visible. Then repeat steps 4 to 6 three more times.
- Do not touch the piercing element inside the clear base.

How to care for your SPIOLTO 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 SPIOLTO RESPIMAT inhaler performance.
If necessary, wipe the outside of your SPIOLTO RESPIMAT inhaler with a damp cloth.

When to get a new SPIOLTO RESPIMAT

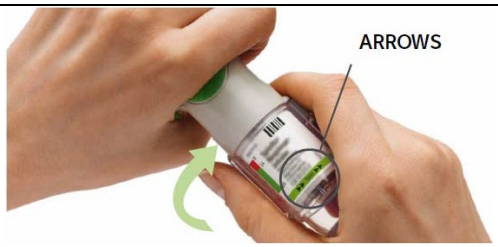


- Your SPIOLTO RESPIMAT inhaler contains 60 puffs (30 doses) if used as indicated (two puffs/Once daily).
- The dose indicator shows approximately how much medication is left.
- When the dose indicator enters the red area of the scale you need to get a new prescription; there is approximately medication for 7 days left (14 puffs).
- Once the dose indicator reaches the end of the red scale, your SPIOLTO 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 SPIOLTO RESPIMAT should be discarded even if it has not been used.

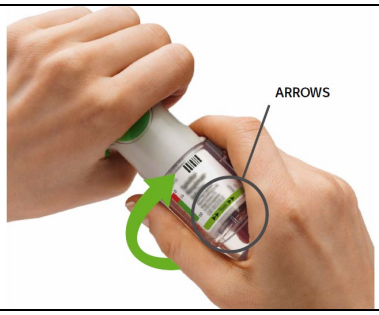
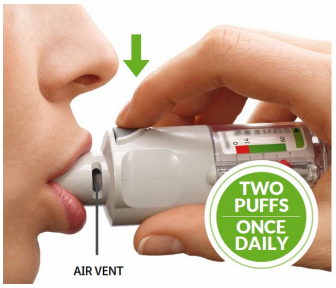
<u>Prepare for first use</u>

The following steps 1-6 are necessary before 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 inhaler is now ready to use. These steps will not affect the number of doses	

available. These steps will not affect the number of dose available. After preparation your inhaler will be able to deliver 60 puffs (30 doses).	

Daily use of your SPIOLTO RESPIMAT inhaler

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 incident
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

R1g/UK/SPC/a 16/06/2015

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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