Spiriva®
18 µg, inhalation powder, hard capsule with HandiHaler® device

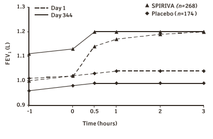
Boehringer Ingelheim

Composition
1 capsule for inhalation contains
tiotropium 18 mcg
equivalent to 22.5 mcg tiotropium bromide monohydrate (INN = tiotropium bromide)

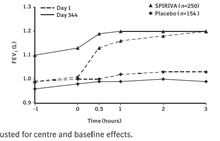
Pharmacological properties
Tiotropium is a long-acting, specific antimuscarinic agent, in clinical medicine often called an anticholinergic. It has a similar affinity to the subtypes of muscarinic receptors M_1 to M_5. In the airways, inhibition of M_3-receptors at the smooth muscle results in relaxation. 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 24 hours. 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 is topically (broncho-) selective when administered by inhalation, demonstrating an acceptable therapeutic range before giving rise to systemic anticholinergic effects. Dissociation from M_3-receptors is faster than from M_2, 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.
The bronchodilation following inhalation of tiotropium is primarily a local effect (on the airways) not a systemic one.
The clinical development program included four one-year and two six-month randomised, double-blind studies in 2663 patients with COPD (1308 receiving SPIRIVA). The one-year program consisted of two placebo-controlled and two ipratropium-controlled trials. The six-month trials were both salmeterol- and placebo-controlled. These studies included evaluation of lung function, dyspnoea, exacerbations of COPD and patients assessments of their health-related quality of life.
In the aforementioned studies, SPIRIVA administered once daily, provided significant improvement in lung function (forced expiratory volume in one second, FEV_1 and forced vital capacity, FVC) within 30 minutes following the first dose and was maintained for 24 hours. Pharmacodynamic steady state was reached within one week with the majority of bronchodilation observed by the third day. SPIRIVA significantly improved morning and evening peak expiratory flow rate (PEFR) as measured by patient's daily recordings. The improvement in lung function with SPIRIVA was demonstrated throughout the period of administration in the six long-term trials (Figures 1–3). These improvements were maintained with no evidence of tolerance.

Figure 1: Mean FEV_1 Over Time (prior to and after administration of study drug) on Days 1 and 344 in Two 1 Year Placebo-Controlled Trials*

Study A



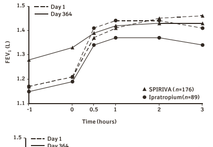
Study B



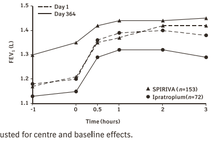
*Means are adjusted for centre and baseline effects.

Figure 2: Mean FEV_1 Over Time (prior to and after administration of study drug) on Days 1 and 364 in Two 1 Year Ipratropium-Controlled Trials*

Study A



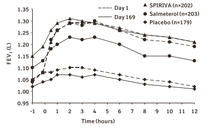
Study B



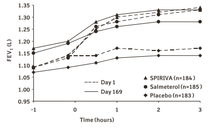
*Means are adjusted for centre and baseline effects.

Figure 3: Mean FEV_1 Over Time (prior to and after administration of study drug) on Days 1 and 169 in Two 6 Month Salmeterol- and Placebo-Controlled Trials*

Study A



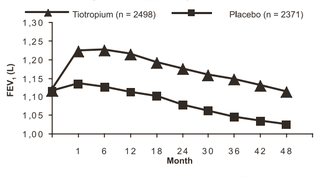
Study B



*Means are adjusted for centre and baseline effects.

A randomised, placebo-controlled clinical study in 105 patients with COPD demonstrated that bronchodilation was maintained throughout the 24 hour dosing interval in comparison to placebo regardless of whether SPIRIVA was administered in the morning or in the evening. The following health outcome effects were dem onstrated in COPD trials with a duration of up to one year.
SPIRIVA significantly improved dyspnoea (as evaluated using the Transition Dyspnoea Index). This improvement was maintained throughout the treatment period.
SPIRIVA significantly reduced the number of COPD exacerbations and delayed the time to first exacerbation in comparison to placebo.
SPIRIVA significantly improved health-related quality of life as demonstrated by the disease-specific St. George's Respiratory Questionnaire. This improvement was maintained throughout the treatment period.
Additionally, in the one year placebo controlled trials SPIRIVA significantly reduced the number of hospitalisations associated with COPD exacerbations and delayed the time to first hospitalisation.
The impact of improvement in dyspnea on functional activities was investigated in two randomised double blind placebo controlled trials in COPD patients. In these trials SPIRIVA significantly improved symptom limited exercise tolerance by 19.7% and 28.3% compared with placebo.
In a dedicated QT study involving 53 healthy volunteers, SPIRIVA 18 mcg and 54 mcg (i.e. three times the therapeutic dose) over 12 days did not prolong QT intervals of the ECG.
In a 4-year trial of 5,993 patients SPIRIVA maintained improvements in FEV_1 throughout 4 years but did not alter the annualized rate of decline of FEV_1.

Figure 4. Morning pre-dose FEV_1 (i.e. trough) in the tiotropium and placebo groups over 4 years.
P<0.001 for all post-randomization time points.



During treatment, there was a 16% reduction in the risk of death. The incidence rate of death was 4.78 per 100 patient years in the placebo group vs. 4.10 per 100 patient years in the tiotropium group (hazard ratio (tiotropium/placebo) = 0.84, 95% CI = 0.73, 0.97). Treatment with tiotropium reduced the risk of respiratory failure by 19% (2.09 vs. 1.68 cases per 100 patient years, relative risk (tiotropium/placebo) = 0.81, 95% CI = 0.65, 1.00).

A one-year randomised, double-blind, double-dummy, parallel-group trial compared the effect of treatment with 18 mcg of SPIRIVA once daily with that of 50 mcg of salmeterol HFA pMDI twice daily on the incidence of moderate and severe exacerbations in 7,376 patients with COPD and a history of exacerbations in the preceding year.

Figure 5: Kaplan-Meier estimates of the time to the first COPD exacerbation / Treated Set

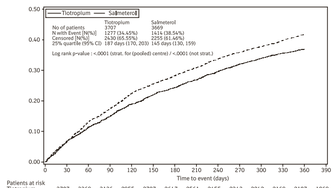


Figure 6: Kaplan-Meier estimates of the time to the first hospitalized COPD exacerbation / Treated Set

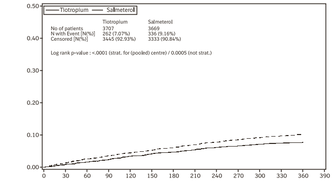


Table 1: Summary of exacerbation endpoints

Endpoint	SPIRIVA 18 microgram (HandiHaler) N = 3,707	Salmeterol 50 microgram (HFA pMDI) N = 3,669	Ratio (95% CI)	p-value
Time [days] to first exacerbation†	187	145	0.83 (0.77–0.90)	<0.001
Time to first severe (hospitalised) exacerbation§	–	–	0.72 (0.61–0.85)	<0.001
Patients with ≥ 1 exacerbation, n (%)*	1,277 (34.4)	1,414 (38.5)	0.90 (0.85–0.95)	<0.001
Patients with ≥ 1 severe (hospitalised) exacerbation, n (%)*	262 (7.1)	336 (9.2)	0.77 (0.66–0.89)	<0.001
Mean exacerbation incidence rate per patient year#	0.64	0.72	0.89 (0.83–0.96)	=0.002
Mean severe (hospitalised) exacerbation incidence rate per patient year#	0.09	0.13	0.73 (0.66–0.82)	<0.001

† Time [days] refers to 1st quartile of patients. Time to event analysis was done using Cox's proportional hazards regression model with (pooled) centre and treatment as covariate; ratio refers to hazard ratio.
§ Time to event analysis was done using Cox's proportional hazards regression model with (pooled) centre and treatment as covariate; ratio refers to hazard ratio. Time [days] for the 1st quartile of patients cannot be calculated, because proportion of patients with severe exacerbation is too low.
* Number of patients with event were analysed using Cochran-Mantel-Haenszel test stratified by pooled centre; ratio refers to risk ratio.
# Number of event analysis was done using Poisson regression correcting for overdispersion and adjusting for treatment exposure; ratio refers to rate ratio.

Compared with salmeterol, SPIRIVA increased the time to the first exacerbation (187 days vs. 145 days), with a 17% reduction in risk (hazard ratio, 0.83; 95% confidence interval [CI], 0.77 to 0.90; P<0.001). SPIRIVA also increased the time to the first severe (hospitalised) exacerbation (hazard ratio, 0.72; 95% CI, 0.61 to 0.85; P<0.001), reduced the annual number of moderate or severe (hospitalised) exacerbations (0.64 vs. 0.72; rate ratio, 0.89; 95% CI, 0.83 to 0.96; P=0.002), and reduced the annual number of severe (hospitalised) exacerbations (0.09 vs. 0.13; rate ratio, 0.73; 95% CI, 0.66 to 0.82; P<0.001).

Pharmacokinetics
Tiotropium is a non-chiral quaternary ammonium compound and is sparingly soluble in water. Tiotropium is administered by dry powder inhalation. Generally with the inhaled route of administration, the majority of the delivered dose is deposited in the gastro-intestinal tract, and to a lesser extent in the intended organ of the lung. Many of the pharmacokinetic data described below were obtained with higher doses as recommended for therapy.
Absorption: Following dry powder inhalation by young healthy volunteers, the absolute bioavailability of 19.5% suggests that the fraction reaching the lung is highly bioavailable. It is expected from the chemical structure of the compound (quaternary ammonium compound) that tiotropium is poorly absorbed from the gastro-intestinal tract. Food is not expected to influence the absorption of tiotropium for the same reason. Oral solutions of tiotropium have an absolute bioavailability of 2–3%. Maximum tiotropium plasma concentrations were observed five minutes after inhalation.
Distribution: The drug is bound by 72% to plasma proteins and shows a volume of distribution of 32 L/kg. At steady state, tiotropium plasma levels in COPD patients at peak were 17–19 pg/ml when measured 5 minutes after dry powder inhalation of a 18 microgram dose and decreased rapidly in a multi-compartmental manner. Steady state trough plasma concentrations were 3–4 pg/ml. 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 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, 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 dependent oxidation and subsequent glutathione conjugation to a variety of Phase I-metabolites. This enzymatic pathway can be inhibited by the CYP450 2D6 (and 3A4) inhibitors, quinidine, ketoconazole and gestodene. Thus CYP450 2D6 and 3A4 are involved in the metabolic pathway that is responsible for the elimination of a smaller part of the dose. Tiotropium even in supra-therapeutic concentrations does not inhibit cytochrome P450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1 or 3A in human liver microsomes.
Elimination: The terminal elimination half-life of tiotropium is between 5 and 6 days following inhalation. Total clearance was 880 ml/min after an intravenous dose in young healthy volunteers with an interindividual variability of 22%. Intravenously administered tiotropium is mainly excreted unchanged in urine (74 %). After dry powder inhalation urinary excretion is 14% 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 creatinine clearance, indicating secretion into the urine. After chronic once daily inhalation by COPD patients, pharmacokinetic steady state was reached after 2–3 weeks with no accumulation thereafter.
Linearity/nonlinearity: Tiotropium demonstrates linear pharmacokinetics in the therapeutic range after both intravenous administration and dry powder inhalation.
Elderly Patients: As expected for all predominantly renally excreted drugs, advanced age was associated with a decrease of tiotropium renal clearance (326 ml/min in COPD patients <58 years to 163 ml/min in COPD patients > 70 years) which may be explained by decreased renal function. Tiotropium excretion in urine after inhalation decreased from 14% (young healthy volunteers) to about 7% (COPD patients), however plasma concentrations did not change significantly with advancing age within COPD patients If compared to inter- and intra-individual variability (43% increase in $AUC_{0-t_{ss}}$ after dry powder inhalation).

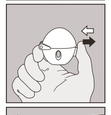
Renally Impaired Patients: In common with all other drugs that undergo predominantly renal excretion, renal impairment was associated with increased plasma drug concentrations and reduced renal drug clearance after both intravenous infusion and dry powder inhalations. Mild renal impairment (CL_{cr} 50–80 ml/min) which is often seen in elderly patients increased tiotropium plasma concentrations slightly (39% increase in $AUC_{0-t_{ss}}$ after intravenous infusion). In COPD patients with moderate to severe renal impairment (CL_{cr} <50 ml/min) the intravenous administration of tiotropium resulted in doubling of the plasma concentrations (82% increase in $AUC_{0-t_{ss}}$), which was confirmed by plasma concentrations after dry powder inhalation.
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 by simple non-enzymatic ester cleavage to products that do not bind to muscarinic receptors.

Indications
SPIRIVA is indicated for the maintenance treatment of patients with COPD (including chronic bronchitis and emphysema), and for reducing COPD exacerbations.

Dosage and administration
The product should be used by physician prescription.
The recommended dosage of SPIRIVA is inhalation of the contents of one capsule once daily with the HandiHaler inhalation device at the same time of day (see Instructions for use).
SPIRIVA capsules must not be swallowed.
Elderly patients can use SPIRIVA at the recommended dose.
Renally impaired patients can use SPIRIVA at the recommended dose. However, as with all predominantly renally excreted drugs, SPIRIVA use should be monitored closely in patients with moderate to severe renal impairment.
Hepatically impaired patients can use SPIRIVA at the recommended dose.
There is no experience with SPIRIVA in infants and children and therefore should not be used in this age group.
Instructions for Use
Remember to carefully follow your doctor's instructions for using SPIRIVA The HandiHaler is an inhalation device especially designed for inhalation from SPIRIVA capsules. You must not use it to take any other medication. You can use your HandiHaler for up to one year to take your medication.

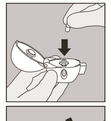
1 dust cap
2 mouthpiece
3 base
4 piercing button
5 centre chamber

1. To release the dust cap press the piercing button completely in and let go.

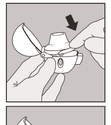


2. Open the dust cap completely by pulling it upwards. Then open the mouthpiece by pulling it upwards.

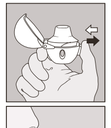
3. Remove a SPIRIVA capsule from the blister (only immediately before use, see blister handling) and place it in the centre chamber (3), as illustrated. It does not matter which way the capsule is placed in the chamber.



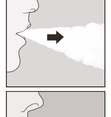
4. Close the mouthpiece firmly until you hear a click, leaving the dust cap open.



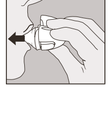
5. Hold the HandiHaler device with the mouthpiece upwards and press the piercing button completely in only once, and release.
This makes holes in the capsule and allows the medication to be released when you breathe in.



6. Breathe out completely.
Important: Please avoid breathing into the mouthpiece at any time.



7. Raise the HandiHaler to your mouth and close your lips tightly around the mouthpiece. Keep your head in an upright position and breathe in slowly and deeply but at a rate sufficient to hear or feel the capsule vibrate. Breathe in until your lungs are full; then hold your breath as long as comfortable and at the same time take the HandiHaler out of your mouth. Resume normal breathing. Repeat steps 6 and 7 once, in order to empty the capsule completely.



8. Open the mouthpiece again. Tip out the used capsule and dispose.
Close the mouthpiece and dust cap for storage of your HandiHaler device.

Cleaning the HandiHaler
Clean the HandiHaler once a month.
Open the dust cap and mouthpiece. Then open the base by lifting the piercing button. Rinse the complete inhaler with warm water to remove any powder. Dry the HandiHaler thoroughly by tipping excess water out onto a paper towel and air-dry afterwards, leaving the dust cap, mouthpiece and base open. It takes 24 hours to air dry, so clean it immediately after use so that it will be ready for your next dose. The outside of the mouthpiece may be cleaned with a moist but not wet tissue if needed.

Blister handling
A. Separate the blister strips by tearing along the perforation.

B. Peel back foil (only immediately before use) using the tab until one capsule is fully visible.
In case a second capsule is exposed to air inadvertently this capsule has to be discarded.

C. Remove capsule.

The capsules should not be exposed to extreme temperatures.
SPIRIVA capsules contain only a small amount of powder so that the capsule is only partially filled.

Contraindications
SPIRIVA inhalation powder is contraindicated in patients with a history of hypersensitivity to atropine or its derivatives, e.g. ipratropium or oxitropium or to the excipient lactose monohydrate which contains milk protein or to any component of this product.

Special warnings and precautions
SPIRIVA, as a once daily maintenance bronchodilator, should not be used for the initial treatment of acute episodes of bronchospasm, i.e. rescue therapy.
Immediate hypersensitivity reactions may occur after administration of SPIRIVA inhalation powder.
As with other anticholinergic drugs, SPIRIVA 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 SPIRIVA capsules. Care must be taken not to allow the powder 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 should not be used more frequently than once daily.
SPIRIVA capsules are to be used only with the HandiHaler device.
This product contains 5.5 mg of lactose monohydrate per capsule.

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, including sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids without clinical evidence of drug interactions.
Limited information about co-administration of other anticholinergic drugs with SPIRIVA is available from two clinical trials: Acute single dose administration of ipratropium bromide with chronically administered SPIRIVA in COPD patients (n=64) and healthy volunteers (n= 35) was not associated with an increase in adverse events, changes in vital signs or electrocardiographic findings. However, chronic co-administration of other anticholinergic drugs with SPIRIVA has not been studied and is, therefore, not recommended.

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.

Fertility, 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.
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 should not be used in pregnant or nursing women unless the expected benefit outweighs any possible risk to the unborn child or the infant.
Clinical data on fertility are not available for tiotropium. A non-clinical study performed with tiotropium showed no indication of any adverse effect on fertility (please refer to section Toxicology).

Side effects
Many of the listed undesirable effects can be assigned to the anticholinergic properties of SPIRIVA.
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 includes 9,647 tiotropium patients from 28 placebo-controlled clinical trials with treatment periods ranging between four weeks and four years, contributing 12,469 person years of exposure to tiotropium .

Metabolism and nutrition disorders:
– dehydration
Nervous system disorders:
– dizziness
– insomnia
Eye disorders:
– vision blurred
– glaucoma
– intraocular pressure increased
Cardiac disorders:
– atrial fibrillation
– supraventricular tachycardia
– tachycardia
– palpitations
Respiratory, thoracic and mediastinal disorders:
– cough
– dysphonia
– pharyngitis
– bronchospasm
– epistaxis
– laryngitis
– sinusitis
Gastrointestinal disorders:
– dry mouth, usually mild
– constipation
– gastrooesophageal reflux disease
– oropharyngeal candidiasis
– intestinal obstruction incl. ileus paralytic
– dysphagia
– gingivitis
– glossitis
– stomatitis
Skin and subcutaneous tissue disorders, Immune system disorders:
– rash
– angioedema
– hypersensitivity (including immediate reactions)
– pruritus
– urticaria
– dry skin
– skin infection and skin ulcer
Musculoskeletal and connective tissue disorders:
– joint swelling
Renal and urinary disorders:
– urinary retention (usually in men with predisposing factors)
– dysuria
– urinary tract infection

Overdose
High doses of SPIRIVA may lead to anticholinergic signs and symptoms.
However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 282 micrograms tiotropium in healthy volunteers.
Bilateral conjunctivitis in addition to dry mouth was seen in healthy volunteers following repeated once daily inhalation of 141 micrograms in healthy volunteers, which resolved while still under treatment. In a multiple dose study in COPD patients with a maximum daily dose of 36 micrograms tiotropium over four weeks dry mouth was the only observed adverse event attributable to tiotropium.
Acute intoxication by oral ingestion of tiotropium capsules is unlikely due to low oral bioavailability.

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 **repeated dose studies** in rats, mice and dogs were related to anticholinergic properties of tiotropium 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 a series of *in vivo* and *in vitro* **mutagenicity assays**, tiotropium bromide monohydrate did not cause gene mutations in prokaryotes and in eucaryotes, chromosomal damage *in vitro* and *in vivo* conditions or primary DNA damage.

Availability
2 × 1000 capsules for inhalation in aluminium blister with paper box plus HANDIHALER device.

Storage conditions
After first opening of the blister, use within 9 days

Store in a safe place out of the reach of children!
Do not store above 25°C!
Do not freeze!

Mfg by
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55216 Ingelheim am Rhein, Germany
For
Boehringer Ingelheim International GmbH
Ingelheim am Rhein, Germany

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Boehringer Ingelheim

Spiriva®
18 µg, inhalation powder, hard capsule with HandiHaler® device

Spiriva®
18 µg, inhalation powder, hard capsule with HandiHaler® device

Boehringer Ingelheim

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適喘樂® 易得噴® 吸入劑

Spiriva®
18μg, inhalation powder, hard capsule with HandiHaler® device

Boehringer Ingelheim

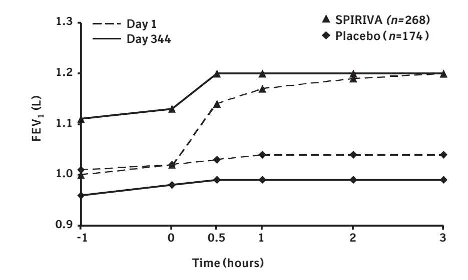
衛署藥輸字第 023706 號

成分
每吸入用膠囊含
tiotropium 18 mcg相當於tiotropium bromide monohydrate(= tiotropium bromide) 22.5 mcg

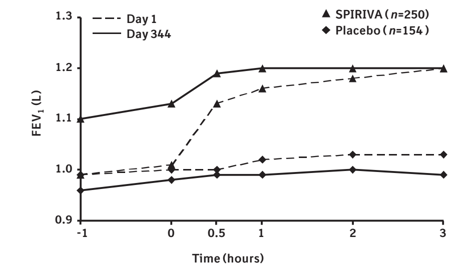
性質
Tiotropium爲一長效、專一性的抗毒蕈劑(antimuscarinic agent)，在臨床藥學上通常稱之爲抗膽鹼藥物。對於各種毒蕈性接受體(muscarinic receptor, M1~M5)有相似的親和力。抑制氣管平滑肌上的M3接受體，會使氣管放鬆。在人類及動物的接受體，與分離的器官組織中，皆可觀察到此競爭性(competitive)與可逆性(reversible)的拮抗作用。在非臨床試驗的體外與體內試驗，可觀察到氣管保護作用與劑量有關，且可持續長達24小時以上。長效作用可能是因爲tiotropium與M3接受體的分離速度很慢，其分離半衰期很明顯地長於ipratropium。Tiotropium爲四級銨(N-quaternary)之抗膽鹼性劑，當吸入時，可局部選擇性作用於支氣管，在產生有效治療濃度時也不會產生全身性抗膽鹼作用。在體外功能性試驗中，tiotropium與M2接受體分離的速度較M3快，因此以動力學的角度而言，對M3接受體的選擇性高於M2。與接受體作用強且分離速度慢，所以在臨床上治療慢性阻塞性肺疾(COPD)之患者有顯著且長效的支氣管擴張作用。
吸入tiotropium後之支氣管擴張作用，主要爲局部作用(作用於氣道)，而非全身性作用。
研究發展計劃包括四個爲期一年和兩個爲期半年之隨機、雙盲性試驗，共有2663位慢性阻塞性肺疾(COPD)病人(其中1308位病人使用SPIRIVA)。在爲期一年之試驗中，有二個試驗以安慰劑爲對照組(圖一)，與兩個使用ipratropium爲對照組試驗(圖二)；爲期半年之兩個試驗，以salmeterol及安慰劑爲對照組(圖三)。這些研究均評估肺功能、呼吸困難、慢性阻塞性肺疾病情惡化和評估患者自我對健康有關之生活品質。
在這些試驗中，每天使用SPIRIVA一次，在使用第一次劑量的三十分鐘內可有效改善肺功能(一秒內用力吐氣量FEV1與肺活量FVC)，作用可持續24小時。藥效學方面，在一週內可達到穩定狀態，在第三天可觀察到大部分的支氣管擴張作用。依據病人每日之紀錄，SPIRIVA可明顯改善早晨及晚上之最高吐氣流速(peak expiratory flow rate, PEFR)。在六個長期使用SPIRIVA之試驗中，在整個治療期間，肺功能可持續顯著改善(見圖一~圖三)。這些改善可維持且不會產生耐藥性。

圖一：在二個爲期一年以安慰劑爲對照組之臨床試驗*，在第1天及344天之平均FEV_1與時間(使用研究藥物前後)之曲線

研究A



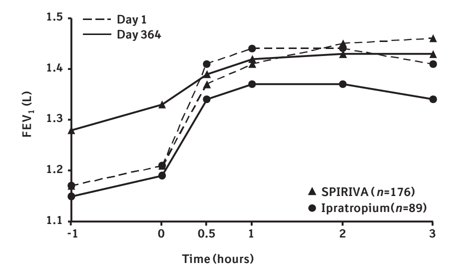
研究B



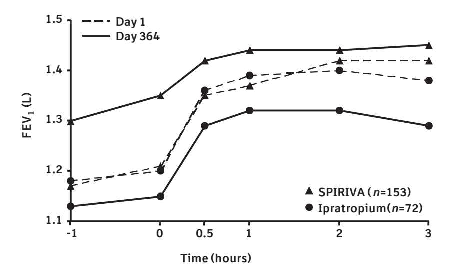
*平均值會依試驗中心及基礎值差異來調整

圖二：在二個爲期一年以Ipratropium爲對照組之臨床試驗*，在第1天及364天之平均FEV_1與時間(使用研究藥物前後)之曲線

研究A



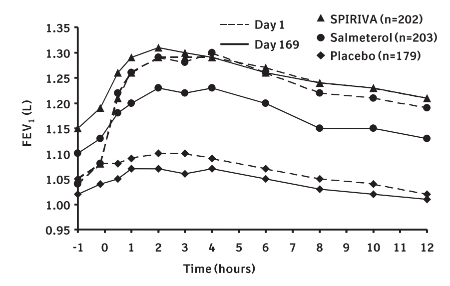
研究B



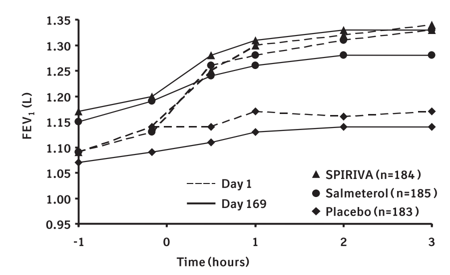
*平均值會依試驗中心及基礎值差異來調整

圖三：二個爲期六個月以salmeterol及安慰劑爲對照組臨床試驗*，在第1天及169天之平均FEV_1與時間(使用研究藥物前後)之曲線

研究A



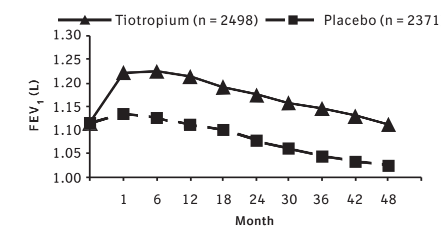
研究B



*平均值會依試驗中心及基礎值差異來調整

在一隨機、以安慰劑爲對照組之臨床試驗，收集105位慢性阻塞性肺疾(COPD)病人，相較於安慰劑，不論早晨或晚上使用SPIRIVA，可觀察到其支氣管擴張作用可維持整個24小時的服藥間隔，在爲期達一年針對慢性阻塞性肺疾(COPD)的臨床試驗，顯示具下列健康結果指標(health outcome)療效。
SPIRIVA顯著改善呼吸困難(依據Transition Dyspnoea Index來評估)。在整個治療期間均可有效維持改善。
相較於安慰劑，SPIRIVA顯著降低慢性阻塞性肺疾病(COPD)惡化之次數，並延緩第一次產生病情惡化的時間。
由特定疾病的St. George's呼吸問卷 (Respiratory Questionnaire) 證實SPIRIVA可明顯改善與有關健康的生活品質。在整個治療期間均可有效維持改善。
此外，在爲期一年以安慰劑爲對照組的臨床試驗中，SPIRIVA可顯著減少因慢性阻塞性肺疾 (COPD) 惡化而住院之次數，並延緩第一次住院之時間。
在慢性阻塞性肺疾(COPD)病人所進行的兩個隨機、雙盲性、以安慰劑爲對照組之臨床試驗中，評估本藥對改善功能性呼吸困難(functional activities)的影響。在此二臨床試驗中，相較於安慰劑，SPIRIVA可顯著改善運動耐受性受限的症狀(symptom limited exercise tolerance)分別爲19.7%和28.3%。在包括53位健康自願者，針對QT的研究，以SPIRIVA 18 mcg和54 mcg(爲治療劑量的3倍)治療超過12天，並未見心電圖的QT intervals延長。
一個爲期四年納入5,993位病人的臨床試驗已證實SPIRIVA能使病人的FEV_1在這四年期間內一直維持改善，但不會改變FEV_1的年下降速率(annualized rate of decline)。

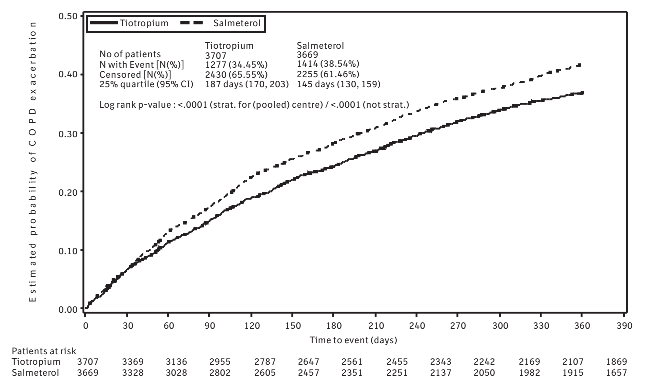
圖四：四年期間tiotropium組及安慰劑組在早晨給藥前之FEV_1 (亦即trough)隨機分組後全部的時間點P<0.001



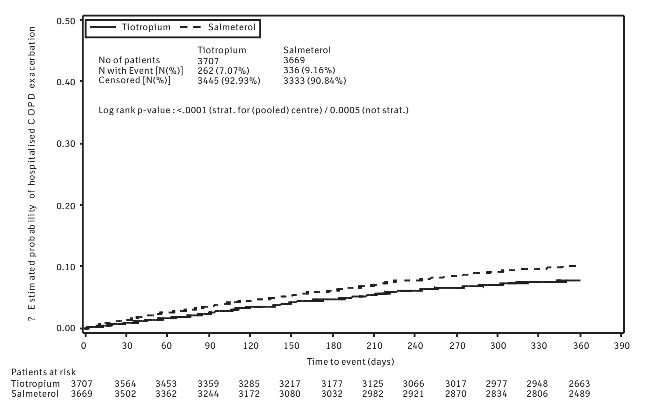
在治療期間，死亡危險性降低16%。死亡發生率在安慰劑組爲每100個病人年(per 100 patient years)4.78，tiotropium組爲每100個病人年4.10 (hazard ratio (tiotropium/placebo) = 0.84, 95% CI = 0.73, 0.97)。
以tiotropium治療可使呼吸衰竭的危險性降低19% (安慰劑組每100個病人年2.09例，tiotropium治療組爲1.68例，相對之危險性relative risk (tiotropium/placebo) = 0.81, 95% CI = 0.65, 1.00)。

一項隨機、雙盲、雙虛擬的平行分組試驗曾針對7,376位在過去一年中有病情惡化病史的COPD患者，比較爲期一年、每日一次18 mcg之SPIRIVA與每日兩次50 mcg之salmeterol HFA pMDI在中度及嚴重惡化之發生率方面的治療效果。

圖五：首次出現COPD惡化之時間的Kaplan-Meier分析圖/治療組


Tiotropium
Salmeterol
No of patients 3707 3669
N with Event [N(%)] 1277 (34.45%) 1414 (38.54%)
Censored [N(%)] 2430 (65.55%) 2255 (61.46%)
25% quartile (95% CI) 187 days (170, 203) 145 days (130, 159)
Log rank p-value : <.0001 (strat. for (pooled) centre) / <.0001 (not strat.)
Estimated probability of COPD exacerbation
Time to event (days)
Patients at risk
Tiotropium 3707 3369 3136 2955 2787 2647 2561 2455 2343 2242 2169 2107 1869
Salmeterol 3669 3328 3028 2802 2605 2457 2351 2251 2137 2050 1982 1915 1657

圖六：首次出現須住院治療之COPD惡化之時間的Kaplan-Meier分析圖/治療組


Tiotropium
Salmeterol
No of patients 3707 3669
N with Event [N(%)] 262 (7.07%) 336 (9.16%)
Censored [N(%)] 3445 (92.93%) 3333 (90.84%)
Log rank p-value : <.0001 (strat. for (pooled) centre) / 0.0005 (not strat.)
Estimated probability of hospitalised COPD exacerbation
Time to event (days)
Patients at risk
Tiotropium 3707 3564 3453 3359 3285 3217 3177 3125 3066 3017 2977 2948 2663
Salmeterol 3669 3502 3362 3244 3172 3080 3032 2982 2921 2870 2834 2806 2489

表一：病情惡化評估指標摘要

評估指標	SPIRIVA 18微公克 (HandiHaler) N = 3,707	Salmeterol 50微公克 (HFA pMDI) N = 3,669	比率 (95% CI)	p值
首次出現病情惡化的時間[天數]†	187	145	0.83 (0.77-0.90)	<0.001
首次出現嚴重[須住院治療]惡化現象的時間[天數]§	–	–	0.72 (0.61 - 0.85)	<0.001
出現≥1次病情惡化的病患人數，n (%)*	1,277 (34.4)	1,414(38.5)	0.90 (0.85 - 0.95)	<0.001
出現≥1次嚴重[須住院治療]病情惡化的病患人數，n (%)*	262 (7.1)	336(9.2)	0.77 (0.66 - 0.89)	<0.001
惡化平均發生率# (人年)	0.64	0.72	0.89 (0.83 - 0.96)	=0.002
嚴重[須住院治療]惡化平均發生率# (人年)	0.09	0.13	0.73 (0.66 - 0.82)	<0.001

† 時間[天數]爲第一四分位數之患者的數據。事件發生時間的分析係採用Cox風險迴歸模型，並以(整合後的)研究中心和治療方式做爲共變數；比率係指風險比。
§ 事件發生時間的分析係採用Cox風險迴歸模型，並以(整合後的)研究中心和治療方式做爲共變數；比率係指風險比。無法計算第一四分位數之患者的時間[天]數據，因爲出現嚴重惡化的病患比例太低。
* 發生事件之病患人數的分析係採用Cochran-Mantel-Haenszel檢定法，並以整合後的研究中心進行分層；比率係指相對危險性(risk ratio)。
# 事件發生次數的分析係採用Poisson迴歸分析法，並依過度離散的情形進行修正，以及依治療方式進行調整；比率係指發生率比率。

和salmeterol相比較，SPIRIVA可延後首次出現病情惡化的時間(187天 vs. 145天)，並可使風險降低17% (風險比，0.83；95%信賴區間[CI]，0.77至0.90；P<0.001)。SPIRIVA亦可延後首次出現嚴重(須住院治療)惡化的時間(風險比率，0.72；95% CI，0.61至0.85；P<0.001)，降低中度或嚴重(須住院治療)惡化的年發生次數(0.64 vs. 0.72；發生率比率，0.89；95% CI，0.83至0.96；P=0.002)，並可降低嚴重(須住院治療)惡化的年發生次數(0.09 vs. 0.13；發生率比率，0.73；95% CI，0.66至0.82；P<0.001)。

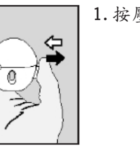
藥物動力學
Tiotropium爲一非光旋活性(non-chiral)四級銨化合物，略溶於水。Tiotropium以乾粉吸入投藥。通常口腔吸入方式投藥，大部分的藥物會沉積在胃腸道，少部分進入目標器官肺部。下述藥物動力學數據大多是使用比推薦劑量高的劑量。
吸收：
年輕健康自願者以乾粉吸入方式用藥，其絕對生體可用率爲19.5%，推測部分進入肺部之藥物具有很高的生體可用率。由於此化合物之化學結構(四級銨化合物)，所以預期tiotropium在胃腸道不易被吸收。同理，食物也不會影響tiotropium吸收。Tiotropium之口服溶液劑之絕對生體可用率爲2-3%。在吸入tiotropium 5分鐘後，可達最高血中濃度。
分佈：
此藥物與血漿蛋白的結合率爲72%，分佈體積爲32 L/kg。測量慢性阻塞性肺疾病 (COPD) 患者吸入tiotropium乾粉18微公克((g)後，在穩定狀態下之血中濃度，五分鐘後達到最高值17-19 pg/ml，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爲3-4 pg/ml。無法得知肺部的局部濃度，但此種給藥方式在肺部應該有更高的濃度。在大白鼠的實驗顯示，tiotropium完全不會穿透血腦障壁。
代謝：
此藥物代謝比例很小，其證據來自年輕健康自願者以靜脈注射後，有74%以原型藥物經由尿液排除。Tiotropium爲一酯類，可不經由酵素而切斷爲alcohol N-methylscopine與dithienylglycolic acid，兩者皆不會與muscarinic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cytochrome P450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)。此酵素代謝途徑會被CYP450 2D6(及3A4)抑制劑，如quinidine、ketoconazole、與gestodene抑制。CYP450 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，也不會抑制人類肝臟微粒體之cytochrome P450 1A1、1A2、2B6、2C9、2C19、2D6、2E1或3A。
排除：
Tiotropium經吸入後，末相排除半衰期約在5到6天之間。年輕健康自願者靜脈注射後之總清除率爲880 ml/min，個體之間的差異爲22%。靜脈注射的tiotropium主要以原型經尿液排除(74%)。以乾粉吸入方式則有14%之總劑量經尿液排除，其餘大部分未被腸道吸收的藥物，經由糞便排除。Tiotropium之腎臟清除率超過肌胺酸酐 (creatinine)之清除率，表示會分泌到尿液中。慢性阻塞性肺疾病(COPD)病人經長期每日吸入一次，在2-3週後藥物動力學可達到穩定狀態，並不會有蓄積的情形。
線性/非線性：Tiotropium在治療範圍內，無論是靜脈注射或乾粉吸入，藥物動力學均呈線性關係。
年老者：
與其他主要以腎臟代謝之藥物相同，可以預期在年紀較大之病人可能因爲腎臟功能降低，而使得tiotropium的清除率降低(小於58歲之COPD病人清除率爲326 ml/min，而大於70歲之COPD病人清除率爲163 ml/min)。Tiotropium吸入後，從尿液的排除程度從年輕健康自願者之14%降到患者之7%。然而若相較於個體間及個體內的差異，年紀較長之COPD病人的血中濃度並沒有顯著的改變(以乾粉吸入方式之AUC_{0-4h}增加43%)。
腎功能受損病人：
與所有其它主要以腎臟代謝之藥物相同，不論是以靜脈注射或乾粉吸入方式，腎臟功能損害會造成藥物血中央濃度升高與腎臟清除率降低。年老患者常有輕微腎臟受損 (CL_{CR} 50-80 ml/min)，會稍微增加tiotropium血中濃度(靜脈輸注後AUC_{0-4h}會增加39%)。中度或嚴重腎臟受損(CL_{CR}< 50 ml/min)之COPD病人，靜脈注射tiotropium或以乾粉吸入方式，會使血中濃度增加二倍(AUC_{0-4h}會增加82%)。
肝功能受損病人：
肝功能不全對於tiotropium之藥物動力學應不會有影響。tiotropium主要是經由腎臟排泄(在年輕健康自願者中佔74%)及藉著簡單的非酵素性酯斷裂形成不會與毒蕈性接受體(muscarinic receptors)結合的代謝物。

適應症
慢性阻塞性肺疾(包括慢性支氣管炎及肺氣腫)維持治療、降低惡化。

用法用量
本藥須由醫師處方使用
SPIRIVA推薦劑量爲每日吸入一顆膠囊，定時以易得噴吸入器(HANDIHALER device) 吸入使用(請參見使用說明使用)。
SPIRIVA膠囊不可口服。
年老者可依SPIRIVA之推薦劑量使用。
腎功能受損病人可依SPIRIVA之推薦劑量使用。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SPIRIVA之推薦劑量使用。
尚未有SPIRIVA使用於嬰兒及兒童的經驗，因此不建議使用於此年齡群。
使用說明

切記必須依照醫師之操作說明正確使用HANDIHALER投與SPIRIVA. HANDIHALER爲SPIRIVA專屬吸入器，不可用於使用其他藥物。
一個HANDIHALER吸入器用來吸入藥物大約可使用一年。

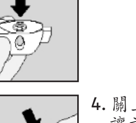
1. 護蓋
2. 含口器
3. 底座
4. 按鈕
5. 中央室



1. 按壓右側按鈕至底使護蓋鬆開，然後放開按扭。

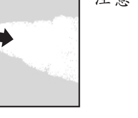
2. 把護蓋向上完全打開，接著向上拉開含口器。

3. 將膠囊從blister中取出來(使用前才取出)，將一顆膠囊放置於中央室中，如圖所示。膠囊任一端朝上均可。



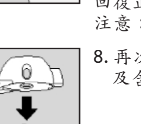
4. 關上含口器，直到聽見"卡搭"聲，表示已關緊。讓護蓋保持開啓著。

5. 握住HANDIHALER，讓含口器朝上，只按壓右側的按鈕一次然後放開。
這個動作可使位於中央室的膠囊有一個孔洞，當你開始吸入時膠囊內的藥物會釋出。



6. 儘可能呼氣
注意：無論何時都不要對著含口器呼氣。

7. 依下列方式吸入藥物：將HANDIHALER放入口中，雙唇緊緊啣住含口器，保持頭部朝上的姿勢，然後慢慢地深吸，其吸入速度爲能夠聽見或感到膠囊振動的聲音。
深呼吸直到肺部已滿，然後秉住呼吸直到無法忍受，同時將HANDIHALER自嘴中取出。
回復正常呼吸。
注意：再一次重複步驟6, 7，以確保吸入完整的劑量。



8. 再次打開含口器，將使用過的膠囊倒出，關上護蓋及含口器，保存HANDIHALER吸入器。

HANDIHALER需一個月清潔一次：
打開護蓋及含口器，然後，掀開綠色按鈕以打開底座，以溫水沖洗整個吸入器以去除任何粉末，傾倒多餘的水在紙巾上，使其完全乾燥，隨後風乾，風乾時需開啓護蓋、含口器及底座，達24個小時。所以使用完後應立即清理，下一次才能即時使用。
必要時含口器的外部可潤濕，但不可用全濕的衛生紙擦拭。

膠囊取出方法
沿著鋁箔片上的齒孔撕開，取下一顆膠囊片。

在使用前將膠囊片背面的鋁箔拉開，直到膠囊完全露出。
如果不小心將下一顆膠囊撕破暴露於空氣中，則必須將此顆膠囊丟棄而不可使用。

拿出膠囊

膠囊無論是在鋁箔(blister)內或放入吸入器時，均不可暴露於高溫下，不可直接曝曬於日光下或加熱。
SPIRIVA膠囊僅含有少量粉末，所以膠囊只有部分被填滿。

禁忌
SPIRIVA吸入粉末不可用於對阿托品及其衍生物(如ipratropium、oxitropium)或對賦型劑lactose monohydrate(含有牛奶蛋白)過敏之病人或其中任一成分有過敏史之病人。

特別注意
SPIRIVA爲每日一次持續性之支氣管擴張劑，不可用於急性支氣管痙攣的最初治療，即不可用於急救治療。
在吸入SPIRIVA後，有可能會發生立即的過敏反應。
與其它抗膽鹼性劑相同，狹角青光眼、攝護腺肥大、或膀胱頸阻塞之病人應小心使用。
吸入性藥物可能會因吸入方式而引發支氣管痙攣。
與其他主要經由腎臟排除的藥物相同，當SPIRIVA用於中度至嚴重腎功能受損(肌酐酸清除率小於每分鐘50毫升)之病人時，應密切監測。
應指導病人正確使用SPIRIVA吸入用膠囊的方法。必須小心不可讓藥粉進入眼睛；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青光眼的症狀。若合併發生以上症狀，應立刻請教醫生。使用縮瞳眼用滴劑並非有效的治療方法。
使用SPIRIVA每日不可超過一次。
SPIRIVA膠囊只可以用易得噴吸入器 (HANDIHALER device) 來吸入使用。
本藥每顆膠囊含有lactose monohydrate 5.5mg。

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吸入用乾粉曾與若干常用於治療COPD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併用，並無證據顯示會發生藥物交互作用。
有關SPIRIVA與其他含抗膽鹼性藥物併用的資訊很有限，目前僅有兩個臨床研究。對64位長期接受SPIRIVA的COPD病人及35位健康的自願者，給予單次劑量之ipratropium bromide，並未觀察到副作用增加、生命徵兆或心電圖的變化。然而，由於SPIRIVA與其他含抗膽鹼性藥物長期併用的影響尚未經研究，故不建議併用。

對駕駛和操作機器的影響：
尚未有SPIRIVA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。

生育力、懷孕與哺乳
目前沒有關於SPIRIVA使用於孕婦之臨床報告。動物實驗並未顯示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。
目前沒有關於SPIRIVA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小孩或胎兒的風險。
目前並無tiotropium對生育力之影響方面的臨床資料可供參考。在一項以tiotropium所進行的非臨床研究中，並未發現任何生育力方面的不良影響(參見毒理學)。

副作用
下列副作用中，許多可被歸因於SPIRIVA的抗膽鹼作用性質。
這些副作用是根據臨床試驗的資料庫及上市後使用本藥的自發性報告。此臨床試驗資料庫含9,647位接受tiotropium治療的病人，共來自28個以安慰劑爲對照組，治療期間介於4週至4年的臨床試驗，相當於有12,469病人年(person year)暴露於tiotropium中。
代謝及營養失調：
脫水
神經系統失調：
暈眩
失眠
眼睛失調：
視力模糊
青光眼
眼內壓上升
心臟失調：
心房纖維顫動
上心室性心搏過速
心搏過快
心悸
呼吸、胸腔及縱隔腔不適：
咳嗽
發聲困難
咽炎
支氣管痙攣
鼻出血
喉炎
竇炎
胃腸失調：
輕微口乾
便秘
胃食道逆流疾病
口咽念珠菌病
腸阻塞包括痲痺性腸阻塞
吞嚥困難
牙齦炎
舌炎
口腔炎
皮膚與皮下組織失調，免疫系統失調：
皮疹
血管水腫
過敏反應(包括立即性的反應)
癢
蕁麻疹
皮膚乾燥
皮膚感染及皮膚潰瘍
肌與骨骼及結締組織障礙：
關節腫脹
腎臟與泌尿障礙：
尿液滯留(易發生於有潛在病因的男性)
排尿困難
尿道感染

過量
高劑量的SPIRIVA可能導致抗膽鹼性徵兆及症狀發生。
然而，在健康自願者使用單一吸入劑量高達282微公克(μg)之tiotropium，並不會發生全身性抗膽鹼性副作用。
在健康自願者重複吸入一天一次之tiotropium 141微公克(μg)，可觀察到兩邊結膜炎及口乾的現象發生。但若持續服用，則會改善。在一個重複劑量試驗研究，以COPD病人使用tiotropium每日最大劑量36微公克(μg)長達四週以上，發現口乾是tiotropium唯一觀察到的不良反應。
口服tiotropium膠囊不太可能引起急性中毒，因其口服生體可用率低。

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。單一劑量安全藥理研究顯示，會出現所預期抗膽鹼性藥物作用，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，發生抗乙醯膽鹼性相關的副作用，包括瞳孔放大、心跳速率增加、便秘、體重減輕、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；在公鼠膀胱造成前列腺炎伴隨蛋白質狀沉積及膀胱結石；增加大白鼠肺臟重量以及降低狗的心臟重量。
利用兔子及大鼠進行生殖毒性試驗，在使母體產生毒性的劑量，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。在一項以大鼠所進行的一般生殖能力與生育力研究中，在任何劑量下皆未於投予藥物的親代或其子代中發現任何生育力或交配能力方面的不良影響。
進行一系列體內及體外的突變性試驗，發現tiotropium bromide monohydrate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。

包裝
2-1000顆吸入用膠囊鋁箔盒裝附易得噴(HANDIHALER)吸入器。

貯存
鋁箔片上的第一顆膠囊打開後，同一片的其他膠囊必須在9日內使用。

請存放於兒童伸手不及處！
請勿存放於25°C以上!
請勿冷凍!

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