

ATTENTION PHARMACIST: Detach “Patient Information” and “Patient’s Instructions for Use” from package insert and dispense with the product.

Spiriva®
HandiHaler®
(tiotropium bromide
inhalation powder)



Do Not Swallow Spiriva Capsules

For Use With HandiHaler Device Only

FOR ORAL INHALATION ONLY

Rx only

Prescribing Information

DESCRIPTION

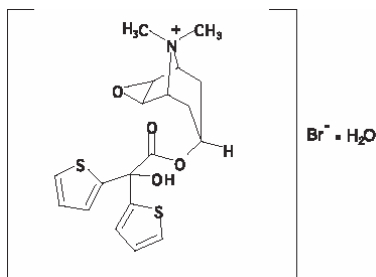
SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder) consists of a capsule dosage form containing a dry powder formulation of tiotropium intended for oral inhalation only with the HandiHaler device.

Each light green, hard gelatin SPIRIVA capsule contains 18 mcg tiotropium (equivalent to 22.5 mcg tiotropium bromide monohydrate) blended with lactose monohydrate 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 $C_{19}H_{22}NO_4S_2Br \cdot H_2O$.

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 (2L total). In a study of 26 adult patients with chronic obstructive pulmonary disease (COPD) and severely compromised lung function [mean FEV₁ 1.02 L (range 0.45 to 2.24 L); 37.6% of predicted (range 16%–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.

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's Instructions for Use**).

CLINICAL PHARMACOLOGY

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 were dose-dependent and lasted longer than 24 hours. The bronchodilation following inhalation of tiotropium is predominantly a site-specific effect.

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. Food is not expected to influence the absorption of tiotropium for the same reason. Oral solutions of tiotropium have an absolute bioavailability of 2–3%. Maximum tiotropium plasma concentrations were observed five minutes after inhalation.

Distribution

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

Biotransformation

The extent of biotransformation 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 bind 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.

Elimination

The terminal elimination half-life of tiotropium is between 5 and 6 days following inhalation. Total clearance was 880 mL/min after an intravenous dose in young healthy volunteers with an inter-individual variability of 22%. Intravenously administered tiotropium is mainly excreted unchanged in urine (74%). After dry powder inhalation, urinary excretion is 14% of the dose, the remainder being mainly non-absorbed drug in the gut which is 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 2–3 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. Therefore, no clinically significant interaction occurred between tiotropium and cimetidine or ranitidine.

Electrophysiology

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 30–60 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 ≥ 60 msec.

Special Populations

Elderly 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 AUC_{0-4} after dry powder inhalation), which was not significant when considered in relation to inter- and intra-individual variability (see **DOSAGE AND ADMINISTRATION**).

Hepatically-impaired Patients

The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied. However, hepatic insufficiency is not expected to have relevant influence on tiotropium pharmacokinetics. Tiotropium is predominantly cleared by renal elimination (74% in young healthy volunteers) and by simple non-enzymatic ester cleavage to products that do not bind to muscarinic receptors (see **DOSAGE AND ADMINISTRATION**).

Renally-impaired Patients

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 ($CrCl$ 50–80 mL/min), which is often seen in elderly patients, increased tiotropium plasma concentrations (39% increase in AUC_{0-4} after

intravenous infusion). In COPD patients with moderate to severe renal impairment (CrCl <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 (see **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS**).

CLINICAL STUDIES

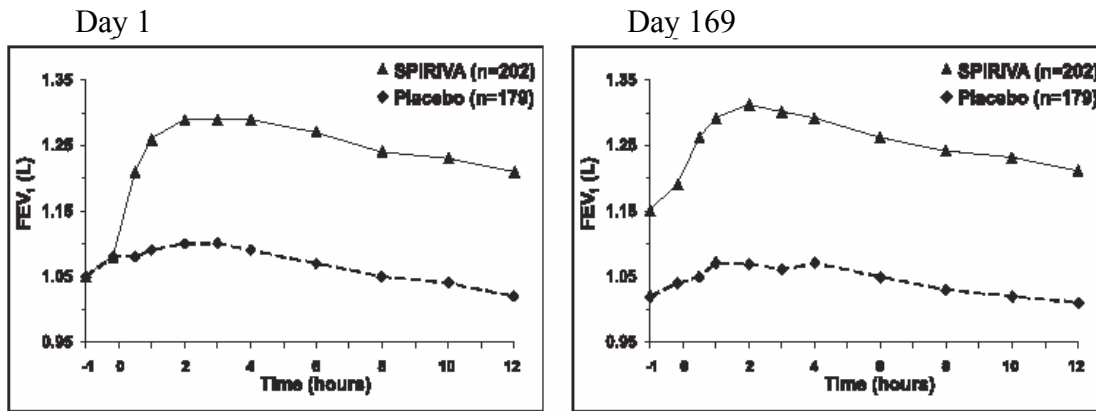
The SPIRIVA HandiHaler (tiotropium bromide inhalation powder) clinical development program consisted of six Phase 3 studies in 2,663 patients with COPD (1,308 receiving SPIRIVA HandiHaler): two 1-year, placebo-controlled studies, two 6-month, placebo-controlled studies and two 1-year, ipratropium-controlled 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 an 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 (forced expiratory volume in one second, FEV₁), with peak effect occurring within 3 hours following the first dose.

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 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.

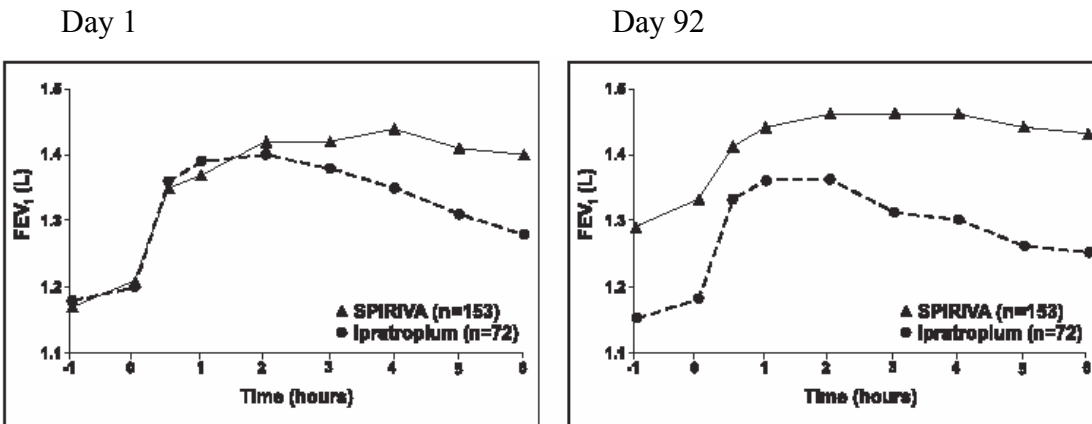
Figure 1 Mean FEV₁ Over Time (prior to and after administration of study drug) on Days 1 and 169 for Trial A (a Six-Month Placebo-Controlled Study)*



* 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 last observation or least favorable observation carried forward.

Results of each of the one-year ipratropium-controlled trials were similar to the results of the one-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 three months of observation. The data for the remaining patients were imputed using 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.

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.

CONTRAINDICATIONS

SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder) is contraindicated in patients with a history of hypersensitivity to atropine or its derivatives, including ipratropium, or to any component of this product.

WARNINGS

SPIRIVA HandiHaler (tiotropium bromide inhalation powder) 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.

Immediate hypersensitivity reactions, including angioedema (including swelling of the lips, tongue or throat), itching, and rash 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.

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

PRECAUTIONS

General

As an anticholinergic drug, SPIRIVA HandiHaler (tiotropium bromide inhalation powder) may potentially worsen symptoms and signs associated with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction and should be used with caution in patients with any of these conditions.

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 (see **CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Renally-impaired Patients**).

Information for Patients

It is important for patients to understand how to correctly administer SPIRIVA capsules using the HandiHaler device (see **Patient's Instructions for Use**). SPIRIVA capsules should only be administered via the HandiHaler device and the HandiHaler device should not be used for administering other medications. **The contents of SPIRIVA capsules are for oral inhalation only and must not be swallowed.**

SPIRIVA capsules should always be stored in sealed blisters. Remove only one SPIRIVA capsule immediately before use, or its effectiveness may be reduced. Additional SPIRIVA capsules that are exposed to air (i.e., not intended for immediate use) should be discarded.

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. Should any of these signs and symptoms develop, consult a physician immediately. Miotic eye drops alone are not considered to be effective treatment.

Care must be taken not to allow the powder to enter into the eyes as this may cause blurring of vision and pupil dilation.

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.

Drug Interactions

SPIRIVA HandiHaler has been used concomitantly with other drugs commonly used in COPD without increases in adverse drug reactions. These include short-acting and long-acting sympathomimetic (beta-agonists) bronchodilators, methylxanthines, and oral and inhaled steroids. However, the co-administration of SPIRIVA HandiHaler with other anticholinergic-containing drugs (e.g., ipratropium) has not been studied and is therefore not recommended.

Drug/Laboratory Test Interactions

None known.

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 25, 35, and 0.5 times the Recommended Human Daily Dose (RHDD) 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 RHDD on a mg/m² basis). No such effects were observed at 0.009 mg/kg/day (approximately 4 times than the RHDD 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 RHDD on a mg/m² basis). These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

Pregnancy

Pregnancy Category C.

No evidence of structural alterations 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 recommended human daily dose (RHDD) on a mg/m² basis. 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 RHDD 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 RHDD 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 RHDD on a mg/m² basis, respectively. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

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.

Use in Labor and Delivery

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

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.

Pediatric Use

SPIRIVA HandiHaler is approved for use in the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. This disease does not normally occur in children. The safety and effectiveness of SPIRIVA HandiHaler in pediatric patients have not been established.

Geriatric Use

Of the total number of patients who received SPIRIVA HandiHaler in the 1-year clinical trials, 426 were <65 years, 375 were 65–74 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.

ADVERSE REACTIONS

Of the 2,663 patients in the four 1-year and two 6-month controlled clinical trials, 1,308 were treated with SPIRIVA HandiHaler (tiotropium bromide inhalation powder) at the recommended dose of 18 mcg once a day. Patients with narrow-angle glaucoma, or symptomatic prostatic hypertrophy or bladder outlet obstruction were excluded from these trials.

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, increased heart rate, blurred vision, glaucoma (new onset or worsening), urinary difficulty, and urinary retention.

Four multicenter, 1-year, controlled studies evaluated SPIRIVA HandiHaler in patients with COPD. Table 1 shows all adverse events 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 events in the ipratropium-controlled trials is included for comparison.

Table 1 Adverse Experience Incidence (% 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				
Accidents	13	11	5	8
Chest Pain (non-specific)	7	5	5	2
Edema, Dependent	5	4	3	5
Gastrointestinal System Disorders				
Abdominal Pain	5	3	6	6
Constipation	4	2	1	1
Dry Mouth	16	3	12	6
Dyspepsia	6	5	1	1
Vomiting	4	2	1	2
Musculoskeletal System Disorders				
Myalgia	4	3	4	3
Resistance Mechanism Disorders				
Infection	4	3	1	3
Moniliasis	4	2	3	2
Respiratory System (upper)				
Epistaxis	4	2	1	1
Pharyngitis	9	7	7	3
Rhinitis	6	5	3	2
Sinusitis	11	9	3	2
Upper Respiratory Tract Infection	41	37	43	35
Skin and Appendage Disorders				
Rash	4	2	2	2
Urinary System Disorders				
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 events that occurred in the SPIRIVA HandiHaler group at a frequency of 1–3% 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 events 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 **PRECAUTIONS, Geriatric Use**).

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

The following adverse reactions have been identified during worldwide post-approval use of SPIRIVA HandiHaler: application site irritation (glossitis, mouth ulceration, and pharyngolaryngeal pain), dizziness, dysphagia, epistaxis, hoarseness, intestinal obstruction including ileus paralytic, intraocular pressure increased, oral candidiasis, palpitations, pruritus, tachycardia, throat irritation, and urticaria.

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 post-marketing 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 (tiotropium bromide inhalation powder) 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 7,300, 120,000, and 850 times the recommended human daily 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.

DOSAGE AND ADMINISTRATION

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 section).

The recommended dosage of SPIRIVA HandiHaler (tiotropium bromide inhalation powder) is the inhalation of the contents of one SPIRIVA capsule, once-daily, with the HandiHaler device (see “**Patient Information**” and “**Patient’s Instructions for Use**”).

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 (see **CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations** and **PRECAUTIONS**).

HOW SUPPLIED

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

Storage

Store at 25°C (77°F); excursions permitted to 15°–30°C (59°–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.

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SPIRIVA® (tiotropium bromide inhalation powder) is covered by U.S. Patent Nos. RE38,912, RE39,820, 5,478,578, 6,777,423, 6,908,928, 7,070,800, and 7,309,707 with other patents pending. The HandiHaler® inhalation device is covered by U.S. Design Patent No. D355,029 with other patents pending.

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Rev: March 2009

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. SPIRIVA HandiHaler should only be inhaled by 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 that you use one time every day (a maintenance medicine) to control symptoms of chronic obstructive pulmonary disease (COPD). 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 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.

SPIRIVA HandiHaler has not been studied in children.

Who should not take SPIRIVA HandiHaler?

Do not use SPIRIVA HandiHaler if you:

- are allergic to any of the ingredients in SPIRIVA capsules.
- have had an allergic reaction to atropine or any medicines like it, such as ipratropium (Atrovent®).

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.

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 “Patient’s 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 “Patient’s 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.

What are the possible side effects of SPIRIVA HandiHaler?

SPIRIVA HandiHaler can cause serious side effects. If you get any of the following side effects, stop taking SPIRIVA HandiHaler and get medical help right away.

- **Allergic reaction.** Symptoms may include: itching, rash, swelling of the lips, tongue, or throat (trouble swallowing).
- **Sudden narrowing and blockage of the airways into the lungs (bronchospasm).** Your breathing suddenly gets worse.
- **New or worsened increased pressure in the eyes (glaucoma).** Symptoms of acute narrow-angle glaucoma may include: eye pain, blurred vision, seeing halos (visual halos) or colored images along with red eyes.

Common side effects with SPIRIVA HandiHaler include:

- dry mouth
- constipation
- upper respiratory infection
- increased heart rate
- blurry vision
- glaucoma (new onset or worsening)
- trouble passing urine

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 [68°–77°F (20°–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, you may also call 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.

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SPIRIVA® (tiotropium bromide inhalation powder) is covered by U.S. Patent Nos.
RE38,912, RE39,820, 5,478,578, 6,777,423, 6,908,928, 7,070,800, and 7,309,707 with

other patents pending. The HandiHaler® device is covered by U.S. Design Patent No. D355,029 with other patents pending.

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Revised March 2009

Patient's Instructions for Use

Spiriva®
HandiHaler®
(tiotropium bromide
inhalation powder)



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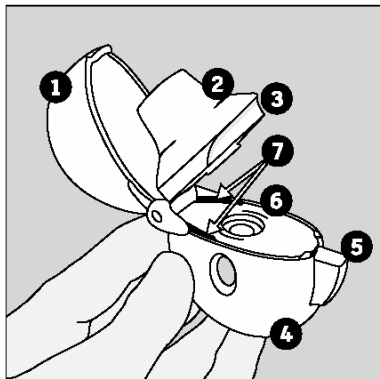
First read the Patient Information that comes with SPIRIVA HandiHaler for important information about using SPIRIVA HandiHaler.

Read these Patient's Instructions for Use before you start to use SPIRIVA HandiHaler and each time you refill your prescription. There may be new information.

For more information, ask your healthcare provider or pharmacist.

SPIRIVA HandiHaler comes with SPIRIVA capsules and a HandiHaler device. The HandiHaler device is an inhalation device that is for use only with SPIRIVA capsules. Do not use the HandiHaler device to take any other medicine.

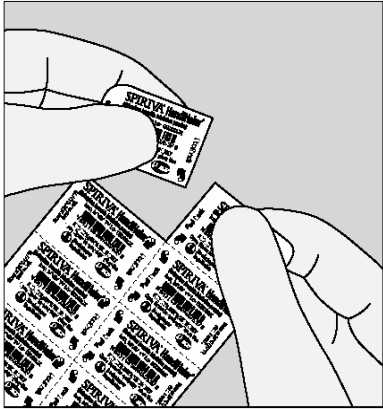
Becoming familiar with SPIRIVA HandiHaler:



Remove the HandiHaler device from the pouch and become familiar with its components. (Figure A)

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

Figure A



Each SPIRIVA capsule is packaged in a blister. Each blister can be separated from the blister card by tearing along the perforation. (Figure B)

Figure B

How do I take my SPIRIVA HandiHaler using the HandiHaler device?

Taking your dose of medicine using the HandiHaler device has four main steps:

1. **Open** the HandiHaler device and the blister
2. **Insert** the SPIRIVA capsule
3. **Press** the green piercing button
4. **Breathe in (inhale)** your medicine

(See below for details)

Opening the HandiHaler device:

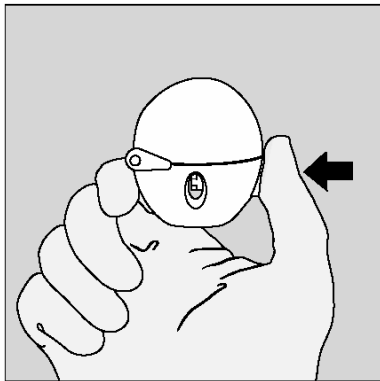


Figure 1

1. Open the dust cap by pressing the green piercing button. (Figure 1)



Figure 2

Pull the dust cap upwards to expose the mouthpiece. (Figure 2)

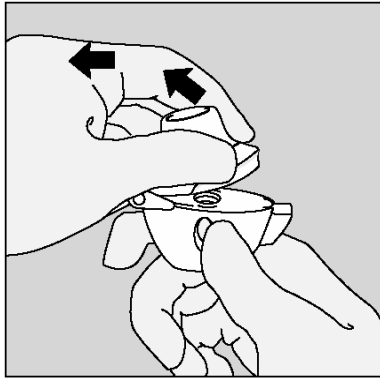


Figure 3

Open the mouthpiece by pulling the mouthpiece ridge upwards away from the base. (Figure 3)

Removing a SPIRIVA capsule:

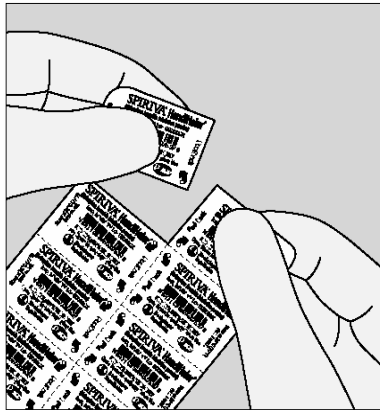


Figure 4

Before removing a SPIRIVA capsule from the blister, separate one of the blisters from the blister card by tearing along the perforation. (Figure 4)

Do not swallow Spiriva capsules.

Always store SPIRIVA capsules in the sealed blisters. Remove only one SPIRIVA capsule from the blister right before use. Do not store SPIRIVA capsules in the HandiHaler device. Inhale the contents of the SPIRIVA capsule using the HandiHaler device right away after the blister packaging of an individual SPIRIVA capsule is opened, or else it may not work as well.

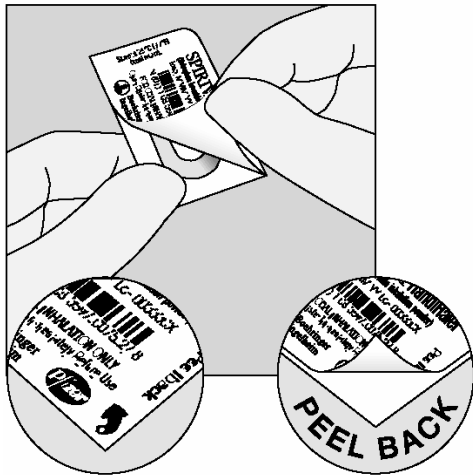


Figure 5

Right before you are ready to use your SPIRIVA HandiHaler:

Bend back and forth one of the corners of the blister that has an arrow and then with your finger separate the aluminum foil layers. Carefully peel back the printed foil until you can see the whole SPIRIVA capsule. (Figure 5)

Turn the blister upside down and tip the SPIRIVA capsule out, tapping the back of the blister, if needed.

Do not cut the foil or use sharp instruments to take out the SPIRIVA capsule from the blister.

If more SPIRIVA capsules are opened to air, they should not be used and should be thrown away.

Inserting the SPIRIVA capsule into the HandiHaler device:

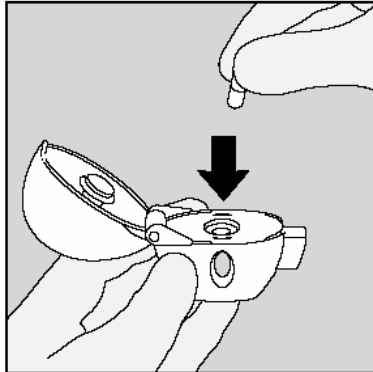


Figure 6

2. Insert (put) the SPIRIVA capsule in the center chamber of the HandiHaler device. It does not matter which end of the SPIRIVA capsule you put in the chamber. (Figure 6)

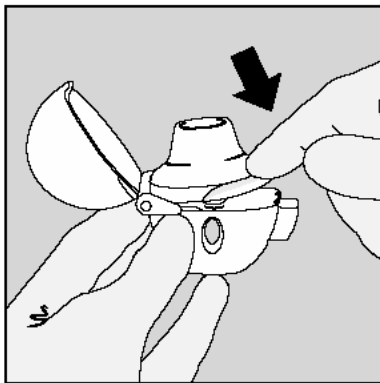


Figure 7

Close the mouthpiece **until you hear a click**, but leave the dust cap open. (Figure 7)

Be sure that you have the mouthpiece sitting firmly against the gray base.

Taking your dose using the HandiHaler device:

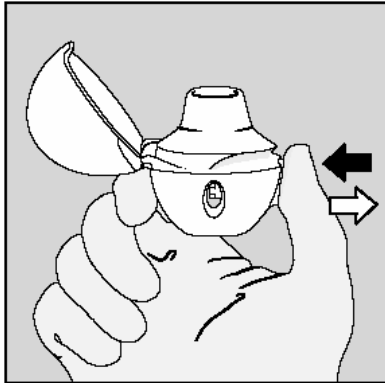


Figure 8

Hold the HandiHaler device with the mouthpiece upright. It is important that you hold the HandiHaler device in an upright position (Figure 8) when pressing the green piercing button.

3. Press the green piercing button until it is flat (flush) against the base, and release. This is how you make holes in the SPIRIVA capsule so that you get the medicine when you breathe in.

Do not press the green button more than one time.

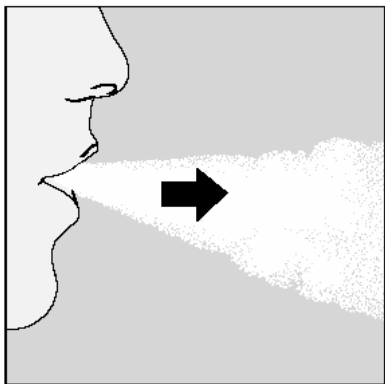


Figure 9

Breathe out completely. (Figure 9)

Important: Do not breathe (exhale) into the mouthpiece of the HandiHaler device at any time.

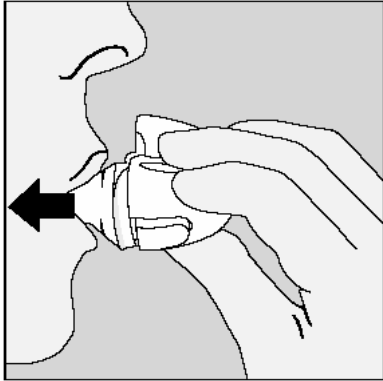


Figure 10

4. Breathe in (inhale)

- Hold the HandiHaler device by the gray base. Do not block the air intake vents.
- Raise the HandiHaler device to your mouth and close your lips tightly around the mouthpiece.
- **Keep your head in an upright position. The HandiHaler device should be in a horizontal position.** (Figure 10)
- Breathe in **slowly and deeply** so that you **hear or feel the SPIRIVA capsule vibrate.**
- Breathe in until your lungs are full.
- Hold your breath as long as is comfortable and at the same time take the HandiHaler device out of your mouth. Breathe normally again.

To make sure you get the full dose, you must breathe out completely, and inhale again as in step 4 above (Figure 10). Do not press the green piercing button again.

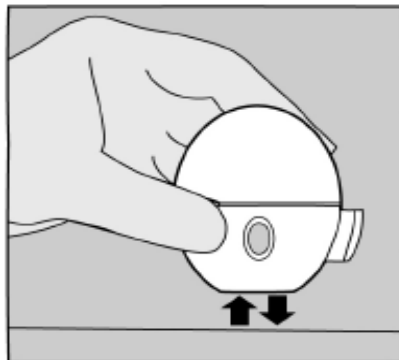


Figure 11

If you do not hear or feel the SPIRIVA capsule vibrate, **do not press the green piercing button again.** Instead, hold the HandiHaler device in an upright position and tap the HandiHaler device gently on a table. (Figure 11)

Check to see that the mouthpiece is completely closed. Then, breathe in again – slowly and deeply.

If you still do not hear or feel the SPIRIVA capsule vibrate 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 fragments). SPIRIVA capsule fragments in the center chamber can cause a SPIRIVA capsule not to vibrate. Turn the HandiHaler device upside down and gently tap to remove the SPIRIVA capsule fragments. Call your doctor for instructions.

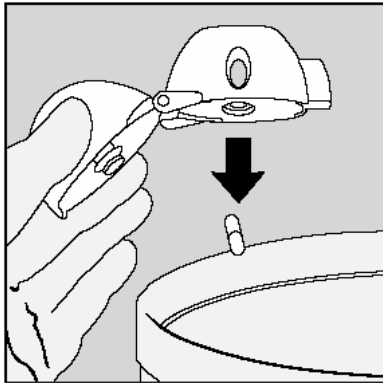


Figure 12

After you finished taking your daily dose of SPIRIVA HandiHaler, open the mouthpiece again. Tip out the used SPIRIVA capsule and throw it away. (Figure 12)

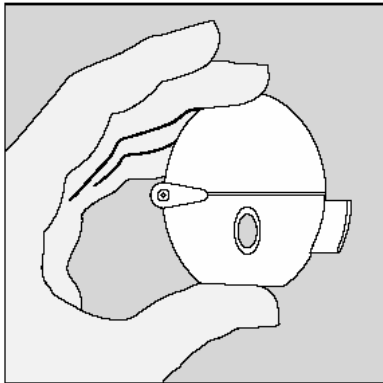


Figure 13

Close the mouthpiece and dust cap for storage of your HandiHaler device. (Figure 13)

Do not store used or unused SPIRIVA capsules in the HandiHaler device.

When and how should I clean my HandiHaler Device?

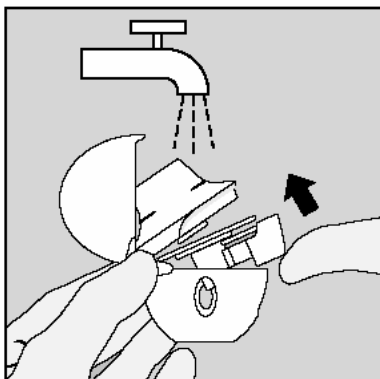


Figure 14

Clean the HandiHaler device one time each month or as needed. (Figure 14)

- Open the dust cap and mouthpiece.
- Open the base by lifting the green piercing button.
- Look at the center chamber for SPIRIVA capsule fragments or powder residue.
- Rinse the HandiHaler device with warm water. Check that any powder buildup or SPIRIVA capsule fragments are removed.
- Do not use cleaning agents or detergents.
- Do not place the HandiHaler device in the dishwasher for cleaning.
- Dry the HandiHaler device well by tipping the

excess water out on a paper towel. Air-dry afterwards, leaving the dust cap, mouthpiece, and base open.

- Do not use a hair dryer to dry the HandiHaler device.
- **It takes 24 hours to air dry, so clean the HandiHaler device right after you use it so that it will be ready for your next dose.**
- Do not use the HandiHaler device when it is wet. If needed, you may clean the outside of the mouthpiece with a clean damp cloth.

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