

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder)
Capsules for Respiratory Inhalation**

**DO NOT Swallow SPIRIVA Capsules
FOR ORAL INHALATION ONLY with the HandiHaler Device**

Initial U.S. Approval: 2004

-----RECENT MAJOR CHANGES-----

Contraindications (4)	11/2011
Warnings and Precautions, Immediate Hypersensitivity Reactions (5.2)	11/2011

-----INDICATIONS AND USAGE-----

SPIRIVA HandiHaler 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-----

DO NOT swallow SPIRIVA capsules (2)
For Use with the HandiHaler Device ONLY (2)
For Oral Inhalation ONLY (2)

- Two inhalations of the powder contents of a single SPIRIVA capsule (18 mcg) once daily (2)

-----DOSAGE FORMS AND STRENGTHS-----

SPIRIVA capsules for oral inhalation: 18 mcg tiotropium powder, for use with HandiHaler device (3)

-----CONTRAINDICATIONS-----

- Hypersensitivity to tiotropium, ipratropium or any components of SPIRIVA capsules (4)

-----WARNINGS AND PRECAUTIONS-----

- Not for acute use: Not for use as a rescue medication (5.1)
- Immediate hypersensitivity reactions: Discontinue SPIRIVA HandiHaler at once and consider alternatives if immediate hypersensitivity reactions, including angioedema, bronchospasm, or anaphylaxis, occur. Use with caution in patients with severe hypersensitivity to milk proteins. (5.2)
- Paradoxical bronchospasm: Discontinue SPIRIVA HandiHaler 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 patients to consult a physician immediately if this occurs. (5.5)

-----ADVERSE REACTIONS-----

- The most common adverse reactions (>5% incidence in the 1-year placebo-controlled trials) were upper respiratory tract infection, dry mouth, sinusitis, pharyngitis, non-specific chest pain, urinary tract infection, dyspepsia, and rhinitis (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 HandiHaler 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: 3/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

- 1 INDICATIONS AND USAGE**
- 2 DOSAGE AND ADMINISTRATION**
- 3 DOSAGE FORMS AND STRENGTHS**
- 4 CONTRAINDICATIONS**
- 5 WARNINGS AND PRECAUTIONS**
 - 5.1 Not for Acute Use
 - 5.2 Immediate Hypersensitivity Reactions
 - 5.3 Paradoxical Bronchospasm
 - 5.4 Worsening of Narrow-Angle Glaucoma
 - 5.5 Worsening of Urinary Retention
 - 5.6 Renal Impairment
- 6 ADVERSE REACTIONS**
 - 6.1 Clinical Trials Experience
 - 6.2 Postmarketing Experience
- 7 DRUG INTERACTIONS**
 - 7.1 Sympathomimetics, Methylxanthines, Steroids
 - 7.2 Anticholinergics
 - 7.3 Cimetidine, Ranitidine
- 8 USE IN SPECIFIC POPULATIONS**
 - 8.1 Pregnancy
 - 8.2 Labor and Delivery
 - 8.3 Nursing Mothers

- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment
- 10 OVERDOSAGE**
- 11 DESCRIPTION**
- 12 CLINICAL PHARMACOLOGY**
 - 12.1 Mechanism of Action
 - 12.2 Pharmacodynamics
 - 12.3 Pharmacokinetics
- 13 NONCLINICAL TOXICOLOGY**
 - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
 - 13.2 Animal Toxicology and Pharmacology
- 14 CLINICAL STUDIES**
- 16 HOW SUPPLIED/STORAGE AND HANDLING**
- 17 PATIENT COUNSELING INFORMATION**
 - 17.1 Instructions for Administering SPIRIVA HandiHaler
 - 17.2 Paradoxical Bronchospasm
 - 17.3 Urinary Retention
 - 17.4 Visual Effects
 - 17.5 Acute Exacerbation

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SPIRIVA HandiHaler (tiotropium bromide inhalation powder) 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 HandiHaler is indicated to reduce exacerbations in COPD

patients.

2 DOSAGE AND ADMINISTRATION

DO NOT SWALLOW SPIRIVA CAPSULES FOR USE WITH HANDIHALER DEVICE ONLY

FOR ORAL INHALATION ONLY

SPIRIVA capsules must not be swallowed as the intended effects on the lungs will not be obtained. The contents of the SPIRIVA capsules are only for oral inhalation and should only be used with the HandiHaler device [see Overdosage (10)].

The recommended dose of SPIRIVA HandiHaler is two inhalations of the powder contents of one SPIRIVA capsule, once-daily, with the HandiHaler device [see Patient Counseling Information (17)].

For administration of SPIRIVA HandiHaler, a SPIRIVA capsule is placed into the center chamber of the HandiHaler device. The SPIRIVA capsule is pierced by pressing and releasing the green piercing button on the side of the HandiHaler device. The tiotropium formulation is dispersed into the air stream when the patient inhales through the mouthpiece [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 HandiHaler 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 HandiHaler consists of SPIRIVA capsules and a HandiHaler device. SPIRIVA capsules contain 18 mcg dry powder formulation of tiotropium in a light green, hard gelatin capsule with TI 01 printed on one side and Boehringer Ingelheim company logo on the other side.

4 CONTRAINDICATIONS

SPIRIVA HandiHaler is contraindicated in patients with a hypersensitivity to tiotropium, ipratropium, or any components of SPIRIVA capsules [see WARNINGS AND PRECAUTIONS (5.2)]. In clinical trials and postmarketing experience with SPIRIVA HandiHaler, immediate hypersensitivity reactions, including angioedema (including swelling of the lips, tongue, or throat), itching, or rash have been reported.

5 WARNINGS AND PRECAUTIONS

5.1 Not for Acute Use

SPIRIVA HandiHaler is intended as a once-daily maintenance treatment for COPD and is not indicated for the initial treatment of acute episodes of bronchospasm (i.e., rescue therapy).

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 HandiHaler. If such a reaction occurs, therapy with SPIRIVA HandiHaler 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 should be closely monitored for similar hypersensitivity reactions to SPIRIVA HandiHaler. In addition, SPIRIVA HandiHaler should be used with caution in patients with severe hypersensitivity to milk proteins.

5.3 Paradoxical Bronchospasm

Inhaled medicines, including SPIRIVA HandiHaler, can produce paradoxical bronchospasm. If this occurs, treatment with SPIRIVA HandiHaler should be stopped and other treatments considered.

5.4 Worsening of Narrow-Angle Glaucoma

SPIRIVA HandiHaler 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 HandiHaler 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.

5.6 Renal Impairment

As a predominantly renally excreted drug, patients with moderate to severe renal impairment (creatinine clearance of ≤ 50 mL/min) treated with SPIRIVA HandiHaler 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, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6-Month to 1-Year Trials

The data described below reflect exposure to SPIRIVA HandiHaler in 2663 patients. SPIRIVA HandiHaler was studied in two 1-year placebo-controlled trials, two 1-year active-controlled trials, and two 6-month placebo-controlled trials in patients with COPD. In these trials, 1308 patients were treated with SPIRIVA HandiHaler at the recommended dose of 18 mcg once a day. The population had an age ranging from 39 to 87 years with 65% to 85% males, 95% Caucasian, and had COPD with a mean pre-bronchodilator forced expiratory volume in one second (FEV₁) percent predicted of 39% to 43%. Patients with narrow-angle glaucoma, or symptomatic prostatic hypertrophy or bladder outlet obstruction were excluded from these trials. An additional 6-month trial conducted in a Veteran's Affairs setting is not included in this safety database because only serious adverse events were collected.

The most commonly reported adverse drug reaction was dry mouth. Dry mouth was usually mild and often resolved during continued treatment. Other reactions reported in individual patients and consistent with possible anticholinergic effects included constipation, tachycardia, blurred vision, glaucoma (new onset or worsening), dysuria, and urinary retention.

Four multicenter, 1-year, placebo-controlled and active-controlled trials evaluated SPIRIVA HandiHaler in patients with COPD. Table 1 shows all adverse reactions that occurred with a frequency of $\geq 3\%$ in the SPIRIVA HandiHaler group in the 1-year placebo-controlled trials where the rates in the SPIRIVA HandiHaler group exceeded placebo by $\geq 1\%$. The frequency of corresponding reactions in the ipratropium-controlled trials is included for comparison.

Table 1 Adverse Reactions (% Patients) in One-Year COPD Clinical Trials

Body System (Event)	Placebo-Controlled Trials		Ipratropium-Controlled Trials	
	SPIRIVA (n = 550)	Placebo (n = 371)	SPIRIVA (n = 356)	Ipratropium (n = 179)
Body as a Whole				
Chest Pain (non-specific)	7	5	5	2
Edema, Dependent	5	4	3	5
Gastrointestinal System Disorders				
Dry Mouth	16	3	12	6
Dyspepsia	6	5	1	1
Abdominal Pain	5	3	6	6
Constipation	4	2	1	1
Vomiting	4	2	1	2
Musculoskeletal System				
Myalgia	4	3	4	3
Resistance Mechanism Disorders				
Infection	4	3	1	3
Moniliasis	4	2	3	2
Respiratory System (Upper)				
Upper Respiratory Tract Infection	41	37	43	35
Sinusitis	11	9	3	2
Pharyngitis	9	7	7	3
Rhinitis	6	5	3	2
Epistaxis	4	2	1	1
Skin and Appendage Disorders				
Rash	4	2	2	2
Urinary System				
Urinary Tract Infection	7	5	4	2

Arthritis, coughing, and influenza-like symptoms occurred at a rate of $\geq 3\%$ in the SPIRIVA HandiHaler treatment group, but were $< 1\%$ in excess of the placebo group.

Other reactions that occurred in the SPIRIVA HandiHaler group at a frequency of 1% to 3% in the placebo-controlled trials where the rates exceeded that in the placebo group include: *Body as a Whole*: allergic reaction, leg pain; *Central and Peripheral Nervous System*: dysphonia, paresthesia; *Gastrointestinal System Disorders*: gastrointestinal disorder not otherwise specified (NOS), gastroesophageal reflux, stomatitis (including ulcerative stomatitis); *Metabolic and Nutritional Disorders*: hypercholesterolemia, hyperglycemia; *Musculoskeletal System Disorders*: skeletal pain; *Cardiac Events*: angina pectoris (including aggravated angina pectoris); *Psychiatric Disorder*: depression; *Infections*: herpes zoster; *Respiratory System Disorder (Upper)*: laryngitis; *Vision Disorder*: cataract. In addition, among the adverse reactions observed in the clinical trials with an incidence of $< 1\%$ were atrial fibrillation, supraventricular tachycardia, angioedema, and urinary retention.

In the 1-year trials, the incidence of dry mouth, constipation, and urinary tract infection increased with age [see *Use in Specific Populations* (8.5)].

Two multicenter, 6-month, controlled studies evaluated SPIRIVA HandiHaler in patients with COPD. The adverse reactions and the incidence rates were similar to those seen in the 1-year controlled trials.

4-Year Trial

The data described below reflect exposure to SPIRIVA HandiHaler in 5992 COPD patients in a 4-year placebo-controlled trial. In this trial, 2986 patients were treated with SPIRIVA HandiHaler at the recommended dose of 18 mcg once a day. The population had an age range from 40 to 88 years, was 75% male, 90% Caucasian, and had COPD with a mean pre-bronchodilator FEV₁ percent predicted of 40%. Patients with narrow-angle glaucoma, or symptomatic prostatic hypertrophy or bladder outlet obstruction were excluded from these trials. When the adverse reactions were analyzed with a frequency of $\geq 3\%$ in the SPIRIVA HandiHaler group where the rates in the SPIRIVA HandiHaler group exceeded placebo by $\geq 1\%$, adverse reactions included (SPIRIVA HandiHaler, placebo): pharyngitis (12.5%, 10.8%), sinusitis (6.5%, 5.3%), headache (5.7%, 4.5%), constipation (5.1%, 3.7%), dry mouth (5.1%, 2.7%), depression (4.4%, 3.3%), insomnia (4.4%, 3.0%), and arthralgia (4.2%, 3.1%).

Additional Adverse Reactions

Other adverse reactions not previously listed that were reported more frequently in COPD patients treated with SPIRIVA HandiHaler than placebo include: dehydration, skin ulcer, stomatitis, gingivitis, oropharyngeal candidiasis, dry skin, skin infection, and joint swelling.

6.2 Postmarketing Experience

Adverse reactions have been identified during worldwide post-approval use of SPIRIVA HandiHaler. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These adverse reactions are: application site irritation (glossitis, mouth ulceration, and pharyngolaryngeal pain), dizziness, dysphagia, hoarseness, intestinal obstruction including ileus paralytic, intraocular pressure increased, oral candidiasis, palpitations, pruritus, tachycardia, throat irritation, and urticaria.

7 DRUG INTERACTIONS

7.1 Sympathomimetics, Methylxanthines, Steroids

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

7.2 Anticholinergics

There is potential for an additive interaction with concomitantly used anticholinergic medications. Therefore, avoid coadministration of SPIRIVA HandiHaler 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)*].

7.3 Cimetidine, Ranitidine

No clinically significant interaction occurred between tiotropium and cimetidine or ranitidine [*see Clinical Pharmacology (12.3)*].

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 HandiHaler 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 inhalation tiotropium doses of up to approximately 660 and 6 times the recommended human daily inhalation dose (RHDID) on a mg/m² basis, 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 35 times the RHDID on a mg/m² basis. 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. Such effects were not observed at inhalation doses of approximately 4 and 80 times the RHDID on a mg/m² basis in rats and rabbits, respectively. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

8.2 Labor and Delivery

The safety and effectiveness of SPIRIVA HandiHaler 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 HandiHaler is administered to a nursing woman.

8.4 Pediatric Use

SPIRIVA HandiHaler is approved for use in the maintenance treatment of bronchospasm associated with COPD and for the reduction of COPD exacerbations. COPD does not normally occur in children. The safety and effectiveness of SPIRIVA HandiHaler in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients who received SPIRIVA HandiHaler in the 1-year clinical trials, 426 were <65 years, 375 were 65 to 74 years, and 105 were ≥75 years of age. Within each age subgroup, there were no differences between the proportion of patients with adverse events in the SPIRIVA HandiHaler and the comparator groups for most events. Dry mouth increased with age in the SPIRIVA HandiHaler group (differences from placebo were 9.0%, 17.1%, and 16.2% in the aforementioned age subgroups). A higher frequency of constipation and urinary tract infections with increasing age was observed in the SPIRIVA HandiHaler group in the placebo-controlled studies. The differences from placebo for constipation were 0%, 1.8%, and 7.8% for each of the age groups. The differences from placebo for urinary tract infections were -0.6%, 4.6%, and 4.5%. No overall differences in effectiveness were observed among these groups. Based on available data, no adjustment of SPIRIVA HandiHaler dosage in geriatric patients is warranted [*see Clinical Pharmacology (12.3)*].

8.6 Renal Impairment

Patients with moderate to severe renal impairment (creatinine clearance of ≤50 mL/min) treated with SPIRIVA HandiHaler should be monitored closely for anticholinergic side effects [*see Dosage and Administration (2), Warnings and Precautions (5.4), 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 in 6 healthy volunteers. In a study of 12 healthy volunteers, bilateral conjunctivitis and dry mouth were seen following repeated once-daily inhalation of 141 mcg of tiotropium.

Accidental Ingestion

Acute intoxication by inadvertent oral ingestion of SPIRIVA capsules is unlikely since it is not well-absorbed systemically.

A case of overdose has been reported from postmarketing experience. A female patient was reported to have inhaled 30 capsules over a 2.5 day period, and developed altered mental status, tremors, abdominal pain, and severe constipation. The patient was hospitalized, SPIRIVA HandiHaler was discontinued, and the constipation was treated with an enema. The patient recovered and was discharged on the same day.

No mortality was observed at inhalation tiotropium doses up to 32.4 mg/kg in mice, 267.7 mg/kg in rats, and 0.6 mg/kg in dogs. These doses correspond to 7300, 120,000, and 850 times the recommended human daily inhalation dose on a mg/m² basis, respectively. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

11 DESCRIPTION

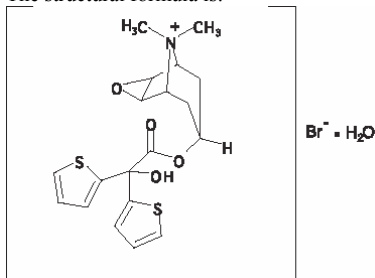
SPIRIVA HandiHaler consists of a capsule dosage form containing a dry powder formulation of tiotropium intended for oral inhalation only with the HandiHaler device.

Each light green, hard gelatin SPIRIVA capsule contains 18 mcg tiotropium (equivalent to 22.5 mcg tiotropium bromide monohydrate) blended with lactose monohydrate (which may contain milk proteins) as the carrier.

The dry powder formulation within the SPIRIVA capsule is intended for oral inhalation only.

The active component of SPIRIVA HandiHaler 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 C₁₉H₂₂NO₄S₂Br • H₂O.

The HandiHaler device is an inhalation device used to inhale the dry powder contained in the SPIRIVA capsule. The dry powder is delivered from the HandiHaler device at flow rates as low as 20 L/min. Under standardized *in vitro* testing, the HandiHaler device delivers a mean of 10.4 mcg tiotropium when tested at a flow rate of 39 L/min for 3.1 seconds (2 L total). In a study of 26 adult patients with COPD and severely compromised lung function [mean FEV₁ 1.02 L (range 0.45 to 2.24 L); 37.6% of predicted (range 16% to 65%)], the median peak inspiratory flow (PIF) through the HandiHaler device was 30.0 L/min (range 20.4 to 45.6 L/min). The amount of drug delivered to the lungs will vary depending on patient factors such as inspiratory flow and peak inspiratory flow through the HandiHaler device, which may vary from patient to patient, and may vary with the exposure time of the SPIRIVA capsule outside the blister pack.

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

Cardiovascular Effects

In a multicenter, randomized, double-blind trial 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 HandiHaler 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 studies with SPIRIVA HandiHaler did not detect an effect of the drug on QTc intervals.

The effect of SPIRIVA HandiHaler on QT interval was also evaluated in a randomized, placebo- and positive-controlled crossover study in 53 healthy volunteers. Subjects received SPIRIVA HandiHaler 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 SPIRIVA HandiHaler 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 by dry powder inhalation. In common with other inhaled drugs, the majority of the delivered dose is deposited in the gastrointestinal tract and, to a lesser extent, in the lung, the intended organ. Many of the pharmacokinetic data described below were obtained with higher doses than recommended for therapy.

Absorption

Following dry powder inhalation by young healthy volunteers, the absolute bioavailability of 19.5% suggests that the fraction reaching the lung is highly bioavailable. It is expected from the chemical structure of the compound (quaternary ammonium compound) that tiotropium is poorly absorbed from the gastrointestinal tract. The effect of food on tiotropium's bioavailability has not been studied. Oral solutions of tiotropium have an absolute bioavailability of 2% to 3%. Maximum tiotropium plasma concentrations were observed 5 minutes after inhalation.

Distribution

Tiotropium shows a volume of distribution of 32 L/kg indicating that the drug binds extensively to tissues. The human plasma protein binding for tiotropium is 72%. At steady state, peak tiotropium plasma levels in COPD patients were 17 to 19 pg/mL when measured 5 minutes after dry powder inhalation of an 18 mcg dose and decreased in a multi-compartmental manner. Steady-state trough plasma concentrations were 3 to 4 pg/mL. Local concentrations in the lung are not known, but the mode of administration suggests substantially higher concentrations in the lung. Studies in rats have shown that tiotropium does not readily penetrate the blood-brain barrier.

Metabolism

The extent of metabolism appears to be 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 did not inhibit CYP450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4.

Elimination

The terminal elimination half-life of tiotropium was between 5 and 6 days following inhalation. Total clearance was 880 mL/min after an intravenous dose in young healthy volunteers with an inter-individual variability of 22%. Intravenously administered tiotropium was mainly excreted unchanged in urine (74%). After dry powder inhalation, urinary excretion was 14% of the dose, the remainder being mainly non-absorbed drug in the gut which was eliminated via the feces. The renal clearance of tiotropium exceeds the creatinine clearance, indicating active secretion into the urine. After chronic once-daily inhalation by COPD patients, pharmacokinetic steady state was reached after 2 to 3 weeks with no accumulation thereafter.

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.

Specific Populations

Geriatric Patients

As expected for drugs predominantly excreted renally, advanced age was associated with a decrease of tiotropium renal clearance (326 mL/min in COPD patients <58 years to 163 mL/min in COPD patients >70 years), which may be explained by decreased renal function. Tiotropium excretion in urine after inhalation decreased from 14% (young healthy volunteers) to about 7% (COPD patients). Plasma concentrations were numerically increased with advancing age within COPD patients (43% increase in AUC₀₋₄ after dry powder inhalation), which was not significant when considered in relation to inter- and intra-individual variability [see *Dosage and Administration (2) and Use in Specific Populations (8.5)*].

Renal Impairment

Since tiotropium is predominantly renally excreted, renal impairment was associated with increased plasma drug concentrations and reduced drug clearance after both intravenous infusion and dry powder inhalation. Mild renal impairment (creatinine clearance of 50 to 80 mL/min), which is often seen in elderly patients, increased tiotropium plasma concentrations (39% increase in AUC₀₋₄ after intravenous infusion). In COPD patients with moderate to severe renal impairment (creatinine clearance of <50 mL/min), the intravenous administration of tiotropium resulted in doubling of the plasma concentrations (82% increase in AUC₀₋₄), which was confirmed by plasma concentrations after dry powder inhalation. Patients with moderate to severe renal impairment (creatinine clearance of ≤50 mL/min) treated with SPIRIVA HandiHaler should be monitored closely for anticholinergic side effects [see *Dosage and Administration (2), Warnings and Precautions (5.4), and Use in Specific Populations (8.6)*].

Hepatic Impairment

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

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. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

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 than 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). These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

13.2 Animal Toxicology and Pharmacology

Reproductive Toxicology Studies

No evidence of fetal structural alteration was observed in rats and rabbits at inhalation tiotropium doses of up to 1.471 and 0.007 mg/kg/day, respectively. These doses correspond to approximately 660 and 6 times the RHDID on a mg/m² basis, respectively. However, in rats, 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 were observed at inhalation tiotropium doses of ≥0.078 mg/kg (approximately 35 times the RHDID on a mg/m² basis). In rabbits, an increase in post-implantation loss was observed at an inhalation dose of 0.4 mg/kg/day (approximately 360 times the RHDID on a mg/m² basis). Such effects were not observed at inhalation doses of 0.009 and up to 0.088 mg/kg/day in rats and rabbits, respectively. These doses correspond to approximately 4 and 80 times the RHDID on a mg/m² basis, respectively. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

The SPIRIVA HandiHaler (tiotropium bromide inhalation powder) clinical development program consisted of six Phase 3 studies in 2663 patients with COPD (1308 receiving SPIRIVA HandiHaler): two 1-year, placebo-controlled studies, two 6-month, placebo-controlled studies and two 1-year, ipratropium-controlled studies. These studies 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 a forced expiratory volume in one second (FEV₁) less than or equal to 60% or 65% of predicted, and a ratio of FEV₁/FVC of less than or equal to 0.7.

In these studies, SPIRIVA HandiHaler, administered once-daily in the morning, provided improvement in lung function (FEV₁), with peak effect occurring within 3 hours following the first dose.

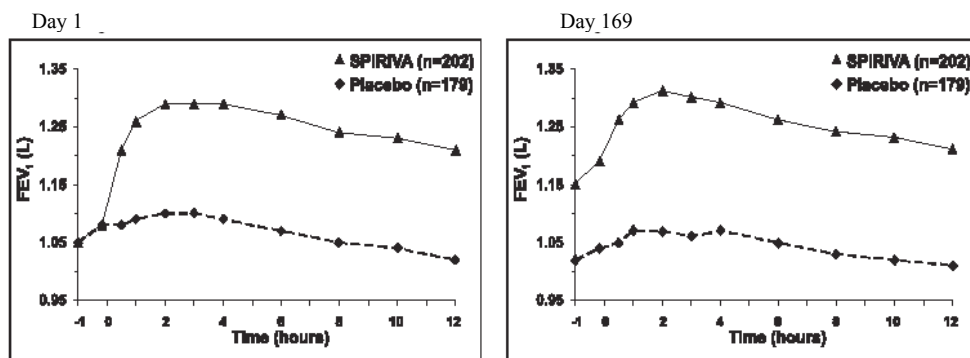
Two additional trials evaluated exacerbations: a 6-month, randomized, double-blind, placebo-controlled, multicenter clinical trial of 1829 COPD patients in a US Veterans Affairs setting and a 4-year, randomized, double-blind, placebo-controlled, multicenter, clinical trial of 5992 COPD patients. Long-term effects on lung function and other outcomes were also evaluated in the 4-year multicenter trial.

6-Month to 1-Year Effects on Lung Function

In the 1-year, placebo-controlled trials, the mean improvement in FEV₁ at 30 minutes was 0.13 liters (13%) with a peak improvement of 0.24 liters (24%) relative to baseline after the first dose (Day 1). Further improvements in FEV₁ and forced vital capacity (FVC) were observed with pharmacodynamic steady state reached by Day 8 with once-daily treatment. The mean peak improvement in FEV₁, relative to baseline, was 0.28 to 0.31 liters (28% to 31%), after 1 week (Day 8) of once-daily treatment. Improvement of lung function was maintained for 24 hours after a single dose and consistently maintained over the 1-year treatment period with no evidence of tolerance.

In the two 6-month, placebo-controlled trials, serial spirometric evaluations were performed throughout daytime hours in Trial A (12 hours) and limited to 3 hours in Trial B. The serial FEV₁ values over 12 hours (Trial A) are displayed in Figure 1. These trials further support the improvement in pulmonary function (FEV₁) with SPIRIVA HandiHaler, which persisted over the spirometric observational period. Effectiveness was maintained for 24 hours after administration over the 6-month treatment period.

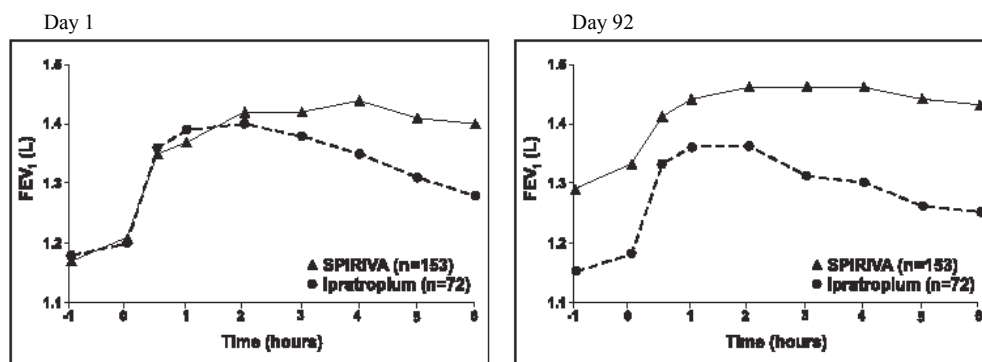
Figure 1 Mean FEV₁ Over Time (prior to and after administration of study drug) on Days 1 and 169 for Trial A (a Six-Month Placebo-Controlled Study)*



*Means adjusted for center, treatment, and baseline effect. On Day 169, a total of 183 and 149 patients in the SPIRIVA HandiHaler and placebo groups, respectively, completed the trial. The data for the remaining patients were imputed using the last observation or least favorable observation carried forward.

Results of each of the 1-year ipratropium-controlled trials were similar to the results of the 1-year placebo-controlled trials. The results of one of these trials are shown in Figure 2.

Figure 2 Mean FEV₁ Over Time (0 to 6 hours post-dose) on Days 1 and 92, Respectively for One of the Two Ipratropium-Controlled Studies*



*Means adjusted for center, treatment, and baseline effect. On Day 92 (primary endpoint), a total of 151 and 69 patients in the SPIRIVA HandiHaler and ipratropium groups, respectively, completed through 3 months of observation. The data for the remaining patients were imputed using the last observation or least favorable observation carried forward.

A randomized, placebo-controlled clinical study in 105 patients with COPD demonstrated that bronchodilation was maintained throughout the 24-hour dosing interval in comparison to placebo, regardless of whether SPIRIVA HandiHaler was administered in the morning or in the evening.

Throughout each week of the one-year treatment period in the two placebo-controlled trials, patients taking SPIRIVA HandiHaler had a reduced requirement for the use of rescue short-acting beta₂-agonists. Reduction in the use of rescue short-acting beta₂-agonists, as compared to placebo, was demonstrated in one of the two 6-month

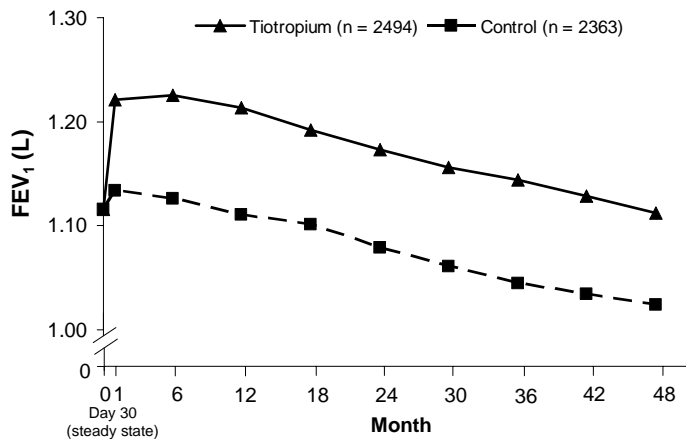
studies.

4-Year Effects on Lung Function

A 4-year, randomized, double-blind, placebo-controlled, multicenter clinical trial involving 5992 COPD patients was conducted to evaluate the long-term effects of SPIRIVA HandiHaler on disease progression (rate of decline in FEV₁). Patients were permitted to use all respiratory medications (including short-acting and long-acting beta-agonists, inhaled and systemic steroids, and theophyllines) other than inhaled anticholinergics. The patients were 40 to 88 years of age, 75% male, and 90% Caucasian with a diagnosis of COPD and a mean pre-bronchodilator FEV₁ of 39% predicted (range = 9% to 76%) at study entry. There was no difference between the groups in either of the co-primary efficacy endpoints, yearly rate of decline in pre- and post-bronchodilator FEV₁, as demonstrated by similar slopes of FEV₁ decline over time (Figure 3).

SPIRIVA HandiHaler maintained improvements in trough (pre-dose) FEV₁ (adjusted means over time: 87 to 103 mL) throughout the 4 years of the study (Figure 3).

Figure 3 Trough (pre-dose) FEV₁ Mean Values at Each Time Point



Repeated measure ANOVA was used to estimate means. Means are adjusted for baseline measurements. Baseline trough FEV₁ (observed mean) = 1.12. Patients with ≥ 3 acceptable pulmonary function tests after Day 30 and non-missing baseline value were included in the analysis.

Exacerbations

The effect of SPIRIVA HandiHaler on COPD exacerbations was evaluated in two clinical trials: a 4-year clinical trial described above and a 6-month clinical trial of 1829 COPD patients in a Veterans Affairs setting. In the 6-month trial, COPD exacerbations were defined as a complex of respiratory symptoms (increase or new onset) of more than one of the following: cough, sputum, wheezing, dyspnea, or chest tightness with a duration of at least 3 days requiring treatment with antibiotics, systemic steroids, or hospitalization. The population had an age ranging from 40 to 90 years with 99% males, 91% Caucasian, and had COPD with a mean pre-bronchodilator FEV₁ percent predicted of 36% (range = 8% to 93%). Patients were permitted to use respiratory medications (including short-acting and long-acting beta-agonists, inhaled and systemic steroids, and theophyllines) other than inhaled anticholinergics. In the 6-month trial, the co-primary endpoints were the proportion of patients with COPD exacerbation and the proportion of patients with hospitalization due to COPD exacerbation. SPIRIVA HandiHaler significantly reduced the proportion of COPD patients who experienced exacerbations compared to placebo (27.9% vs 32.3%, respectively; Odds Ratio (OR) (tiotropium/placebo) = 0.81; 95% CI = 0.66, 0.99; p = 0.037). The proportion of patients with hospitalization due to COPD exacerbations in patients who used SPIRIVA HandiHaler compared to placebo was 7.0% vs 9.5%, respectively; OR = 0.72; 95% CI = 0.51, 1.01; p = 0.056.

Exacerbations were evaluated as a secondary outcome in the 4-year multicenter trial. In this trial, COPD exacerbations were defined as an increase or new onset of more than one of the following respiratory symptoms (cough, sputum, sputum purulence, wheezing, dyspnea) with a duration of three or more days requiring treatment with antibiotics and/or systemic (oral, intramuscular, or intravenous) steroids. SPIRIVA HandiHaler significantly reduced the risk of an exacerbation by 14% (Hazard Ratio (HR) = 0.86; 95% CI = 0.81, 0.91; p < 0.001) and reduced the risk of exacerbation-related hospitalization by 14% (HR = 0.86; 95% CI = 0.78, 0.95; p < 0.002) compared to placebo. The median time to first exacerbation was delayed from 12.5 months (95% CI = 11.5, 13.8) in the placebo group to 16.7 months (95% CI = 14.9, 17.9) in the SPIRIVA HandiHaler group.

16 HOW SUPPLIED/STORAGE AND HANDLING

SPIRIVA HandiHaler consists of SPIRIVA capsules and the HandiHaler device. SPIRIVA capsules contain 18 mcg of tiotropium and are light green, with the Boehringer Ingelheim company logo on the SPIRIVA capsule cap and TI 01 on the SPIRIVA capsule body, or vice versa.

The HandiHaler device is gray colored with a green piercing button. It is imprinted with SPIRIVA HandiHaler (tiotropium bromide inhalation powder), the Boehringer Ingelheim company logo, and the Pfizer company logo. It is also imprinted to indicate that SPIRIVA capsules should not be stored in the HandiHaler device and that the HandiHaler device is only to be used with SPIRIVA capsules.

SPIRIVA capsules are packaged in an aluminum/aluminum blister card and joined along a perforated-cut line. SPIRIVA capsules should always be stored in the blister and only removed immediately before use. The drug should be used immediately after the packaging over an individual SPIRIVA capsule is opened.

The following packages are available:

- carton containing 5 SPIRIVA capsules (1 unit-dose blister card) and 1 HandiHaler inhalation device (NDC 0597-0075-75)
- carton containing 30 SPIRIVA capsules (3 unit-dose blister cards) and 1 HandiHaler inhalation device (NDC 0597-0075-41)
- carton containing 90 SPIRIVA capsules (9 unit-dose blister cards) and 1 HandiHaler inhalation device (NDC 0597-0075-47)

Storage

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

The SPIRIVA capsules should not be exposed to extreme temperature or moisture. Do not store SPIRIVA capsules in the HandiHaler device.

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient Labeling

17.1 Instructions for Administering SPIRIVA HandiHaler

It is important for patients to understand how to correctly administer SPIRIVA capsules using the HandiHaler device [see Patient Counseling Information (17)]. Instruct patients that SPIRIVA capsules should only be administered via the HandiHaler device and the HandiHaler device should not be used for administering other medications. **Remind patients that the contents of SPIRIVA capsules are for oral inhalation only and must not be swallowed.**

Instruct patients always to store SPIRIVA capsules in sealed blisters and to remove only one SPIRIVA capsule immediately before use or its effectiveness may be reduced. Instruct patients to discard unused additional SPIRIVA capsules that are exposed to air (i.e., not intended for immediate use).

17.2 Paradoxical Bronchospasm

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

17.3 Urinary Retention

Difficulty passing urine and dysuria may be symptoms of new or worsening prostatic hyperplasia or bladder outlet obstruction. Patients should be instructed to consult a physician immediately should any of these signs or symptoms develop.

17.4 Visual Effects

Eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema may be signs of acute narrow-angle glaucoma. Inform patients to consult a physician immediately should any of these signs and symptoms develop. Advise patients that miotic eye drops alone are not considered to be effective treatment.

Inform patients that care must be taken not to allow the powder 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 HandiHaler, caution patients about engaging in activities such as driving a vehicle or operating appliances or machinery.

17.5 Acute Exacerbation

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

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

Marketed by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA
and
Pfizer Inc
New York, NY 10017 USA

Licensed from:
Boehringer Ingelheim International GmbH

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

SPIRIVA® and HandiHaler® are registered trademarks and are used under license from Boehringer Ingelheim International GmbH.

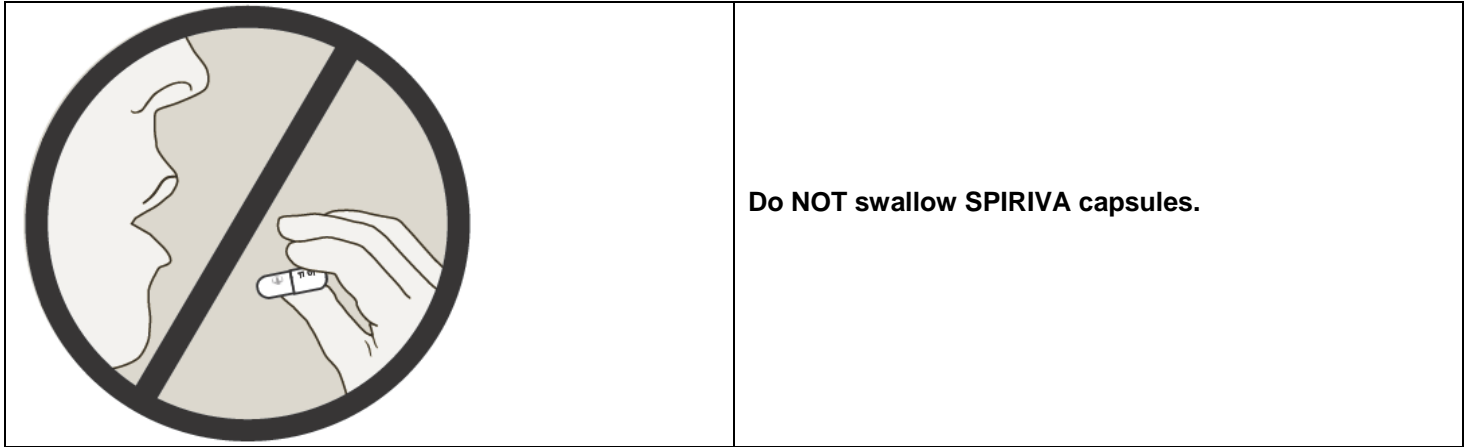
Copyright 2012 Boehringer Ingelheim International GmbH
ALL RIGHTS RESERVED

IT1600ABC192012
10004551/10

IT5300F
75740-05

Patient Information

SPIRIVA® (speh REE vah) HandiHaler® (tiotropium bromide inhalation powder)



Important Information: Do not swallow SPIRIVA capsules. SPIRIVA capsules should only be used with the HandiHaler device and inhaled through your mouth (oral inhalation).

Read the information that comes with your SPIRIVA HandiHaler before you start using it and each time you refill your prescription. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or your treatment.

What is SPIRIVA HandiHaler?

- SPIRIVA HandiHaler is a prescription medicine used each day (a maintenance medicine) to control symptoms of chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.
- SPIRIVA HandiHaler helps make your lungs work better for 24 hours. SPIRIVA HandiHaler relaxes your airways and helps keep them open. You may start to feel like it is easier to breathe on the first day, but it may take longer for you to feel the full effects of the medicine. SPIRIVA HandiHaler works best and may help make it easier to breathe when you use it every day.
- SPIRIVA HandiHaler reduces the likelihood of flare-ups and worsening of COPD symptoms (COPD exacerbations). A COPD exacerbation is defined as an increase or new onset of more than one COPD symptom such as cough, mucus, shortness of breath, and wheezing that requires medicine beyond your rescue medicine.

SPIRIVA HandiHaler is not a rescue medicine and should not be used for treating sudden breathing problems.

Your doctor may give you other medicine to use for sudden breathing problems.

It is not known if SPIRIVA HandiHaler is safe and effective in children.

Who should not take SPIRIVA HandiHaler?

Do not use SPIRIVA HandiHaler if you:

- are allergic to tiotropium, ipratropium (Atrovent®), or any of the ingredients in SPIRIVA HandiHaler. See the end of this leaflet for a complete list of ingredients in SPIRIVA HandiHaler.

Symptoms of a serious allergic reaction to SPIRIVA HandiHaler may include:

- raised red patches on your skin (hives)
- itching
- rash
- swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing

If you have these symptoms of an allergic reaction, stop taking SPIRIVA HandiHaler and call your doctor right away or go to the nearest hospital emergency room.

What should I tell my doctor before using SPIRIVA HandiHaler?

Before taking SPIRIVA HandiHaler, tell your doctor about all your medical conditions, including if you:

- have kidney problems.
- have glaucoma. SPIRIVA HandiHaler may make your glaucoma worse.
- have an enlarged prostate, problems passing urine, or a blockage in your bladder. SPIRIVA HandiHaler may make these problems worse.
- are pregnant or plan to become pregnant. It is not known if SPIRIVA HandiHaler could harm your unborn baby.
- are breast-feeding or plan to breast-feed. It is not known if SPIRIVA HandiHaler passes into breast milk. You and your doctor will decide if SPIRIVA HandiHaler is right for you while you breast-feed.
- have a severe allergy to milk proteins. Ask your doctor if you are not sure.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines and eye drops, vitamins, and herbal supplements. Some of your other medicines or supplements may affect the way SPIRIVA HandiHaler works. SPIRIVA HandiHaler is an anticholinergic medicine. You should not take other anticholinergic medicines while using SPIRIVA HandiHaler, including ipratropium. Ask your doctor or pharmacist if you are not sure if one of your medicines is an anticholinergic.

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist when you get a new medicine.

How should I take SPIRIVA HandiHaler?

- Use SPIRIVA HandiHaler exactly as prescribed. Use SPIRIVA HandiHaler one time every day.
- Read the “Instructions for Use” at the end of this leaflet before you use SPIRIVA HandiHaler. Talk with your doctor if you do not understand the instructions.
- **Do not swallow SPIRIVA capsules.**
- **Only use SPIRIVA capsules with the HandiHaler device.**
- **Do not use the HandiHaler device to take any other medicine.**
- SPIRIVA HandiHaler comes as a powder in a SPIRIVA capsule that fits the HandiHaler device. Each SPIRIVA capsule, containing only a small amount of SPIRIVA powder, is one full dose of medicine.
- Separate one blister from the blister card. Then take out one of the SPIRIVA capsules from the blister package right before you use it.
- After the capsule is pierced, take a complete dose of SPIRIVA HandiHaler by breathing in the powder by mouth two times, using the HandiHaler device (take 2 inhalations from one SPIRIVA capsule). See the “**Instructions for Use**” at the end of this leaflet.
- Throw away any SPIRIVA capsule that is not used right away after it is taken out of the blister package. Do not leave the SPIRIVA capsules open to air; they may not work as well.
- If you miss a dose, take it as soon as you remember. Do not use SPIRIVA HandiHaler more than one time every 24 hours.
- If you use more than your prescribed dose of SPIRIVA HandiHaler, call your doctor or a poison control center.

What should I avoid while using SPIRIVA HandiHaler?

- Do not let the powder from the SPIRIVA capsule get into your eyes. Your vision may get blurry and the pupil in your eye may get larger (dilate). If this happens, call your doctor.
- SPIRIVA HandiHaler can cause dizziness and blurred vision. Should you experience these symptoms you should use caution when engaging in activities such as driving a car or operating appliances or other machines.

What are the possible side effects of SPIRIVA HandiHaler?

SPIRIVA HandiHaler can cause serious side effects, including: Allergic reaction. Symptoms may include:

- raised red patches on your skin (hives)
- itching
- rash
- swelling of the lips, tongue, or throat that may cause difficulty in breathing or swallowing

If you have these symptoms of an allergic reaction, stop taking SPIRIVA HandiHaler and call your doctor right away or go to the nearest hospital emergency room.

- **Sudden narrowing and blockage of the airways into the lungs (bronchospasm).** Your breathing suddenly gets worse.

If you have these symptoms of bronchospasm, stop taking SPIRIVA HandiHaler and call your doctor right away or go to the nearest hospital emergency room.

- **New or worsened increased pressure in the eyes (acute narrow-angle glaucoma).** Symptoms of acute narrow-angle glaucoma may include:
 - eye pain
 - blurred vision
 - seeing halos (visual halos) or colored images along with red eyes

Using only eye drops to treat these symptoms may not work. If you have these symptoms, stop taking SPIRIVA HandiHaler and call your doctor right away.

- **New or worsened urinary retention.** Symptoms of blockage in your bladder and/or enlarged prostate may include: difficulty passing urine, painful urination.

If you have these symptoms of urinary retention, stop taking SPIRIVA HandiHaler and call your doctor right away.

Other side effects with SPIRIVA HandiHaler include:

- upper respiratory tract infection
- dry mouth
- sinus infection
- sore throat
- non-specific chest pain
- urinary tract infection
- indigestion
- runny nose
- constipation
- increased heart rate
- blurred vision

These are not all the possible side effects with SPIRIVA HandiHaler. Tell your doctor if you have any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store SPIRIVA HandiHaler?

- **Do not store SPIRIVA capsules in the HandiHaler device.**
- Store SPIRIVA capsules in the sealed blister package at room temperature between 68°F to 77°F (20° to 25°C).
- Keep SPIRIVA capsules away from heat and cold (do not freeze).
- Store SPIRIVA capsules in a dry place. Throw away any unused SPIRIVA capsules that have been open to air.

Ask your doctor or pharmacist if you have any questions about storing your SPIRIVA capsules.

Keep SPIRIVA HandiHaler, SPIRIVA capsules, and all medicines out of the reach of children.

General information about SPIRIVA HandiHaler

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets. Do not use SPIRIVA HandiHaler for a purpose for which it has not been prescribed. Do not give SPIRIVA HandiHaler to other people even if they have the same symptoms that you have. It may harm them.

For more information about SPIRIVA HandiHaler, talk with your doctor. You can ask your doctor or pharmacist for information about SPIRIVA HandiHaler that is written for health professionals.

For more information about SPIRIVA HandiHaler, go to www.SPIRIVA.com or call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257 or (TTY) 1-800-459-9906.

What are the ingredients in SPIRIVA HandiHaler?

Active ingredient: tiotropium

Inactive ingredient: lactose monohydrate

What is COPD (Chronic Obstructive Pulmonary Disease)?

COPD is a serious lung disease that includes chronic bronchitis, emphysema, or both. Most COPD is caused by smoking. When you have COPD, your airways become narrow. So, air moves out of your lungs more slowly. This makes it hard to breathe.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Distributed by:

Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

Marketed by:

Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

and

Pfizer Inc
New York, NY 10017 USA

Licensed from:

Boehringer Ingelheim International GmbH

SPIRIVA® and HandiHaler® are registered trademarks and are used under license from Boehringer Ingelheim International GmbH.

Copyright 2012 Boehringer Ingelheim International GmbH
ALL RIGHTS RESERVED

Revised: March 2012

IT1600ABC192012
10004551/10

IT5300F
75740-05

Instructions for Use

SPIRIVA® (speh REE vah) **HandiHaler®**
(tiotropium bromide inhalation powder)



Do not swallow SPIRIVA capsules.

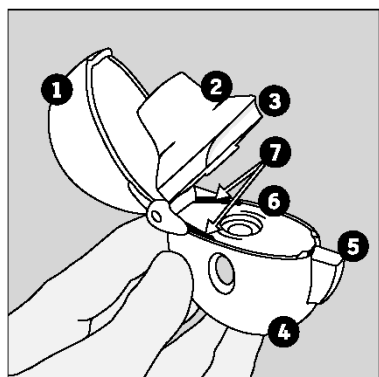
Important Information about using your SPIRIVA HandiHaler

- Do not swallow SPIRIVA capsules.
- SPIRIVA capsules should only be used with the HandiHaler device and inhaled through your mouth (oral inhalation).
- Do not use your HandiHaler device to take any other medicine.

First read the Patient Information, then read these Instructions for Use before you start to use SPIRIVA HandiHaler and each time you refill your prescription. There may be new information.

Becoming familiar with your HandiHaler device and SPIRIVA capsules:

Your SPIRIVA HandiHaler comes with SPIRIVA capsules in blister packaging and a HandiHaler device. Use the new HandiHaler device provided with your medicine.



The parts of your HandiHaler device include:

(See Figure A)

1. dust cap (lid)
2. mouthpiece
3. mouthpiece ridge
4. base
5. green piercing button
6. center chamber
7. air intake vents

Figure A

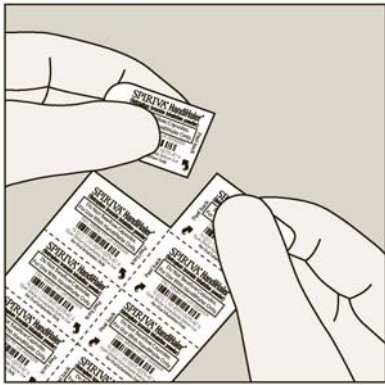


Figure B

Each SPIRIVA capsule is packaged in a blister. (See Figure B)

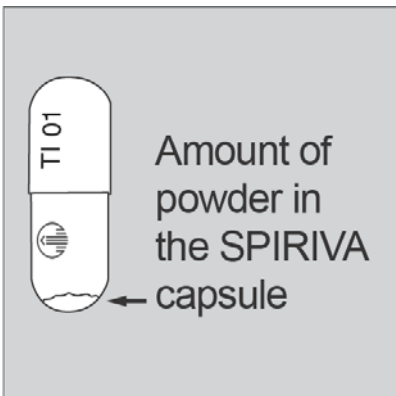


Figure C

- Each SPIRIVA capsule contains only a small amount of powder. (See Figure C) This is 1 full dose.
- **Do not open the SPIRIVA capsule** or it may not work.

Taking your full daily dose of medicine requires 4 main steps.

Step 1. Opening your HandiHaler device:

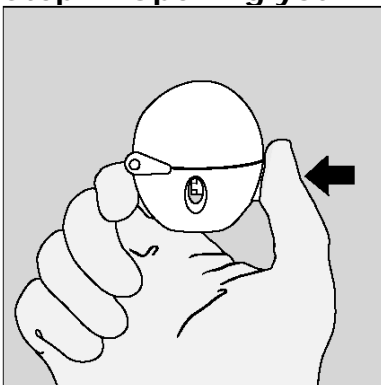


Figure D

After removing your HandiHaler device from the pouch:

- Open the dust cap (lid) by pressing the green piercing button. (See Figure D)

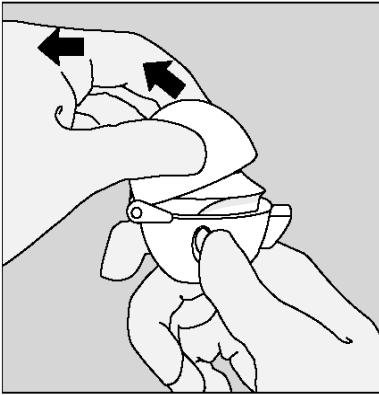


Figure E

- Pull the dust cap (lid) upwards away from the base to expose the mouthpiece. (See Figure E)

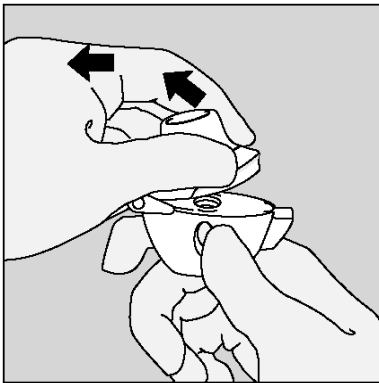


Figure F

- Open the mouthpiece by pulling the mouthpiece ridge up and away from the base so the center chamber is showing. (See Figure F)

Step 2. Inserting the SPIRIVA capsule into your HandiHaler device:

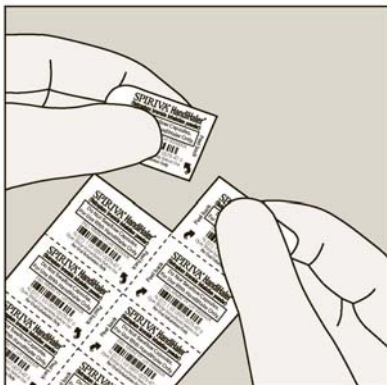


Figure G

Each day, separate only 1 of the blisters from the blister card by tearing along the perforated line. (See Figure G)



Figure H

Remove the SPIRIVA capsule from the blister:

- **Do not** cut the foil or use sharp instruments to take out the SPIRIVA capsule from the blister.
- Bend 1 of the blister corners with an arrow and separate the aluminum foil layers.
- Peel back the printed foil until you see the whole SPIRIVA capsule. (See Figure H)
- If you have opened more than 1 blister to the air, the extra SPIRIVA capsule should not be used and should be thrown away.

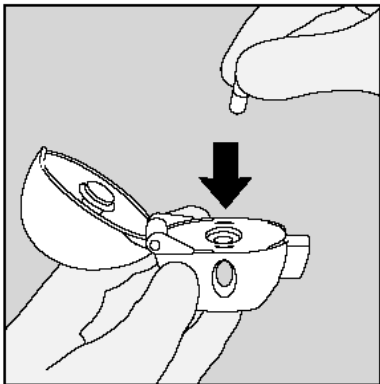


Figure I

Place the SPIRIVA capsule in the center chamber of your HandiHaler device. (See Figure I)

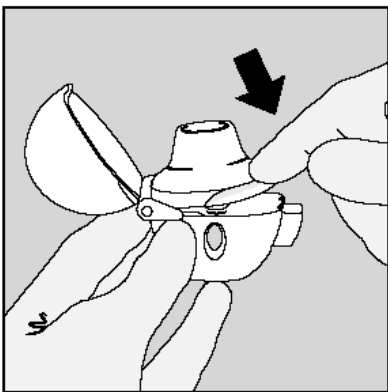


Figure J

Close the mouthpiece firmly against the gray base until you hear a click. Leave the dust cap (lid) open. (See Figure J)

Step 3. Piercing the SPIRIVA capsule:

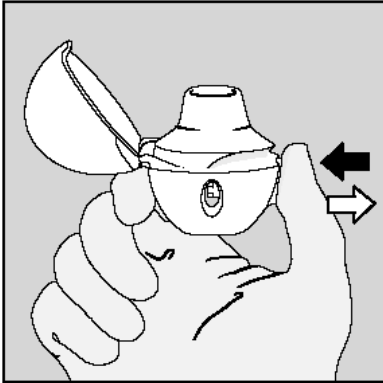


Figure K

- Hold your HandiHaler device with the mouthpiece pointed up. (See Figure K)
- Press the green piercing button once until it is flat (flush) against the base, then release. This is how you make holes in the SPIRIVA capsule so that you get your medicine when you breathe in.
- **Do not** press the green button more than one time.
- **Do not** shake your HandiHaler device.
- The piercing of the SPIRIVA capsule may produce small gelatin pieces. Some of these small pieces may pass through the screen of your HandiHaler device into your mouth or throat when you breathe in your medicine. This is normal. The small pieces of gelatin should not harm you.

Step 4. Taking your full daily dose (2 inhalations from the same SPIRIVA capsule):

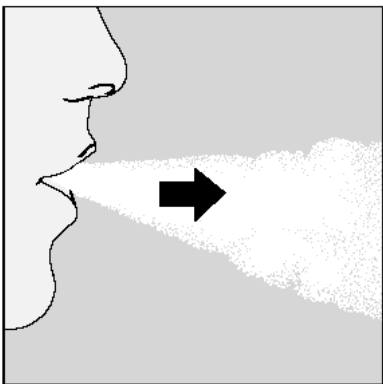


Figure L

Breathe out completely in 1 breath, emptying your lungs of any air. (See Figure L)

Important: Do not breathe into your HandiHaler device.

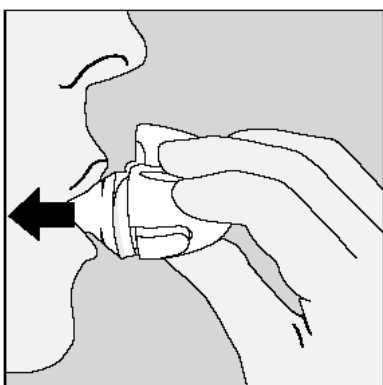


Figure M

With your next breath, take your medicine:

- **Hold your head in an upright position while you are looking straight ahead.** (See Figure M)
- Raise your HandiHaler device to your mouth in a horizontal position. **Do not** block the air intake vents.
- Close your lips tightly around the mouthpiece.
- **Breathe in deeply** until your lungs are full. You should **hear or feel the SPIRIVA capsule vibrate** (rattle). (See Figure M)
- Hold your breath for a few seconds and, at the same time, take your HandiHaler device out of your mouth.
- Breathe normally again.

The rattle tells you that you breathed in correctly. If you do not hear or feel a rattle, see the section, "If you do not hear or feel the SPIRIVA capsule rattle as you breathe in your medicine."

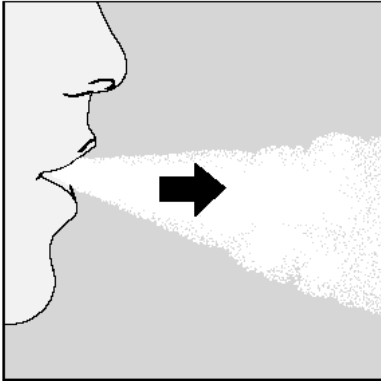


Figure N

To get your full daily dose, you must again, breathe out completely (See Figure N) and for a second time, breathe in (See Figure O) from the same SPIRIVA capsule.

Important: Do not press the green piercing button again.

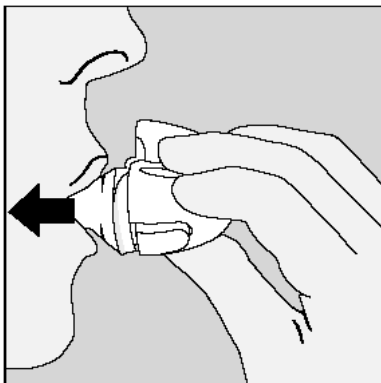


Figure O

Remember: To get your full medicine dose each day, you must breathe in 2 times from the same SPIRIVA capsule. Make sure you breathe out completely each time before you breathe in from your HandiHaler device.

Caring for and storing your SPIRIVA HandiHaler:

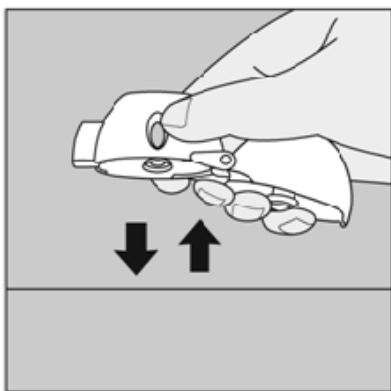


Figure P

- After taking your daily dose, open the mouthpiece and tip out the used SPIRIVA capsule into your trash can, without touching it.
- Remove any SPIRIVA capsule pieces or SPIRIVA powder buildup by turning your HandiHaler device upside down and gently, but firmly, tapping it. (See Figure P) Then, close the mouthpiece and dustcap for storage.
- **Do not** store your HandiHaler device and SPIRIVA capsules (blisters) in a damp moist place. Always store SPIRIVA capsules in the sealed blisters.

If you do not hear or feel the SPIRIVA capsule rattle as you breathe in your medicine:

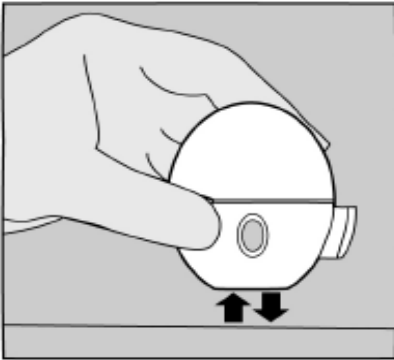


Figure Q

Do not press the green piercing button again.

Hold your HandiHaler device with the mouthpiece pointed up and tap your HandiHaler device gently on a table. (See Figure Q)

Check to see that the mouthpiece is completely closed. Breathe out completely before deeply breathing in again with the mouthpiece in your mouth. (See Figure O)

If you still do not hear or feel the SPIRIVA capsule rattle after repeating the above steps:

- Throw away the SPIRIVA capsule.
- Open the base by lifting the green piercing button and check the center chamber for pieces of the SPIRIVA capsule. SPIRIVA capsule pieces in the center chamber can cause a SPIRIVA capsule not to rattle.
- Turn your HandiHaler device upside down and gently, but firmly, tap to remove the SPIRIVA capsule pieces. Call your doctor for instructions.

Cleaning your HandiHaler device:



Figure R

Clean your HandiHaler device as needed. (See Figure R)

- **It takes 24 hours to air dry your HandiHaler device** after you clean it.
- **Do not** use cleaning agents or detergents.
- **Do not** place your HandiHaler device in the dishwasher for cleaning.

Cleaning Steps:

- Open the dust cap and mouthpiece
- Open the base by lifting the green piercing button.
- Look in the center chamber for SPIRIVA capsule pieces or powder buildup. If seen, tap out.
- Rinse your HandiHaler device with warm water, pressing the green piercing button a few times so that the center chamber and the piercing needle is under the running water. Check that any powder buildup or SPIRIVA capsule pieces are removed.
- Dry your HandiHaler device well by tipping the excess water out on a paper towel. Air-dry afterwards, leaving the dust cap, mouthpiece, and base open by fully spreading it out so that it dries completely.
- **Do not** use a hair dryer to dry your HandiHaler device.
- **Do not** use your HandiHaler device when it is wet. If needed, you may clean the outside of the mouthpiece with a clean damp cloth.

Helpful Hints to help ensure that you are properly taking your full daily dose of SPIRIVA HandiHaler:

- **Press** the green piercing button **1 time**; **Breathe in 2 times**; **Breathe out completely** before each of the **2** inhalations.
- Always use the new HandiHaler device provided with your medicine.
- Keep your HandiHaler device with the mouthpiece pointed up when pressing the green piercing button.
- **Press the green piercing button 1 time** to pierce the SPIRIVA capsule.
- Do not breathe out into your HandiHaler device.
- Keep your HandiHaler device in a horizontal position and keep your head upright, looking straight ahead, when breathing in.
- Check the center chamber of your HandiHaler device for SPIRIVA capsule pieces or powder build-up. If pieces or powder are seen, tap out before use.
- Clean your HandiHaler as needed and dry thoroughly.

For more information, ask your doctor or pharmacist, or go to www.spiriva.com or call 1-800-542-6257.

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

Marketed by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA
and
Pfizer Inc
New York, NY 10017 USA

Licensed from:
Boehringer Ingelheim International GmbH

SPIRIVA® and HandiHaler® are registered trademarks and are used under license from
Boehringer Ingelheim International GmbH.

Copyright 2012 Boehringer Ingelheim International GmbH
ALL RIGHTS RESERVED

Revised: March 2012

IT1600ABC192012
10004551/10

IT5300F
75740-05