

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
021936Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SPIRIVA RESPIMAT safely and effectively. See full prescribing information for SPIRIVA RESPIMAT.

SPIRIVA® RESPIMAT® (tiotropium bromide) Inhalation Spray FOR ORAL INHALATION

Initial U.S. Approval: 2004

INDICATIONS AND USAGE

SPIRIVA RESPIMAT is an anticholinergic indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), and for reducing COPD exacerbations (1)

DOSAGE AND ADMINISTRATION

For oral inhalation only

- Two inhalations (2 inhalations of 2.5 mcg each) of the spray once-daily (2)

DOSAGE FORMS AND STRENGTHS

Inhalation spray: 2.5 mcg tiotropium (equivalent to 3.124 mcg tiotropium bromide monohydrate) per actuation with the SPIRIVA RESPIMAT inhaler. Two actuations equal one dose (3)

CONTRAINDICATIONS

Hypersensitivity to tiotropium, ipratropium, or any component of this product (4)

WARNINGS AND PRECAUTIONS

- Not for acute use, i.e., not a rescue medication (5.1)
- Immediate hypersensitivity reactions: Discontinue SPIRIVA RESPIMAT at once and consider alternatives if immediate hypersensitivity reactions, including angioedema, bronchospasm, or anaphylaxis, occur. (5.2)
- Paradoxical bronchospasm: Discontinue SPIRIVA RESPIMAT and consider other treatments if paradoxical bronchospasm occurs. (5.3)
- Worsening of narrow-angle glaucoma may occur. Use with caution in patients with narrow-angle glaucoma and instruct patients to consult a physician immediately if this occurs. (5.4)
- Worsening of urinary retention may occur. Use with caution in patients with prostatic hyperplasia or bladder-neck obstruction and instruct patient to consult a physician immediately if this occurs. (5.5)

ADVERSE REACTIONS

The most common adverse reactions (>3% incidence in the placebo-controlled trials with treatment durations of between 4 and 48 weeks) were pharyngitis, cough, dry mouth, and sinusitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or (800) 459-9906 TTY or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Anticholinergics: May interact additively with concomitantly used anticholinergic medications. Avoid administration of SPIRIVA RESPIMAT with other anticholinergic-containing drugs. (7.2)

USE IN SPECIFIC POPULATIONS

Patients with moderate to severe renal impairment should be monitored closely for potential anticholinergic side effects. (2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 09/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

- INDICATIONS AND USAGE
- DOSAGE AND ADMINISTRATION
- DOSAGE FORMS AND STRENGTHS
- CONTRAINDICATIONS
- WARNINGS AND PRECAUTIONS
 - Not For Acute Use
 - Immediate Hypersensitivity Reactions
 - Paradoxical Bronchospasm
 - Worsening of Narrow-Angle Glaucoma
 - Worsening of Urinary Retention
 - Renal Impairment
- ADVERSE REACTIONS
 - Clinical Trials Experience
 - Postmarketing Experience
- DRUG INTERACTIONS
 - Sympathomimetics, Methylxanthines, Steroids
 - Anticholinergics
- USE IN SPECIFIC POPULATIONS
 - Pregnancy
 - Labor and Delivery
 - Nursing Mothers
 - Pediatric Use

- Geriatric Use
- Renal Impairment
- Hepatic Impairment
- OVERDOSAGE
- DESCRIPTION
- CLINICAL PHARMACOLOGY
 - Mechanism of Action
 - Pharmacodynamics
 - Pharmacokinetics
- NONCLINICAL TOXICOLOGY
 - Carcinogenesis, Mutagenesis, Impairment of Fertility
- CLINICAL STUDIES
- HOW SUPPLIED/STORAGE AND HANDLING
- PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SPIRIVA RESPIMAT (tiotropium bromide) is indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. SPIRIVA RESPIMAT is indicated to reduce exacerbations in COPD patients.

2 DOSAGE AND ADMINISTRATION

The recommended dose of SPIRIVA RESPIMAT is two inhalations once-daily. Do not take more than one dose (2 inhalations) in 24 hours.

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 not used for more than 3 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 Patient Counseling Information (17)*].

No dosage adjustment is required for geriatric, hepatically-impaired, or renally-impaired patients. However, patients with moderate to severe renal impairment given SPIRIVA RESPIMAT should be monitored closely for anticholinergic effects [*see Warnings and Precautions (5.6), Use in Specific Populations (8.5, 8.6, 8.7), and Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

SPIRIVA RESPIMAT consists of a SPIRIVA RESPIMAT inhaler and an aluminum cylinder (SPIRIVA RESPIMAT cartridge) containing tiotropium bromide (as the monohydrate). The SPIRIVA RESPIMAT cartridge is only intended for use with the SPIRIVA RESPIMAT inhaler.

Each actuation from the SPIRIVA RESPIMAT inhaler delivers 2.5 mcg of tiotropium (equivalent to 3.124 mcg of tiotropium bromide monohydrate) from the mouthpiece. Two actuations equal one dose (5 mcg).

4 CONTRAINDICATIONS

SPIRIVA RESPIMAT is contraindicated in patients with a hypersensitivity to tiotropium, ipratropium, or any component of this product [*see Warnings and Precautions (5.2)*]. In clinical trials with SPIRIVA RESPIMAT, immediate hypersensitivity reactions, including angioedema (including swelling of the lips, tongue, or throat), itching, or rash have been reported [*see Warnings and Precautions (5.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Not for Acute Use

SPIRIVA RESPIMAT is intended as a once-daily maintenance treatment for COPD and should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm.

5.2 Immediate Hypersensitivity Reactions

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.

5.3 Paradoxical Bronchospasm

Inhaled medicines, including SPIRIVA RESPIMAT, may cause paradoxical bronchospasm. If this occurs, it should be treated immediately with an inhaled short-acting beta₂-agonist such as albuterol. Treatment with SPIRIVA RESPIMAT should be stopped and other treatments considered.

5.4 Worsening of Narrow-Angle Glaucoma

SPIRIVA RESPIMAT should be used with caution in patients with 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). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

5.5 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 urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

5.6 Renal Impairment

As a predominantly renally excreted drug, patients with moderate to severe renal impairment (creatinine clearance of <60 mL/min) treated with SPIRIVA RESPIMAT should be monitored closely for anticholinergic side effects [*see Clinical Pharmacology (12.3)*].

6 ADVERSE REACTIONS

The following adverse reactions are described, or described in greater detail, in other sections:

- Immediate hypersensitivity reactions [*see Warnings and Precautions (5.2)*]
- Paradoxical bronchospasm [*see Warnings and Precautions (5.3)*]
- Worsening of narrow-angle glaucoma [*see Warnings and Precautions (5.4)*]
- Worsening of urinary retention [*see Warnings and Precautions (5.5)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the incidence of adverse reactions observed in the clinical trials of a drug cannot be directly compared to the incidences in the clinical trials of another drug and may not reflect the incidences observed in practice.

The SPIRIVA RESPIMAT clinical development program included ten placebo controlled clinical trials in COPD. Two trials were four-week cross-over trials and eight were parallel group trials. The parallel groups trials included a three week dose-ranging trial, two 12-week trials, three 48-week trials, and two trials of 4-week and 24-

week duration conducted for a different program that contained tiotropium bromide 5 mcg treatment arms. The primary safety database consists of pooled data from the 7 randomized, parallel-group, double-blind, placebo-controlled studies of 4-48 weeks in treatment duration: These trials included 6565 adult COPD patients (75% males and 25% females) 40 years of age and older. Of these patients, 3282 patients were treated with SPIRIVA RESPIMAT and 3283 received placebo. The SPIRIVA RESPIMAT group was composed mostly of Caucasians (78%) with a mean age of 65 years and a mean baseline percent predicted post-bronchodilator FEV₁ of 46%.

In these 7 clinical trials, 68.3% of patients exposed to SPIRIVA RESPIMAT reported an adverse event compared to 68.7% of patients in the placebo group. There were 68 deaths in the SPIRIVA RESPIMAT treatment group (2.1%) and 52 deaths (1.6%) in patients who received placebo [see *Clinical Studies (14) Long-term active controlled mortality trial Survival*]. The percentage of SPIRIVA RESPIMAT patients who discontinued due to an adverse event were 7.3% compared to 10% with placebo patients. The percentage of SPIRIVA RESPIMAT patients who experienced a serious adverse event were 15.0% compared to 15.1% with placebo patients. In both groups, the adverse event most commonly leading to discontinuation was COPD exacerbation (SPIRIVA RESPIMAT 2.0%, placebo 4.0%) which was also the most frequent serious adverse event. The most commonly reported adverse reactions were pharyngitis, cough, dry mouth, and sinusitis (Table 1). Other adverse reactions reported in individual patients and consistent with possible anticholinergic effects included constipation, dysuria, and urinary retention.

Table 1 shows all adverse reactions that occurred with an incidence of >3% in the SPIRIVA RESPIMAT treatment group, and a higher incidence rate on SPIRIVA RESPIMAT than on placebo.

Table 1 Number (percentage) of COPD patients exposed to SPIRIVA RESPIMAT with adverse reactions >3% (and higher than placebo): Pooled data from 7 clinical trials with treatment periods ranging between 4 and 48 weeks in COPD patients

| Body System (Reaction)* | SPIRIVA RESPIMAT [n=3282] | Placebo [n=3283] |
|---|------------------------------|---------------------|
| Gastrointestinal Disorders | | |
| Dry mouth | 134 (4.1) | 52 (1.6) |
| Infections and Infestations | | |
| Pharyngitis | 378 (11.5) | 333 (10.1) |
| Respiratory, Thoracic, and Mediastinal | | |
| Cough | 190 (5.8) | 182 (5.5) |
| Sinusitis | 103 (3.1) | 88 (2.7) |

*Adverse reactions include a grouping of similar terms

Other reactions that occurred in the SPIRIVA RESPIMAT group at an incidence of 1% to 3%, and at a higher incidence rate on SPIRIVA RESPIMAT than on placebo included: *Cardiac disorders* palpitations; *Gastrointestinal disorders* constipation; gastroesophageal reflux disease; oropharyngeal candidiasis; *Nervous system disorders* dizziness; *Respiratory system disorders (Upper)* dysphonia; *Skin and subcutaneous tissue disorders* pruritus, rash; *Renal and urinary disorders* urinary tract infection.

Less Common Adverse Reactions

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: dysphagia, gingivitis, intestinal obstruction including ileus paralytic, joint swelling, dysuria, urinary retention, epistaxis, laryngitis, angioedema, dry skin, skin infection, and skin ulcer.

6.2 Postmarketing Experience

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 another tiotropium formulation, SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder): glaucoma, intraocular pressure increased, vision blurred, atrial fibrillation, tachycardia, supraventricular tachycardia, bronchospasm, glossitis, stomatitis, dehydration, insomnia, hypersensitivity (including immediate reactions), and urticaria.

7 DRUG INTERACTIONS

7.1 Sympathomimetics, Methylxanthines, Steroids

SPIRIVA RESPIMAT has been used concomitantly with short-acting and long-acting sympathomimetic (beta-agonists) bronchodilators, methylxanthines, and oral and inhaled steroids, without increases in adverse reactions.

7.2 Anticholinergics

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 [see *Warnings and Precautions (5.4, 5.5) and Adverse Reactions (6)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. SPIRIVA RESPIMAT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

No evidence of structural alterations was observed in rats and rabbits at approximately 660 and 6 times the recommended human daily inhalation dose (RHDID), respectively (on a mg/m² basis at maternal inhalation doses of 1.471 and 0.007 mg/kg/day in rats and rabbits, respectively). However, in rats, tiotropium caused fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pup sexual maturation at inhalation tiotropium doses of approximately 45 times the RHDID (on a mg/m² basis at a maternal inhalation dose of 0.078 mg/kg/day). In rabbits, tiotropium caused an increase in post-implantation loss at an inhalation dose of approximately 360 times the RHDID (on a mg/m² basis at a maternal inhalation dose of 0.4 mg/kg/day). Such effects were not observed at approximately 4 and 80 times the RHDID, respectively (on a mg/m² basis at inhalation doses of 0.009 and 0.088 mg/kg/day in rats and rabbits, respectively).

8.2 Labor and Delivery

The safety and effectiveness of SPIRIVA RESPIMAT has not been studied during labor and delivery.

8.3 Nursing Mothers

Clinical data from nursing women exposed to tiotropium are not available. Based on lactating rodent studies, tiotropium is excreted into breast milk. It is not known whether tiotropium is excreted in human milk, but because many drugs are excreted in human milk and given these findings in rats, caution should be exercised if SPIRIVA RESPIMAT is administered to a nursing woman.

8.4 Pediatric Use

SPIRIVA RESPIMAT is not indicated for use in children. The safety and effectiveness of SPIRIVA RESPIMAT in pediatric patients have not been established.

8.5 Geriatric Use

Based on available data, no adjustment of SPIRIVA RESPIMAT dosage in geriatric patients is warranted [see *Clinical Pharmacology* (12.3)].

Thirty nine percent of SPIRIVA RESPIMAT clinical trial patients were between 65 and 75 years of age and 14% were greater than or equal to 75 years of age. The adverse drug reaction profiles were similar in the older population compared to the patient population overall.

8.6 Renal Impairment

Patients with moderate to severe renal impairment (creatinine clearance of <60 mL/min) treated with SPIRIVA RESPIMAT should be monitored closely for anticholinergic side effects [see *Dosage and Administration* (2), *Warnings and Precautions* (5.6), and *Clinical Pharmacology* (12.3)].

8.7 Hepatic Impairment

The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied.

10 OVERDOSAGE

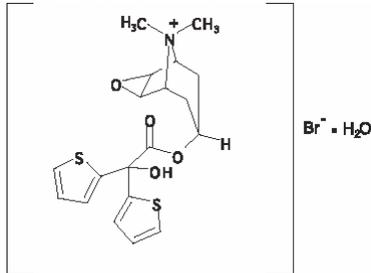
High doses of tiotropium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 282 mcg tiotropium dry powder in 6 healthy volunteers. Dry mouth/throat and dry nasal mucosa occurred in a dose-dependent [10-40 mcg daily] manner, following 14-day dosing of up to 40 mcg tiotropium bromide inhalation solution in healthy subjects.

Treatment of overdosage consists of discontinuation of SPIRIVA RESPIMAT together with institution of appropriate symptomatic and/or supportive therapy.

11 DESCRIPTION

The active component of SPIRIVA RESPIMAT is tiotropium. The drug substance, tiotropium bromide monohydrate, is an anticholinergic with specificity for muscarinic receptors. It is chemically described as (1 α , 2 β , 4 β , 5 α , 7 β)-7-[(Hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.0^{2,4}] nonane bromide monohydrate. It is a synthetic, non-chiral, quaternary ammonium compound. Tiotropium bromide is a white or yellowish white powder. It is sparingly soluble in water and soluble in methanol.

The structural formula is:



Tiotropium bromide (monohydrate) has a molecular mass of 490.4 and a molecular formula of $\text{C}_{19}\text{H}_{22}\text{NO}_4\text{S}_2\text{Br} \cdot \text{H}_2\text{O}$.

The drug product, SPIRIVA RESPIMAT, is composed of a sterile, aqueous solution of tiotropium bromide filled into a 4.5 mL plastic container crimped into an aluminum cylinder (SPIRIVA RESPIMAT cartridge) for use with the SPIRIVA RESPIMAT inhaler. Excipients include water for injection, edetate disodium, benzalkonium chloride and hydrochloric acid. The SPIRIVA RESPIMAT cartridge is only intended for use with the SPIRIVA RESPIMAT inhaler. The RESPIMAT inhaler is a hand held, pocket sized oral inhalation device that uses mechanical energy to generate a slow moving aerosol cloud of medication from a metered volume of the drug solution. The SPIRIVA RESPIMAT inhaler has an aqua-colored cap.

When used with the SPIRIVA RESPIMAT inhaler, each cartridge containing 4 grams of sterile aqueous solution delivers 60 (or 28) metered actuations after preparation for use, the equivalent of 30 days' (or 14 days') medication when used as two actuations once a day. Each dose (one dose equals two actuations) from the SPIRIVA RESPIMAT inhaler delivers 5 mcg of tiotropium in 22.1 mL 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. The duration of inspiration should be at least as long as the spray duration (1.5 seconds).

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 not used for more than 3 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 *Patient Counseling Information* (17)].

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tiotropium is a long-acting, antimuscarinic agent, which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors, M₁ to M₅. In the airways, it exhibits pharmacological effects through inhibition of M₃-receptors at the smooth muscle leading to bronchodilation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In preclinical *in vitro* as well as *in vivo* studies, prevention of methacholine-induced bronchoconstriction effects was dose-dependent and lasted longer than 24 hours. The bronchodilation following inhalation of tiotropium is predominantly a site-specific effect.

12.2 Pharmacodynamics

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 SPIRIVA 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 SPIRIVA 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 \geq 60 msec.

12.3 Pharmacokinetics

Tiotropium is administered as an inhalation spray. Some of the pharmacokinetic data described below were obtained with higher doses than recommended for therapy. A dedicated pharmacokinetic study in patients with COPD evaluating once-daily tiotropium delivered from the RESPIMAT inhaler (5 μ g) and as inhalation powder (18 μ g) from the HandiHaler resulted in a similar systemic exposure between the two products.

Absorption

Following inhalation of the solution by young healthy volunteers, urinary excretion data suggests that approximately 33% of the inhaled dose reaches the systemic circulation. Oral solutions of tiotropium have an absolute bioavailability of 2% to 3%. Food is not expected to influence the absorption of tiotropium for the same reason. Following 4-week SPIRIVA RESPIMAT once daily dosing, maximum tiotropium plasma concentrations were observed 5-7 minutes after inhalation.

Distribution

The drug has a plasma protein binding of 72% and shows a volume of distribution of 32 L/kg after an intravenous dose to young healthy volunteers. 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.

Elimination

The terminal half-life of tiotropium was between 5 and 6 days following dry powder inhalation. Total clearance was 880 mL/min after an intravenous dose in young healthy volunteers. After chronic once-daily dry powder inhalation by COPD patients, pharmacokinetic steady-state was reached by day 7 with no accumulation thereafter.

Metabolism

The extent of metabolism 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, neither of which binds to muscarinic receptors.

In vitro experiments with human liver microsomes and human hepatocytes suggest that a fraction of the administered dose (74% of an intravenous dose is excreted unchanged in the urine, leaving 25% for metabolism) 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 CYP450 2D6 and 3A4 inhibitors, such as quinidine, ketoconazole, and gestodene. Thus, CYP450 2D6 and 3A4 are involved in the metabolic pathway that is responsible for the elimination of a small part of the administered dose. *In vitro* studies using human liver microsomes showed that tiotropium in supra-therapeutic concentrations does not inhibit CYP450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4.

Excretion

Intravenously administered tiotropium bromide is mainly excreted unchanged in urine (74%). Following 21-day, once daily inhalation of the solution by patients with COPD, 24-hour urinary excretion is 18.6% (0.93 mcg) of the dose. The renal clearance of tiotropium exceeds the creatinine clearance, indicating secretion into the urine.

Specific Populations

Geriatric Patients

As expected for all predominantly renally excreted drugs, advancing age was associated with a decrease of tiotropium renal clearance (347 mL/min in COPD patients <65 years to 275 mL/min in COPD patients \geq 65 years). This did not result in a corresponding increase in AUC_{0-6,ss} and C_{max,ss} values following inhalation of the solution.

Renal Impairment

Following 4-week SPIRIVA RESPIMAT once daily dosing in patients with COPD, mild renal impairment (creatinine clearance 60-90 mL/min) resulted in 23% higher AUC_{0-6,ss} and 17% higher C_{max,ss} values; moderate renal impairment (creatinine clearance 30-60 mL/min) resulted in 57% higher AUC_{0-6,ss} and 31% higher C_{max,ss} values compared to COPD patients with normal renal function (creatinine clearance >90 mL/min). There lacks sufficient data of tiotropium exposure in patients with severe renal impairment (creatinine clearance <30 mL/min) following inhalation of the solution. However AUC₀₋₄ and C_{max} were 94% and 52% higher, respectively, in patients with severe renal impairment following intravenous infusion of tiotropium bromide.

Hepatic Impairment

The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied.

Drug Interactions

An interaction study with tiotropium (14.4 mcg intravenous infusion over 15 minutes) and cimetidine 400 mg three times daily or ranitidine 300 mg once-daily was conducted. Concomitant administration of cimetidine with tiotropium resulted in a 20% increase in the AUC_{0-4h}, a 28% decrease in the renal clearance of tiotropium

and no significant change in the C_{max} and amount excreted in urine over 96 hours. Co-administration of tiotropium with ranitidine did not affect the pharmacokinetics of tiotropium.

Common concomitant medications (long-acting beta₂-adrenergic agonists (LABA), inhaled corticosteroids (ICS)) used by patients with COPD were not found to alter the exposure to tiotropium.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of tumorigenicity was observed in a 104-week inhalation study in rats at tiotropium doses up to 0.059 mg/kg/day, in an 83-week inhalation study in female mice at doses up to 0.145 mg/kg/day, and in a 101-week inhalation study in male mice at doses up to 0.002 mg/kg/day. These doses correspond to approximately 25, 35, and 0.5, times the recommended human daily inhalation dose (RHDID) on a mg/m² basis, respectively.

Tiotropium bromide demonstrated no evidence of mutagenicity or clastogenicity in the following assays: the bacterial gene mutation assay, the V79 Chinese hamster cell mutagenesis assay, the chromosomal aberration assays in human lymphocytes *in vitro* and mouse micronucleus formation *in vivo*, and the unscheduled DNA synthesis in primary rat hepatocytes *in vitro* assay.

In rats, decreases in the number of corpora lutea and the percentage of implants were noted at inhalation tiotropium doses of 0.078 mg/kg/day or greater (approximately 35 times the RHDID on a mg/m² basis). No such effects were observed at 0.009 mg/kg/day (approximately 4 times the RHDID on a mg/m² basis). The fertility index, however, was not affected at inhalation doses up to 1.689 mg/kg/day (approximately 760 times the RHDID on a mg/m² basis).

14 CLINICAL STUDIES

The efficacy of SPIRIVA RESPIMAT compared to placebo was evaluated in 6 clinical trials: one dose-ranging trial and 5 confirmatory trials (Trials 1-5). In addition, SPIRIVA RESPIMAT was compared to SPIRIVA HandiHaler in a long-term active-controlled trial in COPD (Trial 6).

Dose-Ranging Trial

Dose selection for the Phase III clinical program was supported by a 3-week randomized, double-blind, placebo and active-controlled, parallel group trial in 202 COPD patients. A total of five doses of tiotropium RESPIMAT (1.25 to 20 mcg) were evaluated compared to placebo. Results demonstrated numerical improvements in FEV₁ at all doses compared to placebo. The difference in trough FEV₁ from placebo for the 1.25, 2.5, 5, 10 and 20 mcg once daily doses were 0.08 L (95% CI -0.03, 0.20), 0.03 L (-0.08, 0.15), 0.13 L (0.02, 0.25), 0.11 L (-0.004, 0.224), and 0.13 L (0.01, 0.24), respectively. Based on these results, the 5 and 10 mcg doses were further evaluated in the confirmatory COPD trials.

Confirmatory Trials

A total of 6614 COPD patients (2801 receiving SPIRIVA RESPIMAT and 2798 receiving placebo) were studied in the five confirmatory trials of SPIRIVA RESPIMAT. Trials 1 and 2 were 12-week, randomized, double-blind, placebo- and active- (ipratropium) controlled trials that evaluated bronchodilation. Trials 3-5 were 48-week, randomized, double-blind, placebo-controlled, trials that evaluated bronchodilation and effects on COPD exacerbations. Trials 1-4 included both the tiotropium RESPIMAT 5mcg and 10mcg doses, whereas Trial 5 included only the 5mcg dose. These trials enrolled patients who had a clinical diagnosis of COPD, were 40 years of age or older, had a history of smoking greater than 10 pack-years, had an FEV₁ less than or equal to 60% of predicted and a ratio of FEV₁/FVC of less than or equal to 0.7. All treatments were administered once-daily in the morning. Change from baseline in trough FEV₁ was a primary endpoint in all trials. Trials 3-5 included COPD exacerbations as primary endpoints.

Baseline patient characteristics were similar across the five individual confirmatory trials, except for race in Trial 5 in which there were more Asian patients (30%) compared to other trials (<1%). The mean age ranged from 62 to 66 years. Most patients were male (64-78%), ex-smokers (57-65%) and Caucasian (69-99%). Mean pre-bronchodilator FEV₁ was between 1.03 and 1.26 L with a mean FEV₁/FVC ratio of 42-50%. Except for LABAs and other inhaled anticholinergic agents, other pulmonary medications were allowed as concomitant therapy in Trials 1-4. LABA use was permitted in Trial 5.

Effect on Lung Function

SPIRIVA RESPIMAT demonstrated significant improvement in trough FEV₁ compared to placebo in all 5 confirmatory trials (Table 2). The change from baseline in trough FEV₁ over time from Trial 4 is depicted in Figure 1 and is representative of the other two 48-week trials. In Trials 3 and 4 patients treated with SPIRIVA RESPIMAT also used less rescue medication compared to patients on placebo.

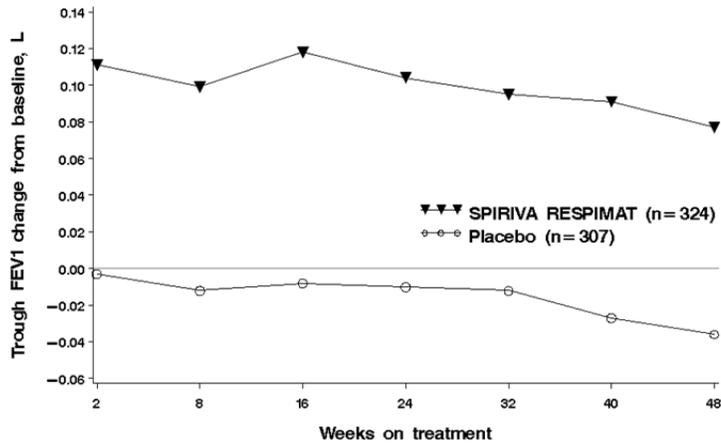
Table 2 Mean Change from Baseline in Trough FEV₁ (L) at End of Treatment

| Trial | SPIRIVA RESPIMAT N | Placebo N | Trough FEV ₁ (L) at End of Treatment Difference from placebo (95% CI) |
|----------|--------------------|-----------|--|
| Trial 1† | 85 | 87 | 0.11 (0.04, 0.18) |
| Trial 2† | 90 | 84 | 0.13 (0.07, 0.18) |
| Trial 3‡ | 326 | 296 | 0.14 (0.10, 0.18) |
| Trial 4‡ | 324 | 307 | 0.11 (0.08, 0.15) |
| Trial 5‡ | 1889 | 1870 | 0.10 (0.09, 0.12) |

† at week 12,

‡ at week 48

Figure 1 Trough FEV₁ change from baseline over 48 weeks (Trial 4)



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

Exacerbations

Trials 3, 4, and 5 also evaluated the effect of SPIRIVA RESPIMAT on COPD exacerbations. For Trials 3 and 4, a pooled analysis of exacerbation rate per patient year was pre-specified as a primary endpoint, while the primary endpoint for Trial 5 was time to first exacerbation. Trial 5 also included exacerbation rate per patient year as a secondary endpoint. Exacerbations were defined as a complex of respiratory events/symptoms with a duration of ≥ 3 days with ≥ 2 of the following (increase of symptoms or new onset): shortness of breath/dyspnea/ shallow, rapid breathing; sputum production (volume); occurrence of purulent sputum; cough; wheezing; chest tightness.

In the pooled analysis of Trials 3 and 4, SPIRIVA RESPIMAT 5mcg significantly reduced the number of COPD exacerbations compared to placebo with 0.78 exacerbations/patient year versus 1.0 exacerbations/patient year, respectively, with a rate ratio of 0.78 (95% CI 0.67, 0.92). Time to first exacerbation was also delayed in SPIRIVA RESPIMAT patients. For Trial 5, in addition to the definition above, an exacerbation also had to result in a change in or requirement of treatment. In Trial 5, treatment with SPIRIVA RESPIMAT delayed the time to first COPD exacerbation compared to treatment with placebo [hazard ratio of 0.69 (95% CI 0.63, 0.77)]. Consistent with the pooled analysis of Trials 3 and 4, for Trial 5, exacerbation rate was also lower in SPIRIVA RESPIMAT compared to placebo. In Trial 5, SPIRIVA RESPIMAT also reduced the risk of COPD exacerbation-related hospitalization (HR = 0.73; 95% CI = 0.59, 0.90) compared to placebo.

Long-term Active-Controlled Mortality Trial

Survival

In a pooled analysis of SPIRIVA RESPIMAT placebo-controlled clinical trials with complete vital status (mortality) follow-up, including the three 48-week trials (Trial 3, 4, and 5) 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. In a 4-year, randomized, double-blind, placebo-controlled, multicenter clinical trial of tiotropium bromide inhalation powder (SPIRIVA HandiHaler) in 5992 COPD patients a similar incidence rate of death had been observed between SPIRIVA HandiHaler and placebo treated groups.

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 was conducted to evaluate the risk of all-cause mortality associated with the use of SPIRIVA RESPIMAT compared to SPIRIVA HandiHaler (Trial 6). 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. Trial 6 also included a lung function sub-study which measured trough FEV₁ measured every 24 weeks for 120 weeks (461 patients receiving SPIRIVA RESPIMAT, 445 patients receiving SPIRIVA HandiHaler).

In Trial 6, 5711 patients received SPIRIVA RESPIMAT and 5694 patients received SPIRIVA HandiHaler. 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 between SPIRIVA RESPIMAT and SPIRIVA HandiHaler with an estimated hazard ratio of 0.96 [(95% CI of (0.84 to 1.09), Table 3].

Table 3 All-cause Mortality of SPIRIVA RESPIMAT vs SPIRIVA HandiHaler (Trial 6)

| | SPIRIVA RESPIMAT (N = 5711) | SPIRIVA HandiHaler (N = 5694) |
|---|--------------------------------|----------------------------------|
| Number (%) of Deaths | 423 (7.4) | 439 (7.7) |
| Incidence Rate per 100 patient years | 3.22 | 3.36 |
| HR (95% CI)^a | 0.96 (0.84, 1.09) | |

^a Hazard ratios were estimated from a Cox proportional hazard model.

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.

Effect on Lung Function and Exacerbations

In the lung function sub-study the effect of SPIRIVA RESPIMAT on trough FEV₁ over 120 weeks was similar to SPIRIVA HandiHaler with a mean difference of -0.010 L (95% CI -0.038 to 0.018 L).

Trial 6 also included time to first exacerbation as a co-primary endpoint (exacerbations defined as in Trials 3-5). SPIRIVA RESPIMAT failed to demonstrate superiority to SPIRIVA HandiHaler with a similar time to first COPD exacerbation between treatment groups [hazard ratio of 0.98 (95% CI 0.93 to 1.03)].

16 HOW SUPPLIED/STORAGE AND HANDLING

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

The SPIRIVA RESPIMAT cartridge is provided as 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 and should not be interchanged with any other RESPIMAT device delivered product.

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. The aqua colored cap and the written information on the label of the gray inhaler body indicate that it is labeled for use with the SPIRIVA RESPIMAT cartridge.

SPIRIVA RESPIMAT Inhalation Spray is available as:

SPIRIVA RESPIMAT Inhalation Spray: 60 metered actuations (NDC 0597-0100-61)

SPIRIVA RESPIMAT Inhalation Spray: 28 metered actuations (NDC 0597-0100-31) (institutional pack)

The SPIRIVA RESPIMAT cartridge has a net fill weight of 4 grams and when used with the SPIRIVA RESPIMAT inhaler, is designed to deliver the labeled number of metered actuations (60 or 28) after preparation for use; which is, respectively, equivalent to 30 or 14 days of medication when used according to the Instructions for Use. Each actuation from the SPIRIVA RESPIMAT inhaler delivers 2.5 mcg of tiotropium (equivalent to 3.124 mcg of tiotropium bromide monohydrate) from the mouthpiece.

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

After assembly, the SPIRIVA RESPIMAT inhaler should be discarded at the latest 3 months after first use or when the locking mechanism is engaged, whichever comes first.

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

Storage

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Avoid freezing.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Instructions for Use)

Paradoxical Bronchospasm:

Inform patients that SPIRIVA RESPIMAT can produce paradoxical bronchospasm. Advise patients that if paradoxical bronchospasm occurs, patients should discontinue SPIRIVA RESPIMAT.

Worsening of Narrow-Angle Glaucoma:

Instruct patients to be alert for signs and symptoms of 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). Instruct patients to consult a physician immediately should any of these signs and symptoms develop.

Inform patients that care must be taken not to allow the aerosol cloud to enter into the eyes as this may cause blurring of vision and pupil dilation.

Since dizziness and blurred vision may occur with the use of SPIRIVA RESPIMAT, caution patients about engaging in activities such as driving a vehicle or operating appliances or machinery.

Worsening of Urinary Retention:

Instruct patients to be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Not for Acute Use:

Instruct patients that SPIRIVA RESPIMAT is a once-daily maintenance bronchodilator and should not be used for immediate relief of breathing problems, (i.e., as a rescue medication).

Instructions for Administering SPIRIVA RESPIMAT:

It is important for patients to understand how to correctly administer SPIRIVA inhalation spray using the SPIRIVA RESPIMAT inhaler. Instruct patients that SPIRIVA inhalation spray should only be administered via the SPIRIVA RESPIMAT inhaler and the SPIRIVA RESPIMAT inhaler should not be used for administering other medications.

Instruct patients that priming SPIRIVA RESPIMAT is essential to ensure appropriate content of the medication in each actuation.

When using the unit for the first time, the SPIRIVA RESPIMAT cartridge is inserted into the SPIRIVA RESPIMAT inhaler and the unit is primed. SPIRIVA RESPIMAT patients are to actuate the inhaler toward the ground until an aerosol cloud is visible and then to repeat the process three more times. The unit is then considered primed and ready for use. If not used for more than 3 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.

Distributed by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

Address medical inquiries to: (800) 542-6257 or (800) 459-9906 TTY.

SPIRIVA[®], HandiHaler[®], and RESPIMAT[®] are registered trademarks and are used under license from Boehringer Ingelheim International GmbH

Copyright © 2014 Boehringer Ingelheim International GmbH
ALL RIGHTS RESERVED

IT5904AI232014
304478-01

Instructions for Use

SPIRIVA® RESPIMAT® (speh REE vah - RES peh mat)

(tiotropium bromide)

inhalation spray

For Oral Inhalation Only

Do not spray SPIRIVA RESPIMAT into your eyes.

Read these Instructions for Use before you start using SPIRIVA RESPIMAT and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your doctor about your medical condition or your treatment.

- **Use SPIRIVA RESPIMAT exactly as your doctor tells you to use it.**
- **Do not** change your dose or how often you use SPIRIVA RESPIMAT without talking with your doctor.
- **Do not** use other inhaled medicines with SPIRIVA RESPIMAT without talking to your doctor.
- Tell your doctor about all of the medicines you take. SPIRIVA RESPIMAT may affect the way some medicines work and some other medicines may affect the way SPIRIVA RESPIMAT works.
- The SPIRIVA RESPIMAT inhaler has a slow-moving mist that helps you inhale the medicine.
- **Use 1 dose (2 puffs) of SPIRIVA RESPIMAT, 1 time each day, at the same time of the day. Do not take** more than 1 dose (2 puffs) in 24 hours.
- Always use the new SPIRIVA RESPIMAT inhaler that is provided with each new prescription. Only use the SPIRIVA RESPIMAT inhaler to take your medicine. **Do not** use the SPIRIVA RESPIMAT inhaler with other medicines.
- **Your SPIRIVA RESPIMAT cartridge contains either 60 puffs (equal to 30 doses of medicine) or 28 puffs (equal to 14 doses of medicine) after you prepare your inhaler for the first use. There is enough medicine for 30 days or 14 days when it is used as 2 puffs 1 time each day.**
- Before your SPIRIVA RESPIMAT inhaler is used for the first time, the SPIRIVA RESPIMAT cartridge must be inserted into the SPIRIVA RESPIMAT inhaler and then primed. The instructions below show you how to prepare and prime the inhaler for first time use and how to use the inhaler for daily dosing.

Do not turn the clear base before inserting the cartridge.

The SPIRIVA RESPIMAT inhaler



Prepare For First Time Use



Figure 1

Step 1. With the aqua cap closed, press the safety catch while pulling off the clear base. See Figure 1.

Be careful not to touch the piercing element located inside the bottom of the clear base.



Figure 2

Step 2. Write the **discard by** date on the label of the SPIRIVA RESPIMAT inhaler. The **discard by** date is 3 months from the date the cartridge is inserted into the inhaler. See Figure 2.

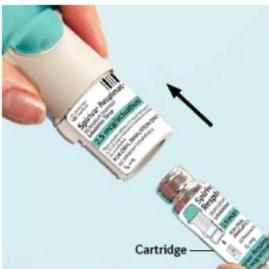


Figure 3

Step 3. Take the SPIRIVA RESPIMAT cartridge out of the box. Push the **narrow** end of the cartridge into the inhaler. The base of the cartridge will not sit flush with the inhaler. **About 1/8 of an inch will remain visible** when the cartridge is correctly inserted. See Figure 3.

The cartridge can be pushed against a firm surface to ensure that it is correctly inserted. See Figure 3.

Do not remove the cartridge once it has been inserted into the inhaler.

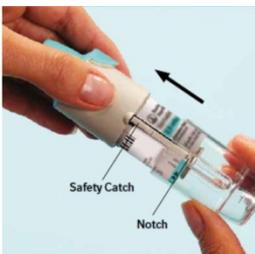


Figure 4

Step 4. Put the clear base back into place. See Figure 4.

Do not remove the clear base again.

Your SPIRIVA RESPIMAT inhaler should not be taken apart after you have inserted the cartridge and put the clear base back.

Prime For First Time Use

The following steps are needed to fill the dosing system the first time you use it and will not affect the number of doses available. After preparation and initial priming, your SPIRIVA RESPIMAT inhaler will be able to deliver the labeled number of doses (30 or 14).

Proper priming of the inhaler is important to make sure the correct amount of medicine is delivered.



Figure 5

Step 5. Hold the SPIRIVA RESPIMAT inhaler upright, with the aqua cap closed, to avoid accidental release of the dose.

Turn the clear base in the direction of the black arrows on the label until it clicks (half a turn). See Figure 5.



Figure 6

Step 6. Flip the aqua cap until it snaps fully open. See Figure 6.



Figure 7

Step 7. Point the SPIRIVA RESPIMAT inhaler toward the ground (away from your face).

Press the dose release button. See Figure 7. Close the aqua cap.

Repeat Steps 5, 6, and 7 until a spray is visible.

Once the spray is visible, you must repeat Steps 5, 6, and 7 three more times to make sure the inhaler is prepared for use.

Your SPIRIVA RESPIMAT inhaler is now ready to use.

These steps will not affect the number of doses available.

After preparation and initial priming, your SPIRIVA RESPIMAT inhaler will be able to deliver the labeled number of doses (30 or 14).

Daily Dosing



Figure A

Step A. Hold the SPIRIVA RESPIMAT inhaler upright, with the aqua cap closed, so you do not accidentally release a dose of medicine.

Turn the clear base in the direction of the black arrows on the label until it clicks (half a turn). See Figure A.



Figure B

Step B. Flip the aqua cap until it snaps fully open.

Breathe out slowly and fully, and then close your lips around the end of the mouthpiece without covering the air vents. See Figure B.

Point your SPIRIVA RESPIMAT inhaler to the back of your throat.

While taking in a slow, deep breath through your mouth, press the dose release button and continue to breathe in slowly for as long as you can.

Hold your breath for 10 seconds or for as long as comfortable.

Step C. **Repeat Steps A and B so that you get the full dose.**

Close the aqua cap until you use your SPIRIVA RESPIMAT inhaler again.

Helpful Hints for Daily Dosing:

Using the SPIRIVA RESPIMAT inhaler requires 3 simple steps. A helpful way to remember the steps for Daily Dosing is to remember **TOP**:

Turn the clear base

Open the cap and close your lips around the mouthpiece

Press the dose-release button and inhale

These steps should be performed two times to receive the proper dose of medicine.

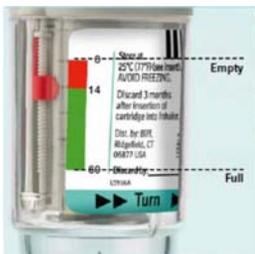
If your SPIRIVA RESPIMAT inhaler has not been used for more than 3 days, spray one puff toward the ground to prepare the inhaler for use.

If your SPIRIVA RESPIMAT inhaler has not been used for more than 21 days, repeat Steps 5, 6, and 7 until a spray is visible. Then repeat Steps 5, 6, and 7 three more times to prepare the inhaler for use.

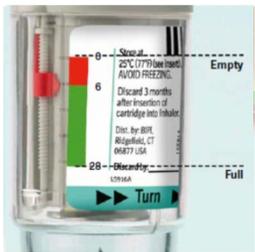
For more information about SPIRIVA RESPIMAT or a video demonstration on how to use SPIRIVA RESPIMAT, go to www.spiriva.com, or scan the code below. You may also call 1-800-542-6257 or (TTY) 1-800-459-9906 for further information about SPIRIVA RESPIMAT.



When should I get a new SPIRIVA RESPIMAT inhaler?



30 dose product



14 dose product

Two puffs from SPIRIVA RESPIMAT equal one dose of medicine. SPIRIVA RESPIMAT is available with 30 or 14 doses of medicine (equal to 60 or 28 puffs). The dose indicator shows approximately how many puffs of medication are left. When the pointer enters the red area of the scale, there is enough medicine for 7 days (30 dose product) or 3 days (14 dose product). This is when you need to refill your prescription or ask your doctor if you need another prescription for SPIRIVA RESPIMAT Inhalation Spray.

Once the dose indicator has reached the end of the scale, all puffs have been used and the RESPIMAT inhaler locks automatically. At this point, the base cannot be turned any further.

Throw away the SPIRIVA RESPIMAT inhaler 3 months after insertion of cartridge into inhaler, even if all the medicine has not been used, or when the inhaler is locked, whichever comes first.

Questions and Answers about your SPIRIVA RESPIMAT inhaler

| What if... | Reason | What to do |
|--|---|---|
| I can not turn the base easily? | The SPIRIVA RESPIMAT inhaler is already prepared and ready to use. | The SPIRIVA RESPIMAT inhaler can be used as it is. |
| | The SPIRIVA RESPIMAT inhaler is locked and all the medicine has been used. | Prepare and use a new SPIRIVA RESPIMAT inhaler. |
| I can not press the dose release button? | The clear base has not been turned. | Turn the clear base until it clicks (half a turn). |
| The clear base springs back after I have turned it and a small amount of moisture is released? | The clear base was not turned far enough. | Prepare the SPIRIVA RESPIMAT inhaler for use by turning the clear base until it clicks (half a turn). |
| I can turn the clear base past the point where it clicks? | Either the dose release button has been pressed, or the clear base has been turned too far. | With the aqua cap closed, turn the clear base until it clicks (half a turn). |

How should I care for my SPIRIVA RESPIMAT inhaler?

Clean the mouthpiece, including the metal part inside the mouthpiece, with a damp cloth or tissue only, at least 1 time a week. Any minor discoloration in the mouthpiece does not affect your SPIRIVA RESPIMAT inhaler.

If the outside of your SPIRIVA RESPIMAT inhaler gets dirty, wipe it with a damp cloth.

How should I store my SPIRIVA RESPIMAT inhaler?

- Store SPIRIVA RESPIMAT at Room Temperature between 59°F to 86°F (15°C to 30°C).
- Do not freeze your SPIRIVA RESPIMAT cartridge and inhaler.

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

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Distributed by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

SPIRIVA[®], HandiHaler[®], and RESPIMAT[®] are registered trademarks and are used under license from Boehringer Ingelheim International GmbH

Copyright © 2014 Boehringer Ingelheim International GmbH.

ALL RIGHTS RESERVED

Revised: 09/2014

IT5904AI232014
304478-01

Spiriva® Respimat®
(tiotropium bromide)
Inhalation Spray

2.5 mcg/actuation*

4 Grams
28 Metered Inhalations

Package Contents:
1 Spiriva® Respimat® Inhaler
1 Spiriva® Respimat® Cartridge
Prescribing Information
Instructions for Use

Only use
Spiriva® Respimat® Inhaler
with
Spiriva® Respimat® Cartridge

Avoid spraying in eyes.
Keep out of reach of children.

Insert cartridge before use.
Discard 3 months after insertion
of the cartridge into inhaler.



Spiriva® Respimat®
(tiotropium bromide)
Inhalation Spray

2.5 mcg/actuation*

4 Grams
28 Metered Inhalations

*Each actuation delivers 2.5 mcg of tiotropium, equivalent to 3.124 mcg of tiotropium bromide monohydrate from the mouthpiece.

Usual Dosage: Two inhalations once daily. Dispense with Instructions for Use.

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F). [see USP Controlled Room Temperature].

AVOID FREEZING.

Excipients: water for injection, edetate disodium, benzalkonium chloride and hydrochloric acid.

Contents of unopened cartridge are sterile.

CT5905A
304455-01

NDC 0597-0100-28

Spiriva® Respimat®
(tiotropium bromide)
Inhalation Spray

2.5 mcg/actuation*

FOR ORAL INHALATION ONLY

Professional Sample: Not For Sale.

Rx only

4 Grams
28 Metered Inhalations
(Two inhalations equal one dose)



Spiriva® Respimat®
(tiotropium bromide)
Inhalation Spray

2.5 mcg/actuation*

4 Grams
28 Metered Inhalations

Lot
Exp.



For more information or a video demonstration visit www.Spiriva.com or scan the code, or call 1-800-542-6257 or (TTY) 1-800-459-9906. Before use, please read Instructions for Use.

Spiriva® Respimat®
(tiotropium bromide)
Inhalation Spray
2.5 mcg/actuation*
4 Grams
28 Metered Inhalations

Spiriva® Respimat®
(tiotropium bromide)
Inhalation Spray

2.5 mcg/actuation*

4 Grams
28 Metered Inhalations

For more information or a video demonstration visit www.Spiriva.com or scan the code, or call 1-800-542-6257 or (TTY) 1-800-459-9906.



Distributed by:
Boehringer Ingelheim
Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

Made in Germany

Licensed from:
Boehringer Ingelheim
International GmbH

Copyright 2014
Boehringer Ingelheim
International GmbH
ALL RIGHTS RESERVED

Spiriva® Respimat®
(tiotropium bromide)
Inhalation Spray

2.5 mcg/actuation*

4 Grams
28 Metered Inhalations

Package Contents:
1 Spiriva® Respimat® Inhaler
1 Spiriva® Respimat® Cartridge
Prescribing Information
Instructions for Use

Only use
Spiriva® Respimat® Inhaler
with
Spiriva® Respimat® Cartridge

Avoid spraying in eyes.
Keep out of reach of children.

Insert cartridge before use.
Discard 3 months after insertion
of the cartridge into inhaler.



N
3 0597-0100-31 7

Spiriva® Respimat®
(tiotropium bromide)
Inhalation Spray

2.5 mcg/actuation*

4 Grams
28 Metered Inhalations

*Each actuation delivers 2.5 mcg of tiotropium, equivalent to 3.124 mcg of tiotropium bromide monohydrate from the mouthpiece.

Usual Dosage: Two inhalations once daily. Dispense with Instructions for Use.

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F). [see USP Controlled Room Temperature].

AVOID FREEZING.

Excipients: water for injection, edetate disodium, benzalkonium chloride and hydrochloric acid.

Contents of unopened cartridge are sterile.

CT5909A
304477-01

Spiriva® Respimat®
(tiotropium bromide)
Inhalation Spray
2.5 mcg/actuation*
4 Grams
28 Metered Inhalations

NDC 0597-0100-31

Spiriva® Respimat®
(tiotropium bromide)
Inhalation Spray

2.5 mcg/actuation*

FOR ORAL INHALATION ONLY

Institutional Pack

Rx only

4 Grams
28 Metered Inhalations
(Two inhalations equal one dose)



Spiriva® Respimat®
(tiotropium bromide)
Inhalation Spray

2.5 mcg/actuation*

4 Grams
28 Metered Inhalations

Lot
Exp.

Spiriva® Respimat®
(tiotropium bromide)
Inhalation Spray

2.5 mcg/actuation*

4 Grams
28 Metered Inhalations

For more information or a video demonstration visit www.Spiriva.com or scan the code, or call 1-800-542-6257 or (TTY) 1-800-459-9906.



Distributed by:
Boehringer Ingelheim
Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

Made in Germany

Licensed from:
Boehringer Ingelheim
International GmbH

Copyright 2014
Boehringer Ingelheim
International GmbH
ALL RIGHTS RESERVED

For more information or a video demonstration visit www.Spiriva.com or scan the code, or call 1-800-542-6257 or (TTY) 1-800-459-9906. Before use, please read Instructions for Use.



Spiriva® Respimat®
(tiotropium bromide)
Inhalation Spray

2.5 mcg/actuation*

4 Grams
60 Metered Inhalations

Package Contents:
1 Spiriva® Respimat® Inhaler
1 Spiriva® Respimat® Cartridge
Prescribing Information
Instructions for Use

Only use
Spiriva® Respimat® Inhaler
with
Spiriva® Respimat® Cartridge

Avoid spraying in eyes.
Keep out of reach of children.

Insert cartridge before use.
Discard 3 months after insertion
of the cartridge into inhaler.



N
3 0597-0100-61 4



Spiriva® Respimat®
(tiotropium bromide)
Inhalation Spray

2.5 mcg/actuation*

4 Grams
60 Metered Inhalations

*Each actuation delivers 2.5 mcg
of tiotropium, equivalent to
3.124 mcg of tiotropium bromide
monohydrate from the
mouthpiece.

Usual Dosage: Two inhalations
once daily. Dispense with
Instructions for Use.

Store at 25°C (77°F);
excursions permitted to
15 to 30°C (59 to 86°F).
[see USP Controlled
Room Temperature].

AVOID FREEZING.

Excipients: water for injection,
edetate disodium, benzalkonium
chloride and hydrochloric acid.

Contents of unopened cartridge
are sterile.

CT5913A
304453-01

NDC 0597-0100-61

Spiriva® Respimat®
(tiotropium bromide)
Inhalation Spray

2.5 mcg/actuation*

FOR ORAL INHALATION ONLY

R_x only

4 Grams
60 Metered Inhalations
(Two inhalations equal one dose)



Spiriva® Respimat®
(tiotropium bromide)
Inhalation Spray

2.5 mcg/actuation*

4 Grams
60 Metered Inhalations

Lot
Exp.

Spiriva® Respimat®
(tiotropium bromide)
Inhalation Spray
2.5 mcg/actuation*
4 Grams
60 Metered Inhalations

Spiriva® Respimat®
(tiotropium bromide)
Inhalation Spray

2.5 mcg/actuation*

4 Grams
60 Metered Inhalations

For more information or a video
demonstration visit www.Spiriva.com
or scan the code, or call 1-800-542-6257
or (TTY) 1-800-459-9906.



Distributed by:
Boehringer Ingelheim
Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

Made in Germany

Licensed from:
Boehringer Ingelheim
International GmbH

Copyright 2014
Boehringer Ingelheim
International GmbH
ALL RIGHTS RESERVED

For more information or a video
demonstration visit
www.Spiriva.com or scan the code,
or call 1-800-542-6257
or (TTY) 1-800-459-9906.
Before use, please read Instructions
for Use.





**Spiriva®
Respimat®**
(tiotropium bromide)
Inhalation Spray

2.5 mcg/actuation*



FOR ORAL
INHALATION ONLY
Professional Samples
Not For Sale
28 Metered Inhalations
Rx only

**Spiriva® Respimat®
2.5 mcg/actuation***



*Each actuation delivers
2.5 mcg of tiotropium, equivalent
to 3.124 mcg of tiotropium
bromide monohydrate from the
mouthpiece. Discard 3 months
after insertion of cartridge into
inhaler. Store at 25°C (77°F)
Use Insert. AVOID FREEZING.
Contents of unopened cartridge
are sterile.

LS906A 301415-01

Lot
Exp.

Spiriva® Respimat®
(tiotropium bromide)
Inhalation Spray

2.5 mcg/actuation*

*Each actuation delivers 2.5 mcg of tiotropium, equivalent to 3.125 mcg of tiotropium bromide monohydrate from the mouthpiece.

FOR ORAL INHALATION ONLY
Professional Sample: Not For Sale.
28 Metered Inhalations L3907A
Rx only 304458-01



**Spiriva®
Respimat®**
(tiotropium bromide)
Inhalation Spray

2.5 mcg/actuation*



FOR ORAL
INHALATION ONLY
Institutional Pack
28 Metered Inhalations
Rx only

**Spiriva® Respimat®
2.5 mcg/actuation***



*Each actuation delivers
2.5 mcg of tiotropium, equivalent
to 3.124 mcg of tiotropium
bromide monohydrate from the
mouthpiece. Discard 3 months
after insertion of cartridge into
inhaler. Store at 25°C (77°F)
Use Inseal®, AVOID FREEZING.
Contents of unopened cartridge
are sterile.

LS91.00A 301446-01

Lot
Exp.

Spiriva® RespiMat®
(tiotropium bromide)
Inhalation Spray

2.5 mcg/actuation*

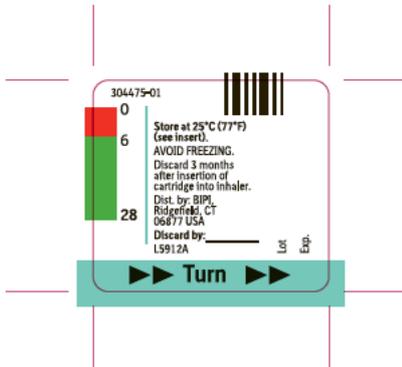
*Each actuation delivers 2.5 mcg of tiotropium, equivalent to 3.125 mcg of tiotropium bromide monohydrate from the mouthpiece.

FOR ORAL INHALATION ONLY

Institutional Pack
25 Metered Inhalations

Rx only

L5911A
304476-01





**Spiriva®
Respimat®**
(tiotropium bromide)
Inhalation Spray

2.5 mcg/actuation*



FOR ORAL
INHALATION ONLY
60 Metered Inhalations
Rx only

**Spiriva® Respimat®
2.5 mcg/actuation***



*Each actuation delivers
2.5 mcg of tiotropium, equivalent
to 3.124 mcg of tiotropium
bromide monohydrate from the
mouthpiece. Discard 3 months
after insertion of cartridge into
inhaler. Store at 25°C (77°F)
(see insert). AVOID FREEZING.
Contents of unopened cartridge
are sterile.

304459-01
L59144

Lot
Exp.

Spiriva® Respimat®
(tiotropium bromide)
Inhalation Spray

2.5 mcg/actuation*

*Each actuation delivers 2.5 mcg of tiotropium, equivalent to 3.125 mcg of tiotropium bromide monohydrate from the mouthpiece.

FOR ORAL INHALATION ONLY
60 Metered Inhalations

Rx only

L591.SA
304454-01

304492-01



0
14
60

Store at
25°C (77°F) (see insert).
AVOID FREEZING.
Discard 3 months
after insertion of
cartridge into inhaler.
Dist. by: BIPV,
Ridgefield, CT
06877 USA.
Discard by: _____ Lot _____ Exp. _____

▶▶ Turn ▶▶

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BADRUL A CHOWDHURY
09/24/2014