

PRODUCT MONOGRAPH

Pr **SPIRIVA[®] RESPIMAT[™]**

Tiotropium (as tiotropium bromide monohydrate)
Inhalation Solution

2.5 mcg per actuation

Bronchodilator
Long-Acting Muscarinic Antagonist (LAMA)

SPIRIVA[®] RESPIMAT[™] cartridge for use only with the SPIRIVA[®] RESPIMAT[™] Inhaler

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Date of Revision:
May 7, 2019

Submission Control No: 224205

BICL #-0269-10

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Pr **SPIRIVA[®] RESPIMAT[™]**

Tiotropium Bromide Monohydrate

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral Inhalation	Solution for Inhalation/2.5 mcg per actuation	Benzalkonium chloride, disodium edetate, hydrochloric acid and purified water.

INDICATIONS AND CLINICAL USE

COPD

SPIRIVA RESPIMAT (tiotropium bromide monohydrate) is indicated as a long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, and for the reduction of exacerbations.

ASTHMA

SPIRIVA RESPIMAT is indicated as add-on maintenance bronchodilator treatment in adult patients with asthma who remain symptomatic on a combination of inhaled corticosteroid (equivalent to, but not limited to ≥ 500 mcg fluticasone/day or ≥ 800 mcg budesonide/day) and a long acting β_2 agonist and who experienced one or more severe exacerbations in the previous year.

SPIRIVA RESPIMAT is **not** indicated as rescue medication for the relief of acute bronchospasm in COPD or asthma.

Geriatrics (>65 years of age):

Elderly patients can use SPIRIVA RESPIMAT at the recommended dose.

Pediatrics (<18 years of age):

Safety and efficacy of SPIRIVA RESPIMAT in patients less than 18 years of age have not been established.

CONTRAINDICATIONS

SPIRIVA RESPIMAT (tiotropium bromide monohydrate) is contraindicated in:

- patients with a history of hypersensitivity to tiotropium bromide, atropine or its derivatives (e.g., ipratropium) or to any component of this product (see [DOSAGE FORMS, COMPOSITION AND PACKAGING](#)).

WARNINGS AND PRECAUTIONS

General

Not for Acute Use

SPIRIVA RESPIMAT (tiotropium bromide monohydrate), as a once daily maintenance bronchodilator, should not be used for the initial treatment of acute episodes of bronchospasm or for the relief of acute symptoms. In the event of an acute attack, a rapid-acting beta-2 agonist should be used.

COPD

When beginning treatment with SPIRIVA RESPIMAT, patients who have been taking inhaled, short-acting bronchodilators on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs.

When prescribing SPIRIVA RESPIMAT, the healthcare professional should also provide the patient with an inhaled, short-acting bronchodilator (i.e., short-acting beta-agonist) for treatment of COPD symptoms that occur acutely, despite regular once-daily use of SPIRIVA RESPIMAT.

SPIRIVA RESPIMAT should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. If SPIRIVA RESPIMAT no longer controls the symptoms of bronchoconstriction, or the patient's inhaled, short-acting beta₂-agonist becomes less effective or the patient needs more inhalation of a short-acting bronchodilator than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dosage of SPIRIVA RESPIMAT beyond the recommended dose is not appropriate in this situation.

Not for First Line Use in Asthma

SPIRIVA RESPIMAT should not be used as a first-line treatment or monotherapy for asthma. Asthma patients must be advised to continue taking their current therapy as per usual care (i.e. inhaled corticosteroid and long-acting beta-agonist), after the introduction of SPIRIVA RESPIMAT, even when their symptoms improve.

Excessive Use

SPIRIVA RESPIMAT should not be used more frequently than once daily or at higher doses than recommended. SPIRIVA RESPIMAT should not be administered concomitantly with other medicines containing a short- or long-acting muscarinic antagonist (e.g. ipratropium, tiotropium, glycopyrronium, aclidinium, umeclidinium), as an overdose may result.

Effects on Ability to Drive or 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.

Anticholinergic Effects

Like other anticholinergic drugs, SPIRIVA RESPIMAT should be used with caution in patients with narrow-angle glaucoma or urinary retention.

Worsening of Narrow-Angle Glaucoma

SPIRIVA RESPIMAT should be used with caution in patients with narrow-angle glaucoma. Patients should be cautioned to avoid getting the mist into their eyes. They should be advised that this may result in precipitation or worsening of narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Patients should be instructed to consult a physician immediately should any of these signs or symptoms develop. Miotic drops alone are not considered to be effective treatment.

Worsening of Urinary Retention

SPIRIVA RESPIMAT should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of prostatic hyperplasia or bladder-neck obstruction (e.g., difficulty passing urine, painful urination). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Cardiovascular

Cardiovascular effects, such as cardiac arrhythmias (e.g. atrial fibrillation and tachycardia), may be seen after the administration of muscarinic receptor antagonists (see [ADVERSE REACTIONS](#)).

Immune

Hypersensitivity

Immediate hypersensitivity reactions, including urticaria, angioedema (including swelling of the lips, tongue or throat), rash, bronchospasm, anaphylaxis, or itching may occur after administration of SPIRIVA RESPIMAT. If such a reaction occurs, therapy with SPIRIVA RESPIMAT should be stopped at once and alternative treatments should be considered. Given the similar structural formula of atropine to tiotropium, patients with a history of hypersensitivity

reactions to atropine or its derivatives should be closely monitored for similar hypersensitivity reactions to SPIRIVA RESPIMAT.

Ophthalmologic

Worsening of Narrow-Angle Glaucoma (see [WARNINGS AND PRECAUTIONS, Anticholinergic Effects](#)).

Renal

As with all predominantly renally excreted drugs, SPIRIVA RESPIMAT should be used only if the expected benefit outweighs the potential risk in patients with moderate to severe renal impairment (creatinine clearance of ≤ 50 ml/min). These patients should be monitored closely for potential adverse drug reactions.

Worsening of Urinary Retention (see [WARNINGS AND PRECAUTIONS, Anticholinergic Effects](#)).

Respiratory

Benzalkonium chloride

This medicine contains 0.0011 mg benzalkonium chloride in each actuation.

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

Paradoxical bronchospasm

Inhaled medicines may cause inhalation-induced bronchospasm. If this occurs, treatment with SPIRIVA RESPIMAT should be discontinued immediately.

Special Populations

Pregnant Women: There is a limited amount of data from the use of tiotropium in pregnant women. Pre-clinical studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity(see [TOXICOLOGY](#)). Because animal reproduction studies are not always predictive of human response, SPIRIVA RESPIMAT should be used during pregnancy only if the benefits outweigh any possible risk to the unborn child.

Labour and Delivery: The safety and effectiveness of SPIRIVA RESPIMAT have not been studied during labour and delivery.

Nursing Women: Clinical data from nursing women exposed to tiotropium are not available. Based on lactating rodent studies, a small amount of tiotropium is excreted into breast milk. Therefore, SPIRIVA RESPIMAT should not be used in nursing women unless the expected benefit outweighs any possible risk to the infant.

Pediatrics (<18 years of age): Safety and efficacy of SPIRIVA RESPIMAT in patients less than 18 years has not been established.

ADVERSE REACTIONS

Adverse Drug Reactions Overview

Adverse reactions to SPIRIVA RESPIMAT are similar in nature to reactions to other anticholinergic bronchodilators and may include cardiovascular effects (atrial arrhythmias and tachycardia), ocular disorders (e.g. blurred vision), dysuria, urinary retention, gastrointestinal disorders (e.g., constipation and dry mouth), cough and immediate hypersensitivity reactions.

Many of the listed adverse reactions can be assigned to the anticholinergic properties of tiotropium bromide.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

COPD

In controlled clinical studies, the most common adverse reactions (>3% incidence in the placebo-controlled trials with treatment durations between 4 and 48 weeks) were pharyngitis, cough, dry mouth, and sinusitis, which were usually mild.

The clinical trial database for COPD includes 3282 SPIRIVA RESPIMAT patients from 7 placebo-controlled clinical trials with treatment periods ranging between four weeks and 48 weeks, contributing 2440 person-years of exposure. Patients with severe unstable cardiac disease, narrow-angle glaucoma, symptomatic prostatic hyperplasia or bladder-neck obstruction were excluded from these studies.

Table 1 shows all common adverse reactions that occurred with an incidence of $\geq 1\%$ in the SPIRIVA RESPIMAT treatment group, and a higher incidence rate on SPIRIVA RESPIMAT than on placebo.

Table 1: Incidence (% Patients) of Adverse Reactions in seven COPD Clinical Trials with treatment periods ranging between 4 and 48 weeks

Body System (Event)	SPIRIVA RESPIMAT [n=3282]	Placebo [n=3283]
Cardiac disorders		
Palpitations	1.2	0.9
Gastrointestinal Disorders		
Dry mouth	4.1	1.6
Gastroesophageal reflux disease	2.0	1.6
Constipation	1.7	1.5
Oropharyngeal candidiasis	1.3	1.2
Respiratory System Disorders (Upper)		
Pharyngitis	11.5	10.1
Cough	5.8	5.5
Sinusitis	3.1	2.7
Dysphonia	1.2	0.7
Nervous system disorder		
Dizziness	2.4	1.9
Skin and subcutaneous tissue disorders		
Rash	1.8	1.3
Pruritus	1.0	0.6
Renal and urinary disorders		
Urinary tract infection	1.9	1.8

Less Common Clinical Trial Adverse Drug Reactions (<1%)

In addition, among the adverse reactions observed in the clinical trials with an incidence of <1% and at a higher incidence rate on SPIRIVA RESPIMAT than on placebo were:

Gastrointestinal disorders: dysphagia, gingivitis, intestinal obstruction including ileus paralytic

Musculoskeletal and connective tissue disorders: joint swelling

Renal and urinary disorders: dysuria, urinary retention

Respiratory disorders: epistaxis, laryngitis

Skin and immune system disorders: angioedema, dry skin, skin infection and skin ulcer

Long-term Active-Controlled Mortality Trial

In the following section, cardiovascular and overall mortality information is presented from placebo controlled data of the two tiotropium formulations, SPIRIVA RESPIMAT and SPIRIVA HANDIHALER, as well as the large scale long term TIOSPIR study, comparing both formulations. The information provided below is for context only. Mortality is not an adverse reaction of SPIRIVA RESPIMAT.

In a retrospective pooled analysis of SPIRIVA RESPIMAT placebo-controlled clinical trials with complete vital status (mortality) follow-up, including three 48-week trials and one 24-week

placebo-controlled trial, 68 deaths (Incidence Rate 2.64 deaths per 100 patient years) were observed in the SPIRIVA RESPIMAT treatment group compared to 51 deaths (Incidence Rate 1.98 deaths per 100 patient years) in those treated with placebo. Treatment exposure to SPIRIVA RESPIMAT was 2,395 patient-years. In a 4-year, randomized, double-blind, placebo-controlled, multicenter clinical trial of tiotropium bromide inhalation powder (SPIRIVA HANDIHALER, the UPLIFT® study) in 5992 COPD patients a similar incidence rate of death had been observed between SPIRIVA HANDIHALER (430 deaths, Incidence Rate 3.94 deaths per 100 patient-years) and placebo treated groups (491 deaths, Incidence Rate 4.52 deaths per 100 patient-years). Treatment exposure to SPIRIVA HANDIHALER was 9,222 patient-years.

For clarification of the observed difference in fatal events, a long-term, randomized, double-blind, double dummy, active-controlled trial with an observation period up to 3 years (the TIOSPIR® study) was conducted to evaluate the risk of all-cause mortality and the effect on exacerbations associated with the use of SPIRIVA RESPIMAT compared to SPIRIVA HANDIHALER. The objective of this trial was to rule out a relative excess mortality risk of 25% for SPIRIVA RESPIMAT versus SPIRIVA HANDIHALER. The primary endpoints were all-cause mortality and time to first COPD exacerbation. The trial also included a lung function sub-study which measured trough FEV₁ every 24 weeks for 120 weeks (461 patients receiving SPIRIVA RESPIMAT, 445 patients receiving SPIRIVA HANDIHALER).

In this trial, 5711 patients received SPIRIVA RESPIMAT and 5694 patients received SPIRIVA HANDIHALER. Respective treatment exposure was 11,343 and 11,337 patient-years. All patients were followed for vital status (mortality) at the end of the trial. At baseline, patient characteristics were balanced between the two treatment arms. The mean age was 65 years and approximately 70% of subjects were male. Approximately, 82% of patients were Caucasian, 14% were Asian, and 2% were Black. Mean post-bronchodilator FEV₁ was 1.34 L with a mean FEV₁/FVC ratio of 50%. The majority of patients were GOLD II or III (48% and 40%, respectively). The vital status was confirmed in 99.7% of patients. The median exposure to treatment was 835 days for both treatment groups. All-cause mortality was similar during the study with SPIRIVA RESPIMAT (423 events, IR=3.22) and SPIRIVA HANDIHALER (439 events, IR=3.36), HR = 0.96 (95% CI 0.84 to 1.09).

The results of the trial demonstrated similar safety of SPIRIVA RESPIMAT compared with SPIRIVA HANDIHALER. Cause of death was adjudicated by a blinded, independent committee. Cardiovascular deaths included cardiac death, sudden cardiac death, and sudden death; as well as fatal events caused by a cardiac disorder, vascular disorder, or stroke. There were 113 patients (2%) treated with SPIRIVA RESPIMAT who had cardiovascular deaths compared to 101 (2%) patients treated with SPIRIVA HANDIHALER. Of the cardiovascular deaths, 11(0.2%) and 3 (0.1%) deaths were due to myocardial infarction in SPIRIVA RESPIMAT patients and SPIRIVA HANDIHALER patients, respectively. For cardiac deaths, sudden cardiac death, and sudden death, there were a total of 69 (1.2%) and 68 (1.2%) deaths in SPIRIVA RESPIMAT patients and SPIRIVA HANDIHALER patients, respectively.

Subgroup Analysis

In the pooled analysis of SPIRIVA RESPIMAT placebo-controlled clinical trials with complete vital status follow-up, there were 405 SPIRIVA RESPIMAT patients and 321 placebo patients

with cardiac arrhythmia at baseline. The all-cause mortality in this subgroup was higher during the study in the SPIRIVA RESPIMAT group (21 events, 5.2%) than in the placebo group (5 events, 1.6%). In the 4-year placebo-controlled SPIRIVA HANDIHALER study with complete vital status follow-up, there were 211 SPIRIVA HANDIHALER and 196 placebo patients with cardiac arrhythmia at baseline. The all-cause mortality was similar during the study with SPIRIVA HANDIHALER (43 events, 20.4%) and placebo (50 events, 25.5%). In the TIOSPIR study there were 614 SPIRIVA RESPIMAT patients and 607 SPIRIVA HANDIHALER patients with cardiac arrhythmia at baseline. The all-cause mortality in this subgroup was similar during the study with SPIRIVA RESPIMAT (65 events, 10.6%) and SPIRIVA HANDIHALER (78 events, 12.9%).

Asthma

In controlled clinical studies, the most common adverse reactions (>2% incidence in the placebo-controlled trials with treatment durations of between 12 weeks and 1 year) were cough and sinusitis, which were usually mild.

The clinical trial database for asthma includes 1256 SPIRIVA RESPIMAT patients from 6 placebo-controlled clinical trials, with treatment periods ranging between twelve weeks and one year, contributing 705 person years of exposure.

Table 2 shows all common adverse reactions that occurred with an incidence of $\geq 1\%$ in the SPIRIVA RESPIMAT treatment group, and a higher incidence rate on SPIRIVA RESPIMAT than on placebo.

Table 2 - Incidence (% Patients) of Adverse Reactions in six asthma Clinical Trials with treatment periods ranging between 12 weeks and 1 year

Body System (Event)	SPIRIVA RESPIMAT [n=1256]	Placebo [n=1260]
Gastrointestinal Disorders		
Oropharyngeal candidiasis	1.8	0.9
Dry mouth	1.5	0.6
Gastroesophageal reflux disease	1.4	1.0
Respiratory System Disorders (Upper)		
Sinusitis	3.3	3.3
Cough	2.1	1.7
Dysphonia	1.5	0.9
Skin and subcutaneous tissue disorders		
Rash	1.7	0.9

Less Common Clinical Trial Adverse Drug Reactions (<1%)

In addition, among the adverse reactions observed in the clinical trials with an incidence of <1% and at a higher incidence rate on SPIRIVA RESPIMAT than on placebo were:

Cardiac disorders: atrial fibrillation, supraventricular tachycardia

Eye disorders: vision blurred

Gastrointestinal disorders: gingivitis

Musculoskeletal and connective tissue disorders: joint swelling

Nervous system disorders: dizziness

Respiratory disorders: epistaxis, laryngitis

Skin and immune system disorders: dry skin

Post-Market Adverse Drug Reactions

In addition to the adverse reactions observed during the SPIRIVA RESPIMAT clinical trials, the following adverse reactions have been identified during the worldwide use of SPIRIVA RESPIMAT and SPIRIVA HANDIHALER:

Eye disorders: glaucoma, intraocular pressure increased

Cardiac disorder: tachycardia

Gastrointestinal disorders: glossitis, stomatitis

Metabolism and nutrition disorders: dehydration

Nervous system disorders: insomnia

Respiratory disorders: bronchospasm

Skin and immune system disorders: hypersensitivity (including immediate reactions), urticaria

Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

DRUG INTERACTIONS

Drug-Drug Interactions

Tiotropium is mainly excreted renally (approximately 74% of the intravenously administered dose). The remaining dose is mainly nonenzymatically cleared with a minor portion (<20% of intravenous dose) being metabolized by CYP2D6 and CYP3A4 ([see ACTION AND CLINICAL PHARMACOLOGY, Metabolism](#)). Tiotropium does not inhibit cytochrome P450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, 3A4 even in supratherapeutic concentrations, which makes clinically relevant metabolic interactions with tiotropium unlikely.

Although no formal drug interaction studies have been performed, tiotropium bromide has been used concomitantly with other drugs commonly used in the treatment of COPD and asthma including sympathomimetic bronchodilators, methylxanthines, and oral and inhaled steroids, antihistamines, mucolytics, leukotriene modifiers, cromones and anti-IgE treatment without clinical evidence of drug interactions.

Anticholinergics

The chronic co-administration of tiotropium bromide with other anticholinergic-containing drugs has not been studied. There is potential for an additive interaction with concomitantly used anticholinergic medications. Therefore, avoid coadministration of SPIRIVA RESPIMAT with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects.

Drug-Lifestyle Interactions

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.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Elderly patients, hepatically impaired patients, and renally impaired patients can use SPIRIVA RESPIMAT at the recommended dose. However, as with all renally excreted drugs, SPIRIVA RESPIMAT use should be monitored closely in patients with moderate to severe renal impairment.
- The safety and efficacy of SPIRIVA RESPIMAT in pediatric patients have not been established.

General considerations for COPD

Counselling by doctors on smoking cessation should be the first step in treating patients with COPD, who smoke, independent of the clinical presentation i.e. chronic bronchitis (with or without airflow limitation) or emphysema. Cessation of smoking produces dramatic symptomatic benefits and has been shown to confer a survival advantage.

General considerations for Asthma

Use SPIRIVA RESPIMAT as add-on maintenance bronchodilator treatment in adult patients with asthma who remain symptomatic on a combination of inhaled corticosteroid (equivalent to, but not limited to ≥ 500 mcg fluticasone/day or ≥ 800 mcg budesonide/day) and a long acting β_2 agonist.

The need for continued therapy should be periodically reassessed based upon the patient's disease severity and level of asthma control.

Recommended Dose The recommended dose of SPIRIVA RESPIMAT (tiotropium bromide monohydrate) is 2 inhalations of 2.5 micrograms once daily from the RESPIMAT inhaler at the same time of day, every day.

Spacer device is not required.

Asthma

SPIRIVA RESPIMAT must be taken with an inhaled corticosteroid and a long-acting beta-agonist.

In the treatment of asthma, the full benefit will be apparent after several doses.

Missed Dose

Patients should be advised that if they forget to take a dose (2 inhalations), they should take the missed dose as soon as they remember. SPIRIVA RESPIMAT should not be taken more than one dose (2 inhalations) every 24 hours.

Administration

SPIRIVA RESPIMAT should be administered once daily, at the same time of day, every day via inhalation only through the RESPIMAT inhalation device.

To ensure proper administration of SPIRIVA RESPIMAT, the doctor or other qualified health care professional should teach the patient how to operate the RESPIMAT inhalation device (see [Part III CONSUMER INFORMATION](#)).

SPIRIVA RESPIMAT cartridges are to be used only with the SPIRIVA RESPIMAT inhaler.

OVERDOSAGE

High doses of tiotropium bromide may lead to signs and symptoms of exaggerated anticholinergic effects, such as constipation, voiding difficulties or increased intraocular pressure causing pain, vision disturbances or reddening of the eye.

No adverse events, beyond dry mouth/throat and dry nasal mucosa in a dose-dependent (10-40 mcg daily) incidence, were observed following 14-day dosing of up to 40 mcg tiotropium inhalation solution in healthy subjects with the exception of pronounced reduction in salivary flow from day 7 onwards.

Should signs of serious anticholinergic toxicity appear, vital signs should be carefully monitored and appropriate therapy should be initiated.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Tiotropium is a long acting muscarinic receptor antagonist (LAMA), also known as an anticholinergic. It has a similar affinity to the subtypes of muscarinic receptors M1 to M5 . In the lungs, inhibition of M3-receptors at the smooth muscle results in relaxation of the airways. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. Tiotropium bromide is a quaternary ammonium molecule with duration of action sufficient to provide 24 hours of bronchoprotection with once-a-day inhalational administration.

The long duration of action of tiotropium is thought to be due to its slow dissociation kinetics from the muscarinic M₃-receptor subtype. Dissociation from M₂-receptors is faster than from M₃, which in functional in vitro studies, elicited (kinetically controlled) receptor subtype selectivity of M₃ over M₂. As an N-quaternary anticholinergic, tiotropium is topically selective when administered by inhalation to the lung. Pharmacological in vitro and in vivo studies profiled tiotropium as a potent, long acting bronchodilator suitable for a once-daily dose regimen.

Pharmacodynamics

Primary Pharmacodynamic Effects

The primary pharmacodynamic effect in subjects with COPD following inhalation of tiotropium is bronchodilation, which is primarily a site-specific, rather than a systemic effect. Tiotropium bromide, administered once daily in the COPD population, provided significant improvement in lung function (forced expiratory volume in one second, FEV₁ and forced vital capacity, FVC) within 30 minutes following the first dose which was maintained for 24 hours.

Pharmacodynamic steady state was reached within one week with the majority of bronchodilation observed by the third day. Repeated inhalation of SPIRIVA RESPIMAT has not been linked with tolerance towards the bronchodilatory effects of the drug. Bronchodilatory effects gradually returned to baseline levels upon cessation of treatment with no evidence of rebound.

Secondary Pharmacodynamic Effects

Cardiac Electrophysiology:

In a multicenter, randomized, double-blind trial using tiotropium dry powder for inhalation that enrolled 198 patients with COPD, the number of subjects with changes from baseline-corrected QT interval of 30 to 60 msec was higher in the tiotropium group as compared with placebo. This difference was apparent using both the Bazett (QTcB) [20 (20%) patients vs., 12 (12%) patients] and Fredericia (QTcF) [16 (16%) patients vs. 1 (1%) patient] corrections of QT for heart rate. No patients in either group had either QTcB or QTcF of >500 msec. Other clinical trials with tiotropium did not detect an effect of the drug on QTc intervals.

The effect of tiotropium dry powder for inhalation on QT interval was also evaluated in a randomized, placebo- and positive-controlled crossover study in 53 healthy volunteers. Subjects received tiotropium inhalation powder 18 mcg, 54 mcg (3 times the recommended dose), or placebo for 12 days. ECG assessments were performed at baseline and throughout the dosing interval following the first and last dose of study medication. Relative to placebo, the maximum mean change from baseline in study-specific QTc interval was 3.2 msec and 0.8 msec for tiotropium inhalation powder 18 mcg and 54 mcg, respectively. No subject showed a new onset of QTc >500 msec or QTc changes from baseline of ≥ 60 msec.

Pharmacokinetics

Tiotropium bromide is a non-chiral quaternary ammonium compound and is sparingly soluble in water. It is available as an inhalation solution that is administered via the RESPIMAT inhaler as an inhalation spray. Approximately 40% of the labelled dose delivered by the RESPIMAT inhaler is deposited in the lungs, the target organ, the remaining amount being deposited in the gastrointestinal tract. Some of the pharmacokinetic data described below were obtained with higher doses than recommended for therapy.

Table 3: Summary of tiotropium pharmacokinetic parameters following inhalation of 5 mcg via SPIRIVA RESPIMAT to steady-state in patients with COPD

$C_{max,ss}^1$ [pg/mL]	$t_{1/2,ss}^2$ [h]	$AUC_{0-6,ss}^1$ [pg·h/mL]	Clearance ³ [mL/min]	Volume of distribution ³ [L/Kg]
10.5 (66.4)	27-45	22.1 (47.8)	880 (22.1)	32.0 (32.1)

¹= Geometric mean (gCV%) values from COPD patients following once daily treatment with 5 mcg Tiotropium Respimat[®] for 4 weeks

²= Geometric mean effective half-life from COPD patients following once daily treatment with 18 mcg Tiotropium HandiHaler[®] for 14 days

³=Healthy volunteers administered single dose of 14.4 mcg via intravenous infusion

Table 4: Summary of tiotropium pharmacokinetic parameters following inhalation of 5 mcg via SPIRIVA RESPIMAT to steady-state in patients with asthma

$C_{max,ss}^1$ [pg/mL]	$t_{1/2,ss}^2$ [h]	$AUC_{0-6,ss}^1$ [pg·h/mL]	$AUC_{0-24,ss}^1$ [pg·h/mL]
5.15 (65.1)	34	16.5 (46.9)	56.0 (40.0)

¹= Geometric mean (gCV%) values from asthma patients following once daily treatment with 5 mcg Tiotropium RESPIMAT[®] for 4 weeks.

²= Geometric mean effective half-life from asthma patients following once daily treatment with 5 mcg Tiotropium RESPIMAT[®] for 4 weeks.

Absorption:

Following inhalation by young healthy volunteers, urinary excretion data suggests that approximately 33% of the dose reaches the systemic circulation. Oral solutions of tiotropium have an absolute bioavailability of 2-3%. Food is not expected to influence the absorption of tiotropium. Maximum tiotropium plasma concentrations were observed 5-7 minutes after inhalation. At steady state, peak tiotropium plasma concentrations of 10.5 pg/mL were achieved in COPD patients and decreased rapidly in a multi-compartmental manner. Steady state trough plasma concentrations were 1.60 pg/mL and was reached by day 7 with no accumulation thereafter.

For patients with asthma, a steady state tiotropium peak plasma concentration of 5.15 pg/mL was attained 5 minutes after the administration of 5 mcg.

Distribution:

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

Metabolism:

The extent of biotransformation is small. This is evident from a urinary excretion of approximately 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 metabolized by cytochrome P450 dependent oxidation and subsequent glutathione conjugation to a variety of Phase II-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 bromide even in supra-therapeutic concentrations does not inhibit cytochrome P450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1 or 3A in human liver microsomes.

Excretion:

The effective half-life of tiotropium ranges between 27 to 45 h following inhalation by COPD patients.

In patients with asthma, the effective half-life of tiotropium following inhalation is approximately 34 hours.

Intravenously administered tiotropium bromide to young healthy volunteers is mainly excreted unchanged in urine (74%) with a total clearance of 880 mL/min.

Following 21-day, once daily inhalation of the solution by patients with COPD, 24-hour urinary excretion is 18.6% (0.93mcg) of the dose, the remainder being mainly non-absorbed drug in gut that is eliminated via the feces.

In patients with asthma, 11.9% (0.60 mcg) of the dose is excreted unchanged in the urine over 24 hours post-dose at steady state.

The renal clearance of tiotropium exceeds the creatinine clearance indicating secretion into the urine. After chronic once daily inhalation, pharmacokinetic steady state was reached by day 7 with no accumulation thereafter.

Dose Proportionality: Independent of the formulation and indication, tiotropium demonstrates dose proportional pharmacokinetics.

Special Populations and Conditions

Geriatrics: 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. Similarly, exposure to tiotropium was not found to differ with age in patients with asthma.

Pediatrics: Pharmacokinetics in children was not investigated as tiotropium development is currently restricted to therapy for asthma in adults.

Gender: Based on a pooled analysis of pharmacokinetic data, the exposure to tiotropium was not found to differ by sex.

Hepatic Insufficiency: The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied. However, impaired liver function is not expected to have any clinically relevant influence on tiotropium pharmacokinetics since tiotropium is predominantly cleared by renal elimination and by non-enzymatic ester cleavage to products that do not bind to muscarinic receptors.

COPD

Renal Insufficiency: Once daily inhaled administration of tiotropium to steady-state in COPD patients with mild renal impairment (creatinine clearance 60-90 mL/min) resulted in slightly higher $AUC_{0-6,ss}$ (between 6% to 23% higher) and $C_{max,ss}$ (between 6% to 17% higher) values compared to patients with normal renal function. Moderate renal impairment (creatinine clearance 30-60 mL/min) resulted in modestly higher $AUC_{0-6,ss}$ (between 54% to 57% higher) and $C_{max,ss}$ (between 15% to 31% higher) values compared to COPD patients with normal renal function (creatinine clearance >90 mL/min). In patients with severe renal impairment (creatinine clearance <30 mL/min), a single intravenous administration of tiotropium bromide resulted in approximately 94% higher AUC_{0-4} and 52% higher C_{max} compared to patients with normal renal function.

Asthma

Renal Insufficiency: Once daily inhaled administration of tiotropium to steady-state to patients with asthma with mild renal impairment (creatinine clearance 60-90 mL/min) resulted in slightly higher AUC_{0-6,ss} (13% higher) but similar C_{max,ss} (4% higher) values compared to patients with normal renal function. Moderate renal impairment (creatinine clearance 30-60 mL/min) resulted in modestly higher AUC_{0-6,ss} (59% higher) and C_{max,ss} (76% higher) values compared to patients with asthma and normal renal function (creatinine clearance >90 mL/min).

STORAGE AND STABILITY

Store at 15-30°C. Do not freeze.

SPECIAL HANDLING INSTRUCTIONS

Prior to first use, the SPIRIVA RESPIMAT cartridge is inserted into the SPIRIVA RESPIMAT inhaler and the unit is primed.

When using the unit for the first time, patients are to actuate the inhaler toward the ground until an aerosol cloud is visible and then repeat the process three more times. The unit is then considered primed and ready for use. If used every day, no further priming is necessary. If not used for more than 7 days, patients are to actuate the inhaler once to prepare the inhaler for use. If not used for more than 21 days, patients are to actuate the inhaler until an aerosol cloud is visible and then repeat the process three more times to prepare the inhaler for use (see [PART III: CONSUMER INFORMATION, PROPER USE OF THIS MEDICATION](#)).

When the labeled number of metered actuations (60 or 28) has been dispensed from the inhaler, the SPIRIVA RESPIMAT locking mechanism will be engaged and no more actuations can be dispensed.

After insertion of the cartridge into the inhaler, SPIRIVA RESPIMAT should be discarded at the latest 3 months after first use or when the locking mechanism is engaged (60 actuations or 28 actuations), whichever comes first.

Keep out of reach of children. Do not spray into eyes.

DOSAGE FORMS, COMPOSITION AND PACKAGING

SPIRIVA RESPIMAT is supplied in a carton containing one SPIRIVA RESPIMAT cartridge and one SPIRIVA RESPIMAT inhaler.

The SPIRIVA RESPIMAT cartridge is an aluminum cylinder with a tamper protection seal on the cap. The SPIRIVA RESPIMAT cartridge is only intended for use with the SPIRIVA RESPIMAT inhaler.

The SPIRIVA aqueous solution is contained in a specifically designed plastic container crimped inside an aluminum cartridge.

The SPIRIVA RESPIMAT inhaler is a propellant free hand-held, pocket-sized, multi-dose, oral inhalation device. The SPIRIVA RESPIMAT inhaler is a cylindrical shaped plastic inhalation device with a gray colored body and a clear base. The clear base is removed to insert the cartridge. The inhaler contains a dose indicator and a locking mechanism that engages after the declared number of doses has been delivered. The green coloured cap on the SPIRIVA RESPIMAT inhaler is colour coded to match the SPIRIVA RESPIMAT cartridge. There is information on the cartridge label to indicate it should be used with the SPIRIVA RESPIMAT inhaler.

The SPIRIVA RESPIMAT cartridge when used with the SPIRIVA RESPIMAT inhaler, is designed to deliver at least 60 or 28 metered actuations after preparation for use; the equivalent of 30 or 14 days medication when used according to the directions for use (one dose equals two actuations).

Each dose (1 dose equals 2 actuations) from the SPIRIVA RESPIMAT inhaler delivers 5 mcg tiotropium from the mouthpiece.

As with all inhaled drugs, the actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between the actuation of the inhaler and inspiration through the delivery system.

Excipients include purified water, benzalkonium chloride, disodium edetate, and hydrochloric acid. The SPIRIVA RESPIMAT cartridge is only intended for use with the SPIRIVA RESPIMAT inhaler.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

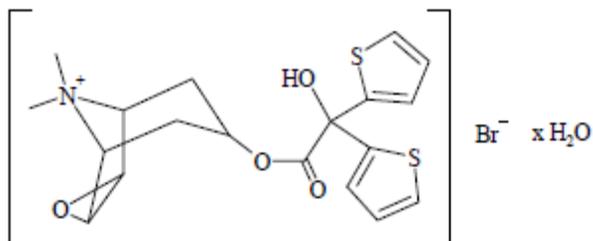
Drug Substance

Proper name: tiotropium bromide monohydrate

Chemical name: (1 α ,2 β ,4 β ,5 α ,7 β)-7-[Hydroxydi-2-thienylacetyl]oxy]-9,9dimethyl-3-oxa-9-azoniatricyclo[3.3.1.0^{2,4}]nonane bromide monohydrate

Molecular formula and molecular mass: C₁₉H₂₂NO₄S₂Br • H₂O

Structural formula:



Physicochemical properties:

Description:	white or yellowish white powder. It is sparingly soluble in water and soluble in methanol.
Polymorphism:	three crystalline forms are possible, the monohydrate and two anhydrous forms
Melting Point:	between 225° C and 235° C
pH (1% aqueous solution):	5.0 - 5.6
Apparent Partition Coefficient:	$\log P_{\text{app}} = -2.28$

CLINICAL TRIALS

Clinical Studies in COPD

Study demographics and trial design

The efficacy and safety of SPIRIVA RESPIMAT were evaluated in two 12-week and three 48-week, randomised, double-blind studies in 6614 COPD patients (2801 receiving SPIRIVA RESPIMAT 5 mcg dose). The two 12-week trials were both active (ipratropium) and placebo-controlled. The 48-week programme consisted of three placebo-controlled trials. All studies included lung function measurements, with trough FEV₁ (i.e. FEV₁ measured approximately 10 minutes before the last dose) as the primary endpoint. In addition, the three 48-week studies included the effect on exacerbations as a co-primary endpoint and two of the three 48-week studies also included health outcome measures of dyspnea and health-related quality of life as co-primary endpoints.

Table 5- Summary of patient demographics for clinical trials in COPD

Study #	Trial design	Dosage, route of administration and duration	Study subjects (number) COPD patients	Mean age (years)	Gender
205.251	Multi-centre, randomised, double-dummy, double-blind, placebo and active-controlled, parallel group	Tio R 5 mcg or 10 mcg once daily IB MDI 36 mcg four times a day oral inhalation 12 weeks duration	Tio R 5 (88) Tio R 10 (93) IB MDI 36 (89) PL (91)	62	M-269 F-92
205.252	Multi-centre, randomised, double-dummy, double-blind, placebo and active-controlled, parallel group	Tio R 5 mcg or 10 mcg once daily, IB MDI 36 mcg four times a day oral inhalation 12 weeks duration	Tio R 5 (92) Tio 10= (87) IB MDI 36 (89) PL (90)	66	M-230 F-128
205.254	Multi-centre, randomised, double-blind, placebo-controlled, parallel group	Tio R 5 mcg or 10 mcg once daily oral inhalation 48 weeks duration	Tio R 5 (332) Tio R 10 (332) PL (319)	65	M- 747 F- 236
205.255	Multi-centre, randomised, double-blind, placebo-controlled, parallel group	Tio R 5 mcg or 10 mcg once daily oral inhalation 48 weeks duration	Tio R 5 (338) Tio R 10 (335) PL (334)	65	M-729 F-278
205.372	Multi-centre, randomised, double-blind, placebo controlled parallel group	Tio R 5 mcg oral inhalation 48 weeks duration	Tio R 5 (1952) PL (1965)	65	M-3037 F-880

Tio R – Tiotropium Respimat

IB MDI –Ipratropium Bromide MDI

PL -Placebo

The main inclusion criteria in all the studies were patients 40 years of age or older, diagnosis of COPD with screening of FEV₁ equal or less than 60% of predicted normal, and a history of smoking of 10 pack-years or more and a ratio of FEV₁/FVC of ≤0.7. The main exclusion criterion was significant disease other than COPD which in the opinion of the investigator, precluded the patient's participation in this study.

Lung Function

SPIRIVA RESPIMAT administered once daily, provided rapid (within 30 minutes) and significant improvement in lung function (forced expiratory volume in one second and forced vital capacity) following the first dose, compared to placebo. Improvement of lung function was maintained for 24 hours at steady state. Pharmacodynamic steady state was reached within one week.

The combined two 48-week studies (205.254 and 205.255) demonstrated statistically ($p < 0.0001$) and clinically significant differences in mean trough FEV₁ over placebo (127 mL) on test day 337 (see **Table 6** for individual study results and **Figure 1** for combined results below).

The bronchodilator effects of SPIRIVA RESPIMAT were maintained throughout the 48-week period of administration with no evidence of tolerance.

Table 6: Change from Baseline in Trough FEV₁ (L) in COPD patients

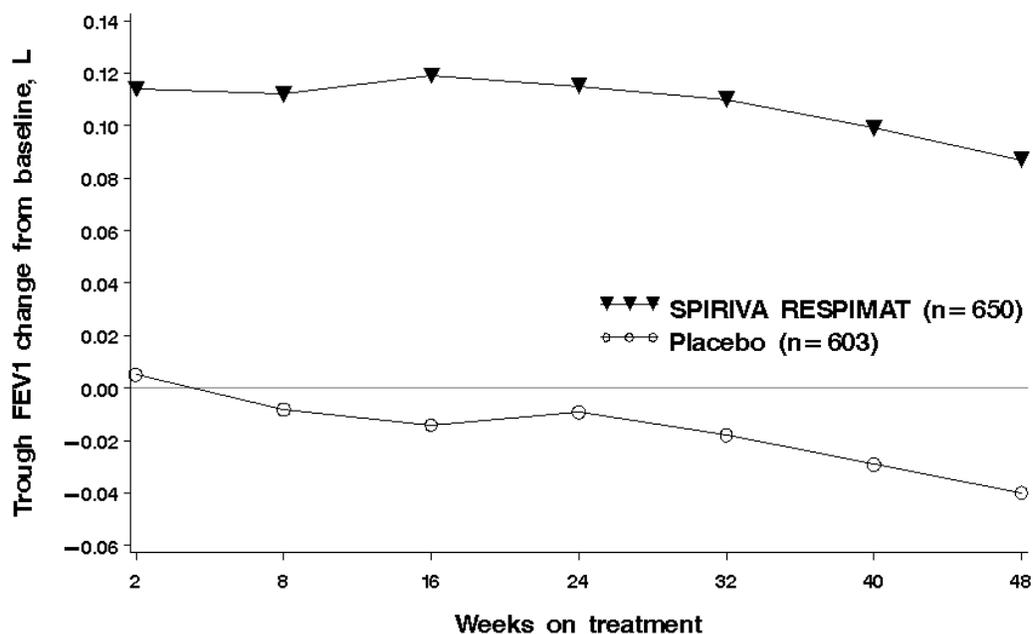
Trial	Treatment Arm (number)*	Adjusted Mean Change from Baseline (L)	Adjusted Mean of Difference (L)	95% CI	p value
12 weeks					
205.251	Tio R 5 mcg (85) Placebo (87)	Tio R 5=0.112 PL=0.003	Tio R 5 vs PL=0.109	Tio R 5 vs PL=0.037, 0.181	Tio R 5 vs PL=0.0032
205.252	Tio R 5 mcg (90) Placebo (84)	Tio R 5=0.094 PL=0.030	Tio R 5 vs PL=0.125	Tio R 5 vs PL=0.067, 0.182	Tio R 5 vs PL <0.0001
48 weeks					
205.254	Tio R 5 mcg (326) Placebo (296)	Tio R 5=0.097 PL=-0.046	Tio R 5 vs PL=0.142	Tio R 5 vs PL=0.104, 0.181	Tio R 5 vs PL <0.0001
205.255	Tio R 5 mcg (324) Placebo (307)	Tio R 5=0.077 PL=0.036	Tio R 5 vs PL=0.113	Tio R 5 vs PL=0.078, 0.147	Tio R 5 vs PL <0.0001
205.372	Tio R 5 mcg (1889) Placebo (1870)	Tio R 5=0.119 PL=0.018	Tio R 5 vs PL=0.102	Tio R 5 vs PL=0.085, 0.118	<0.0001

* Treated patients with both a baseline and at least one on-treatment trough FEV₁ value

Tio R 5= Tiotropium Respimat 5 mcg

PL = Placebo

Figure 1: Trough FEV₁ change from baseline over 48 weeks in pooled studies (205.254/205.255) of COPD patients



The means are adjusted for center, smoking status at entry and baseline value.

COPD Exacerbations

In three 48 week randomised, double-blind, placebo-controlled clinical trials, SPIRIVA RESPIMAT treatment resulted in a significantly reduced risk of a COPD exacerbation in comparison to placebo. Exacerbations of COPD were defined as “a complex of at least two respiratory events/symptoms with duration of three days or more requiring a change in treatment (prescription of antibiotics and/or systemic corticosteroids and/or a significant change of the prescribed respiratory medication)”.

The pooled primary endpoint analysis of two Phase III trials and separate primary endpoint analysis of an additional exacerbation trial are displayed in **Table 7**. All respiratory medications except anticholinergics and long-acting beta-agonists, i.e. rapidly acting beta-agonists, inhaled corticosteroids and xanthines, were allowed as concomitant treatment in the two pooled 48-week exacerbation studies. In addition, long-acting beta-agonists were allowed in the third 48-week exacerbation trial.

Table 7: Statistical Analysis of Exacerbations of COPD in Patients with Moderate to Very Severe COPD

Study (N _{Tio R 5} , N _{placebo})	Endpoint	Tiotropium Respimat	Placebo	% Risk Reduction (95% CI)	p-value (primary endpoint only)
48-week, Ph III studies, pooled analysis ^a (205.254,205.255) (N _{Tio R 5} =670, N _{placebo} =653)	Mean exacerbation incidence rate per patient year	0.78 ^b	1.00 ^b	22 (8, 33) ^b	0.002 ^b
48-week, Ph IIIb exacerbation study (205.372) (N _{Tio R 5} =1939, N _{placebo} =1953)	Days to first COPD exacerbation	169 ^c	119 ^c	31 (23 to 37) ^d	<0.0001 ^d

^a Pooling was specified when the studies were designed.

^b Poisson regression. Risk reduction is 100(1 - rate ratio).

^c Time to first event: days on treatment by when 25% of patients had at least one exacerbation of COPD.

^d Hazard ratios were estimated from a Cox proportional hazard model. The percentage risk reduction is 100(1 - hazard ratio).

In the pooled Phase III 48-week studies (205.254 and 205.255), SPIRIVA RESPIMAT treatment resulted in a 29% reduced risk of a COPD exacerbation, a 25% reduced risk of a hospitalised COPD exacerbation and 20% fewer hospitalised COPD exacerbations (all secondary endpoints). In the Phase IIIb study (205.372), SPIRIVA RESPIMAT treatment resulted in 21% fewer COPD exacerbations, a 27% reduced risk of a hospitalised COPD exacerbation and 19% fewer hospitalised COPD exacerbations (all secondary endpoints).

Symptom Related Outcomes

Pooled analysis of the Transition Dyspnea Index (TDI) from the two 48-week studies showed that SPIRIVA RESPIMAT significantly improved dyspnea by 1.05 units at day 337 (p<0.0001 vs. placebo).

SPIRIVA RESPIMAT improved the patients' health-related quality of life as measured using the St. George's Respiratory Questionnaire (SGRQ). The difference in mean total score between SPIRIVA RESPIMAT and placebo at the end of the two 48-week studies was 3.5 for SPIRIVA RESPIMAT (p<0.0001 vs. placebo).

Long-term Active-Controlled Mortality Trial

A long-term, randomized, double-blind, double dummy, active-controlled trial with an observation period up to 3 years was conducted to evaluate all cause mortality and time to first COPD exacerbation (primary endpoints) of SPIRIVA RESPIMAT compared to SPIRIVA HANDIHALER (TIOPIR[®]). This trial also included a lung function sub-study which measured trough FEV₁ every 24 weeks for 120 weeks (461 patients receiving SPIRIVA RESPIMAT, 445 patients receiving SPIRIVA HANDIHALER).

The spirometry sub-study provided evidence that the bronchodilator effect of SPIRIVA RESPIMAT was sustained over 120 weeks.

Clinical Studies in Asthma

Study demographics and trial design

The pivotal clinical Phase III programme for persistent asthma included two replicate 1-year randomised, double-blind, placebo-controlled studies in a total of 912 adult asthma patients (456 receiving SPIRIVA RESPIMAT) who remain symptomatic despite treatment with stable high dose of ICS (equivalent to, but not limited to ≥ 500 mcg fluticasone/day or ≥ 800 mcg budesonide/day) and a LABA and with a history of 1 or more asthma exacerbations in the past year that required treatment with systemic corticosteroids. Both studies included lung function measurements, with peak FEV₁ measured within the first 3 hours of dosing (FEV_{1peak0-3h}) and trough FEV₁ (i.e. FEV₁ measured 10 minutes before the last dose) as co-primary endpoints. The time to first severe asthma exacerbation of the pooled analysis of the 2 replicate trials was the third co-primary endpoint.

The 2 Phase III parallel-group trials were conducted in male and female outpatients between 18 and 75 years old with a current diagnosis of severe persistent asthma who remain symptomatic on a combination of ICS/LABA (see above). The diagnosis of asthma had to be made before the patient was 40 years old. To be eligible for the trials, patients had to have never smoked or had to be ex-smokers with <10 pack-years, who had quit smoking at least 1 year prior to enrolment. All patients had to be symptomatic (i.e. uncontrolled), as indicated by an ACQ score of ≥ 1.5 at screening and randomization. Apart from standard exclusion criteria to ensure patient safety, the tiotropium in asthma clinical program only specifically excluded patients with lung diseases other than asthma (i.e. COPD). The main inclusion criteria was severe persistent asthma in adults (18 to 75 years) who had a history of at least one asthma exacerbation in the past year and who remained symptomatic on a combination of an inhaled corticosteroid (equivalent to, but not limited to ≥ 500 mcg fluticasone/day or ≥ 800 mcg budesonide/day) and a long-acting β_2 agonist.

Table 8: Summary of patient demographics for clinical trials in Asthma

Study #	Trial design	Dosage, route of administration and duration	Study subjects (number) Mean Age (Range) Gender	Primary Efficacy Endpoint
205.416	Multi-centre, randomised, double-blind, placebo-controlled, parallel group study	5 mcg once daily oral inhalation 48 weeks duration	Total:n=459 Tio R 5 (237) PL (222) <u>Mean age (Range)</u> 53.4 years (18-75) <u>Gender</u> Male: 170 Female: 289	<ul style="list-style-type: none"> Adjusted mean FEV₁ peak_{0-3 h} Trough FEV₁ response after 24 weeks of treatment
205.417	Multi-centre, randomised, double-blind, placebo-controlled, parallel group study	5 mcg once daily oral inhalation 48 weeks duration	Total:n=453 Tio R 5 (219) PL (234) <u>Mean age (Range)</u> 52.5 years (19-75) <u>Gender</u> Male: 191 Female: 262	<ul style="list-style-type: none"> Adjusted mean FEV₁ peak_{0-3 h} Trough FEV₁ response after 24 weeks of treatment
205.416 /205.417 (pooled data)			Total:n=912 Tio R 5 (456) PL (456) <u>Mean age (Range)</u> 53.0 years (18-75) <u>Gender</u> Male: 361 Female: 551	<ul style="list-style-type: none"> Time to the first severe asthma exacerbation during 48 weeks of treatment

Abbreviations:

Tio R: tiotropium in Respimat®

PL: Placebo

Results

Lung Function

In the two 1-year studies in patients who were symptomatic on maintenance treatment of at least high-dose ICS/LABA, SPIRIVA RESPIMAT showed significant improvements in lung function over ICS/LABA alone when used as add-on to background treatment as evidenced by the significantly increased FEV₁peak_{0-3h} response, and the significantly larger mean trough FEV₁ increase after 24 weeks of treatment (see **Table 9**).

Table 9: Adjusted mean (SE) FEV₁ peak_{0-3h} response and trough FEV₁ response at 24 weeks for the two Phase III trials in severe asthma

Co-primary endpoints	Adjusted ¹ mean response ²		Adjusted ¹ mean difference SPIRIVA RESPIMAT+ICS/LABA – placebo + ICS/LABA		
	N ³	Adjusted ¹ Mean (SE)	Adjusted ¹ Mean (SE)	95% CI	p-value-superiority
FEV₁ peak_{0-3h}(L) (first)					
205.416					
Placebo	211	0.315 (0.026)			
Tio R5	217	0.401 (0.025)	0.086 (0.034)	0.020, 0.152	0.0110
205.417					
Placebo	218	0.248 (0.024)			
Tio R5	205	0.401 (0.025)	0.154 (0.032)	0.091, 0.217	<0.0001
Trough FEV₁ (L) (second)					
205.416					
Placebo	211	0.056 (0.025)			
Tio R5	217	0.144 (0.024)	0.088 (0.031)	0.027, 0.149	0.0050
205.417					
Placebo	218	0.044 (0.022)			
Tio R5	204	0.155 (0.023)	0.111 (0.030)	0.053, 0.169	0.0002

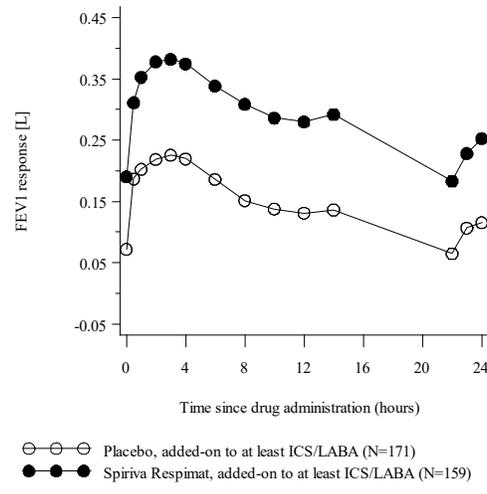
1 Adjusted for study treatment, centre, visit, baseline, visit-by-treatment and baseline-by-visit (centre replaced with study for combined model). Spatial power covariance structure was used. Patient is considered random for the model used in the combined analysis.

2 Change from study baseline.

3 Number of patients with measurements at Week 24.

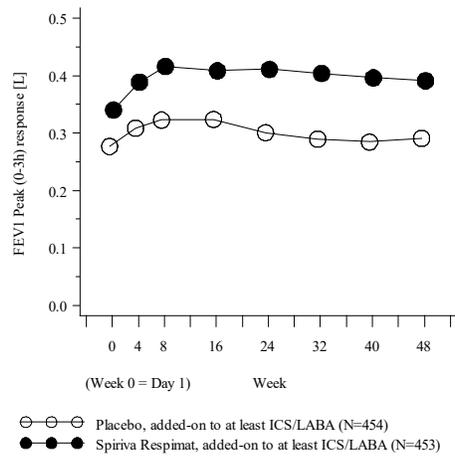
24-hour spirometry was performed at 24 weeks for a subset of patients (ICS/LABA: 171 patients, ICS/LABA + SPIRIVA RESPIMAT: 159 patients) in the two 1-year trials in patients with severe asthma. The improvement of lung function was maintained for 24 hours duration with SPIRIVA RESPIMAT+ ICS/LABA compared to ICS/LABA alone (**Figure 2**).

Figure 2: FEV₁ profiles over 24 hours in a subset of asthma patients (who underwent 24 h spirometry) in the pooled 1-year (205.416/205.417) studies at week 24



The bronchodilator effects of SPIRIVA RESPIMAT were maintained throughout the 1 year period of administration, with no evidence of tachyphylaxis or tolerance (**Figure 3**).

Figure 3: Peak FEV₁ response over 48 weeks in the pooled 1-year (205.416/205.417) studies in asthma patients



Exacerbations

In the two 48-week randomised, double-blind, placebo-controlled clinical trials, SPIRIVA RESPIMAT treatment resulted in a significantly reduced risk of an asthma exacerbation (including severe exacerbations) in comparison to ICS/LABA alone.

SPIRIVA RESPIMAT + ICS/LABA significantly reduced the risk of severe asthma exacerbations by 21%, and the risk of first asthma worsening by 31% compared to ICS/LABA alone.

DETAILED PHARMACOLOGY

Non Clinical Pharmacology

In-vitro studies have shown that tiotropium is a potent, reversible, M3 muscarinic receptor antagonist. Dissociation from M2-receptors is faster than from M3, which in functional *in-vitro* studies, led to (kinetically controlled) receptor subtype selectivity of M3 over M2 receptor subtypes.

The high potency and long duration of action of tiotropium, suggested by the *in vitro* studies, has been confirmed *in-vivo* in various animal models. Following single inhaled doses in guinea pigs and dogs, tiotropium was shown to provide a strong and long-lasting bronchoprotection against acetylcholine-induced bronchoconstriction. Bronchoprotection was maintained over 24 hours after the single inhaled dose.

A battery of safety pharmacology studies included the evaluation of possible peripheral anticholinergic effects normally associated with systemic drug exposure. After inhalation administration, however, bronchoprotective doses were shown to be devoid of systemic anticholinergic effects in both guinea pigs and dogs.

The absence of CNS-related effects of tiotropium is in accordance with the assumption that this quaternary charged molecule is unable to penetrate the blood-brain barrier.

TOXICOLOGY

Acute Toxicity

The acute inhalation and oral toxicity in mice, rats and dogs was low and independent of the formulation type used (aqueous aerosol, lactose powder). Non-lethal dosages produced clinical signs characteristic of the pharmacodynamic activity of tiotropium (mydriasis, dry mouth and nose) as well as non-specific signs of toxicity (dyspnea, tremor, ataxia, convulsions, loss of motility and body weight). In mice, deaths occurred at 131 mg/kg tiotropium when administered as an aqueous aerosol through nose only exposure (the LD₅₀-value could not be established).

No lethal dosage was achieved by the inhalation of either formulation in rats ($LD_{50} >334.5$ mg/kg) or dogs ($LD_{50} >3.6$ and >0.7 mg/kg). Necropsy of decedents revealed pulmonary emphysema and/or congestion of liver and kidneys. No gross lesions were detected among survivors. The oral LD_{50} for mice and rats are 219,099 and 1,279,279 times respectively the maximum recommended human dose on a mg/m^2 basis.

Chronic Toxicity

The repeated-dose toxicity was investigated by inhalation of tiotropium by rats and Beagle dogs for 13 and 52 weeks, by intravenous injection over 4 weeks, and by oral gavage for 13 weeks. In rats and dogs, most in-life and morphological changes were directly or indirectly attributable to the anticholinergic activity of the compound. These changes included mydriasis, increased heart rate, and dry mucous membranes due to lowered secretory activity of the lacrimal glands as well as of the glands of the digestive and upper respiratory tract. The anticholinergic activity of the compound most probably also accounted for distension of the large bowel, and for the species-specific deposition of proteinaceous material in the urinary bladder of male rats. Subsequently, secondary indirect changes developed, such as rhinitis and keratoconjunctivitis sicca, as well as decreased food consumption, body weight gain, liver lipids, serum glucose and triglycerides. Thymic involution and changes of the Harderian gland including chromodacryorrhea were regarded as non-specific responses to stress.

Even low dosages induced signs characteristic of the anticholinergic activity of tiotropium; therefore, a NOTEL could only be established in a limited number of studies. In the rat, the inhalation NOTEL was <0.013 mg/kg and the inhalation NOTEL in the dog was >0.010 mg/kg. The few changes that were perhaps unexpected include urogenital tract changes and cataracts in rats. The urogenital changes are nevertheless considered as sequelae to pharmacological effects and as such are part of a syndrome that includes the prostate. In view of the species-specificity of the syndrome and its harmless nature, it is unlikely to have any influence on human safety assessment. Similarly, although the precise mechanism remains unknown, cataract formation appears to be specific to Wistar rats and to the mode of administration. As the method of administration to the patient avoids direct eye exposure to tiotropium, any risk to patients is negligible.

Reproductive Toxicity

The effects of tiotropium administered via inhalation on the fertility and early embryonal development (Segment I), and on the peri- and postnatal development (Segment III) were assessed in rats, and those on the embryo-fetal development (Segment II) were investigated in rats and rabbits. Dose dependent paternal and maternal toxicity was observed. Embryo-fetal toxicity, considered secondary to maternal toxicity, was observed at high doses in rats and rabbits. There was no impairment of reproductive function of the F_0 generation and no effect on the postnatal development of the F_1 generation. The incidence of variations was increased at dose levels above 0.01 mg/kg but they were of the types encountered in the historical controls. No teratogenicity was noted.

The No Observed Toxic Effect Level (NOTEL) for maternal/paternal toxicity in the rat and rabbit was <0.01 mg/kg Ba 679 BR and for developmental toxicity 0.01 mg/kg in all three segments when administered by inhalation.

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 clinically relevant dosages.

Carcinogenicity and Mutagenicity

Inhalation carcinogenicity studies in mice and rats have revealed no carcinogenic potential at target tiotropium doses up to 2.54, 180 and 75 µg/kg/day (male mice, female mice and rats, respectively). These doses correspond to about 0.45, 92 and 27 times the maximum recommended human dose (MRHD) on a mg/m² basis.

Results of various mutagenicity studies (Ames test and E coli bacterial gene mutation test, gene mutation test in V79 Chinese hamster cells, *in-vitro* cytogenetic study with human lymphocytes, *in-vitro* unscheduled DNA-synthesis test, and *in-vivo* micronucleus test) were negative.

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PART III: CONSUMER INFORMATION**PrSpiriva® Respimat®**

Tiotropium Bromide Monohydrate Inhalation Solution

Read this carefully before you start taking SPIRIVA RESPIMAT and each time you get a refill. This leaflet is a summary and will not tell you everything about SPIRIVA RESPIMAT. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about SPIRIVA RESPIMAT.

ABOUT THIS MEDICATION**What the medication is used for:****COPD**

SPIRIVA RESPIMAT is used long term to help open the airways of people with breathing difficulties due to a lung disease called chronic obstructive pulmonary disease (COPD). It is also used to reduce the likelihood of “flare-ups” in people with COPD. In COPD, a “flare-up” is when your condition is getting worse. You will know you are having a “flare-up” if two of the following symptoms get worse for more than two days:

- Unusual increase in the severity of breathlessness; cough, wheezing, or fatigue;
- Unusual colour, amount or thickness of mucus;
- Tightness in the chest or symptoms of a cold.

Asthma

SPIRIVA RESPIMAT is used only as add-on therapy to an inhaled corticosteroid and a long-acting beta agonist when those medications are not adequate to control your asthma.

When used to treat asthma, you should use SPIRIVA RESPIMAT in addition to another anti-asthma inhaler as prescribed by your doctor.

What it does:

SPIRIVA RESPIMAT contains tiotropium which belongs to a group of medicines called bronchodilators. SPIRIVA RESPIMAT helps the muscles around the airways in your lungs stay relaxed making it easier for air to get in and out of the lungs. When you inhale it, it helps you breathe more easily.

In COPD patients, it also helps to prevent flare-up symptoms, such as wheezing, cough, chest tightness and shortness of breath.

When it should not be used:

Do not take SPIRIVA RESPIMAT:

- if you are allergic to ipratropium bromide or other drugs which are anticholinergic (contain atropine or its derivatives) or to any component of SPIRIVA RESPIMAT;
- without also taking an inhaled corticosteroid and a long-acting beta-agonist if you are being treated for asthma;
- if you are under 18 years of age.

SPIRIVA RESPIMAT is not a rescue medicine and should not be used on as needed basis for treating sudden breathing problems during exacerbations (flare-ups or asthma attack) of the disease. Your doctor may give you other medicine to use for sudden breathing problems.

What the medicinal ingredient is:

Tiotropium bromide monohydrate

What the non-medicinal ingredients are:

Benzalkonium chloride, disodium edetate, hydrochloric acid and purified water.

What dosage forms it comes in:

Inhalation Solution

Each puff delivers 2.5 mcg tiotropium from the mouthpiece (as tiotropium bromide monohydrate).

WARNINGS AND PRECAUTIONS

The solution is intended for inhalation only. Avoid getting the mist into your eyes. This may result in eye pain and/or discomfort, temporary blurring of vision, and/or coloured images in association with red eyes. Should any of these symptoms develop, consult a doctor immediately.

BEFORE you use SPIRIVA RESPIMAT talk to your doctor or pharmacist if:

- you are pregnant or intend to become pregnant;
- you are breast-feeding;
- you are using any medications including eye drops, other bronchodilators or medications you can buy without a prescription;
- you have any other medical problems such as difficult urination or enlarged prostate;
- you have eye problems, such as glaucoma, or eye

- pain;
- you have any allergies to food or drugs;
- you have kidney disease;
- you have unstable heart disease;
- you have any other medical problems.

SPIRIVA RESPIMAT is indicated for the treatment of COPD and asthma. Do not use this medicine to treat a sudden attack of breathlessness or wheezing. Your doctor should have given you another inhaler ("rescue medication") for this. Please follow the instructions your doctor has given you.

If you have been prescribed SPIRIVA RESPIMAT for your asthma, it should be added on to your inhaled corticosteroid and a long-acting beta-agonist medications. Continue taking your other medications as prescribed by your doctor, even if you feel better.

Your doctor will recommend when and how you should use SPIRIVA RESPIMAT. You must follow any other direction that your doctor has given you for the treatment and/or monitoring of your condition.

Contact your doctor immediately if:

- you require more than one dose (2 actuations) per day to relieve your breathing problems;
- your shortness of breath becomes worse;
- you don't get the same benefit from your medicine as you did before;
- you have breathing difficulties and chest pain;
- you experience difficulty with urination.

SPIRIVA RESPIMAT may cause dizziness, difficulty in focusing the eye, dilated pupils, and blurred vision. You should not drive or operate machinery if this occurs.

Benzalkonium chloride may cause wheezing and breathing difficulties (bronchospasm), especially if you have asthma.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

SPIRIVA RESPIMAT should not be used together with other medicines containing a short- or long-acting muscarinic blocker as an overdose may result. For

example, these other medicines include ipratropium, tiotropium, glycopyrronium, aclidinium, umeclidinium.

PROPER USE OF THIS MEDICATION

SPIRIVA RESPIMAT has been prescribed to treat your current condition. DO NOT give it to other people. Always use SPIRIVA RESPIMAT exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Appropriate use of SPIRIVA RESPIMAT includes an understanding of the way it should be administered. Therefore, it is important that you read and understand how to use the inhaler before starting SPIRIVA RESPIMAT therapy.

It is very important that you use SPIRIVA RESPIMAT regularly every day. Do not stop taking SPIRIVA RESPIMAT suddenly even if you feel better.

FOR ORAL INHALATION ONLY

Take care to avoid spraying SPIRIVA RESPIMAT into your eyes.

Usual Adult Dose:

COPD

Take 2 puffs once a day, if possible at the same time of the day, every day.

Asthma

Take 2 puffs once a day, if possible at the same time of the day, every day.

In the treatment of asthma, the full benefits will be seen after several doses of SPIRIVA RESPIMAT.

Overdose:

If you think you have taken too much SPIRIVA RESPIMAT, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed dose:

If you forget to inhale a dose, inhale the next dose as soon as possible but do not inhale two doses on the same day. Then inhale the next dose as usual.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- Cough, dry mouth or throat, bad taste;
- Dizziness;
- Hoarse voice;
- Rash, itching;
- Difficulty in sleeping;
- Heartburn;
- Constipation;
- Sore throat;
- Sinus infection;
- Inflammation of the mouth, gums and/or tongue;
- Nosebleed;
- Infections or ulcerations of the skin;
- Dry skin.

Check with your doctor if the dry mouth or bad taste persists or if you experience constipation for a prolonged period of time.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor, nurse or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Uncommon (<1/100 patients)	Urinary Retention: difficulty and pain when passing urine, urinating frequently, urination in a weak stream or drips		✓	
	Oropharyngeal Candidiasis: fungal infection of the oral cavity and throat		✓	
	Skin rash/hives	✓		

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor, nurse or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
	Paradoxical Bronchospasm: tightness of the chest associated with coughing, wheezing, or breathlessness immediately after inhalation			✓
Rare (<1/1000 patients)	Serious Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
	Urinary tract infection		✓	
	Difficulty in swallowing			✓
	Fast or irregular heart beat			✓
	Eye disorders: new or worsened pressure in your eyes, eye pain or discomfort, blurred vision, seeing halos or rainbows around items or red eyes			✓
Not Known	Swelling of joints	✓		
	Dehydration	✓		
	Intestinal Obstruction: absence of bowel movements			✓

This is not a complete list of side effects. For any unexpected effects while taking SPIRIVA RESPIMAT, contact your doctor, nurse or pharmacist.

HOW TO STORE IT

Store SPIRIVA RESPIMAT between 15-30°C.

Do not freeze your SPIRIVA RESPIMAT cartridge and inhaler.

Keep your SPIRIVA RESPIMAT cartridge and inhaler out of the sight and reach of children.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about SPIRIVA RESPIMAT:

Talk to your healthcare professional.

Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>), the manufacturer's website (<https://www.boehringer-ingelheim.ca>), or by calling the manufacturer, Boehringer Ingelheim (Canada) Ltd., at: 1-800-263-5103, extension 84633.

This leaflet was prepared by Boehringer Ingelheim (Canada) Ltd. The information in this leaflet is current up to the time of the last revision date shown below, but more current information may be available from the manufacturer.

Last revised: May 7, 2019

INSTRUCTIONS FOR USE



Introduction

Read these **Instructions for Use** before you start using SPIRIVA RESPIMAT.

You will need to use the inhaler only ONCE A DAY. Each time you use it take 2 PUFFS.

Each box contains:

- 1 RESPIMAT inhaler
- 1 cartridge

Each cartridge provides 60 puffs (30 doses). Physician samples and hospital packs provide 28 puffs (14 doses).

The colour of the cap of the RESPIMAT inhaler is colour coded to match the cartridge.



How to store my SPIRIVA RESPIMAT inhaler

Store SPIRIVA RESPIMAT (the cartridge and inhaler) between 15-30°C. Do not freeze.

Keep out of the sight and reach of children.

Do not use your inhaler after the expiry date.

Do not touch the piercing element inside the clear base.

If you have not used your inhaler in more than:

- 7 days: release 1 puff towards the ground
- 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.

How to care for your SPIRIVA RESPIMAT

Clean the mouthpiece including the metal part inside the mouthpiece with a damp cloth or tissue only. You should do this at least once a week. Any minor changes in the colour of the mouthpiece will not affect how your SPIRIVA RESPIMAT works.

When to get a new SPIRIVA RESPIMAT



- Your SPIRIVA RESPIMAT inhaler contains either 60 puffs (30 doses) or 28 puffs (14 doses) if you use it as directed (2 puffs/once a day). The 28 puff (14 dose) product is for physician samples and the hospital pack.
- The dose indicator shows you about how much medication is left.
- When the dose indicator **enters** the red area of the scale, there is about:
 - 7 days of medication left for the 60 puff product
 - 3 days of medication left for the 28 puff product.
 You need to get a new prescription or refill your prescription.
- Once the dose indicator reaches the **end** of the red scale:
 - Your SPIRIVA RESPIMAT locks automatically. No more doses can be released. At this point, the clear base cannot be turned any further.
- You should throw out the SPIRIVA RESPIMAT when one of the following happens first:
 - 3 months after first use, even if all the medication has not been used, or
 - it locks automatically.

Prepare for First Use

1

Remove clear base

- Keep the cap closed.
- Press the safety catch while firmly pulling off the clear base with your other hand.



2

Insert cartridge

- Insert the **narrow** end of the cartridge into the inhaler.
- Place the inhaler on a firm surface and push down firmly until it snaps into place.
- You should hear a “click” when it has gone in all the way.



3

Replace clear base

- Put the clear base back into place until it “clicks”.
- Do not remove the clear base again.



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 to 6 **until** a cloud is visible.
- **After a cloud is visible**, repeat steps 4 to 6 three more times.



Your inhaler is now ready to use.

Daily Use

TURN

- Keep the cap closed.
- **T**URN the clear base in the direction of the arrows on the label until it “clicks” (half a turn).



OPEN

- **O**PEN 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, **P**RESS the dose-release button and continue to breathe in.
- Hold your breath for 10 seconds or for as long as you feel comfortable.

To take your second puff, repeat the 3 steps, TURN, OPEN and PRESS (TOP) one more time.

Close the cap.



Answers to Common Questions

It is difficult to insert the cartridge deep enough:

The dose indicator on the SPIRIVA RESPIMAT reaches zero too soon:

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 use SPIRIVA RESPIMAT as indicated (2 puffs/once daily)? SPIRIVA RESPIMAT will last 30 days if used at 2 puffs once daily. Physician samples and hospital packs will last 14 days if used at 2 puffs once daily.

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

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 SPIRIVA RESPIMAT is working? Once you have prepared SPIRIVA RESPIMAT, no test-spraying is required if used daily.

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

I cannot press the dose-release button:

My SPIRIVA RESPIMAT doesn't spray:

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

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

Is the dose indicator on the SPIRIVA RESPIMAT pointing to zero? The SPIRIVA RESPIMAT inhaler is locked after 60 puffs (30 doses). Physician samples and hospital packs will be locked after 28 puffs (14 doses). Prepare and use your new SPIRIVA RESPIMAT inhaler.

Did you repeat Turn, Open, Press (TOP) less than three times after inserting the cartridge? Repeat Turn, Open, Press (TOP) three times after inserting the cartridge as shown in steps 4 to 6 under "Prepare for first Use".

Is the dose indicator on the SPIRIVA 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 SPIRIVA RESPIMAT is assembled, do not remove the clear base or the cartridge. Always insert a new cartridge into a **NEW** SPIRIVA RESPIMAT.

I cannot turn the clear base:

My SPIRIVA RESPIMAT sprays automatically:

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

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

Is the dose indicator on the SPIRIVA RESPIMAT pointing to zero? The SPIRIVA RESPIMAT inhaler is locked after 60 puffs (30 doses). Physician samples and hospital packs will be locked after 28 puffs (14 doses). Prepare and use your new SPIRIVA RESPIMAT inhaler.

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).