PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**SPIRIVA®**

Tiotropium inhalation powder capsules

Inhalation powder capsules, 18 mcg tiotropium (as tiotropium bromide monohydrate), Oral Inhalation

Bronchodilator (Long-Acting Muscarinic Antagonist (LAMA))

Capsules to be used only with the supplied HandiHaler® inhalation device

ATC R03BB04

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RECENT MAJOR LABEL CHANGES

4 Dosage and Administration	04/2022
7 Warnings and Precautions	04/2022

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Sections or subsections that are not applicable at the time of authorization are not listed .

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

SPIRIVA (tiotropium bromide monohydrate) is indicated for:

- long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

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

1.1 Pediatrics

- Pediatrics (< 18 years of age): Safety and effectiveness of SPIRIVA in patients less than 18 years of age were not studied.

1.2 Geriatrics

- Geriatrics (≥ 65 years of age): No dose adjustment is required for patients 65 years of age or older.

2 CONTRAINDICATIONS

- SPIRIVA (tiotropium bromide monohydrate) is contraindicated in patients with a history of hypersensitivity to tiotropium bromide, atropine or its derivatives (e.g. ipratropium), or to any component of this product (see 7 WARNINGS AND PRECAUTIONS and 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Counselling by doctors on smoking cessation should be the first step in treating patients with COPD, who smoke, independent of the clinical presentation i.e. chronic bronchitis (with or without airflow limitation) or emphysema. Cessation of smoking produces dramatic symptomatic benefits and has been shown to confer a survival advantage.
- Elderly patients, hepatically impaired patients, and renally impaired patients can use SPIRIVA at the recommended dose. However, as with all renally excreted drugs, SPIRIVA use should be monitored closely in patients with moderate to severe renal impairment.
- SPIRIVA should not be used for the initial treatment of acute episodes of bronchospasm. Patients should be prescribed a rapid onset, short duration inhaled bronchodilator to relieve acute symptoms such as shortness of breath and be advised to have this available for use at all times.
- Patients should be made aware that for optimum benefit, SPIRIVA must be used regularly, even when asymptomatic.

- There is no experience with SPIRIVA in infants and children and therefore should not be used in this age group.

4.2 Recommended Dose and Dosage Adjustment

- The recommended dosage of SPIRIVA is oral inhalation of the contents of one capsule (18 mcg) once daily using the HANDIHALER inhalation device.
- **The capsule must not be swallowed**.

Pediatrics (< 18 years of age): SPIRIVA should not be used in patients under 18 years of age.

Geriatrics (≥ 65 years of age): No dose adjustment is required for patients 65 years of age or older.

4.4 Administration

SPIRIVA should be administered once daily, at the same time of day, by oral inhalation only through the HANDIHALER inhalation device.

When prescribing SPIRIVA, patients should be instructed on the correct use of the HANDIHALER inhalation device. Patients who do not experience improvement in breathing should be asked if they are swallowing the medicine rather than inhaling it (see PATIENT MEDICATION INFORMATION).

4.5 Missed Dose

Patients should be advised that if they forget to take a dose, they should take one as soon as they remember but do not take two doses at the same time or on the same day. Then take the next dose as usual.

Patients should be advised that if they take more SPIRIVA 18 microgram than they should – talk to their doctor immediately.

5 OVERDOSAGE

High doses of tiotropium bromide may lead to signs and symptoms of exaggerated anticholinergic effects, such as constipation, voiding difficulties or increased intraocular pressure causing pain, vision disturbances or reddening of the eye. Should signs of serious anticholinergic toxicity appear, vital signs should be carefully monitored and appropriate therapy should be initiated.

There were no systemic anticholinergic adverse effects following a single inhaled dose of up to 282 mcg tiotropium in healthy volunteers. Additionally, no relevant adverse effects, beyond bilateral conjunctivitis and dry mouth were observed following 7 day dosing with up to 141 mcg tiotropium/day in healthy volunteers, (which resolved while still under treatment). In a multiple dose study in COPD patients with a maximum daily dose of 36 mcg tiotropium over four weeks, dry mouth was the only observed adverse event attributable to tiotropium.

Accidental Ingestion

Acute intoxication by inadvertent oral ingestion of SPIRIVA capsules is unlikely since the drug has a low oral bioavailability.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral Inhalation	capsule / 18 mcg / equivalent to 22.5 mcg tiotropium bromide monohydrate	gelatin, lactose monohydrate (which contains milk protein)

SPIRIVA capsules, containing 18 mcg tiotropium (equivalent to 22.5 mcg tiotropium bromide monohydrate), are light green, with TI 01 printed on one side of the capsule and the Boehringer Ingelheim company logo on the other side. SPIRIVA capsules also contain lactose monohydrate (which contains milk protein) as a "carrier". The dry powder within the capsule is intended for oral inhalation only.

SPIRIVA capsules are partially filled but contain exact amount of medication as declared on the label.

Ten SPIRIVA capsules are packaged in an aluminum/PVC/aluminum blister card. One blister card consists of two 5-cavity strips joined along a perforated line.

The following pack types are available:

- Carton of 30 SPIRIVA capsules (3 blister cards) and one HANDIHALER device.
- Carton of 10 SPIRIVA capsules (1 blister card) and one HANDIHALER device.

Refill packs:

- Carton of 30 SPIRIVA capsules (3 blister cards)

INHALATION DEVICE

The HANDIHALER inhalation device is a reusable plastic device used for the administration of SPIRIVA capsules. It is gray colored with "HandiHaler®", "Boehringer Ingelheim", and the Boehringer Ingelheim company logo, printed on the front face.

The HANDIHALER operates with flow rates as low as 20 L/min. *All patients, regardless of their disease severity, achieved sufficient flows through the HANDIHALER.* To use the delivery

system, a SPIRIVA capsule is placed in the centre chamber of the HANDIHALER inhalation device and the capsule is pierced by pressing and releasing the green piercing button on the side of the device. The tiotropium formulation is dispersed into the air stream when the patient inhales slowly and deeply through the mouthpiece.

The HANDIHALER inhalation devices are available individually.

7 WARNINGS AND PRECAUTIONS

General

SPIRIVA capsules contains 5.5 mg of lactose monohydrate per capsule. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Not for Acute Use

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

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

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

COPD Deterioration

SPIRIVA should not be initiated in patients with acutely deteriorating COPD (over a period of hours or days), which may be a life-threatening condition.

If SPIRIVA no longer controls the symptoms of bronchoconstriction, or the patient's inhaled, short-acting beta-2 agonist becomes less effective or the patient needs more inhalation of a short-acting bronchodilator than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dosage of SPIRIVA beyond the recommended dose is not appropriate in this situation.

Excessive Use

SPIRIVA should not be used more frequently than once daily or at higher doses than recommended. SPIRIVA should not be administered concomitantly with other medicines containing a long-acting muscarinic antagonist, as this has not been studied, and an overdose may result.

Anticholinergic Effects

Like other anticholinergic drugs, SPIRIVA should be used with caution in patients with symptomatic prostatic hyperplasia, narrow-angle glaucoma (see Ophthalmologic) or urinary retention (see Renal).

Cardiovascular

Cardiovascular effects, such as cardiac arrhythmias (e.g. atrial fibrillation and tachycardia), may be seen after the administration of muscarinic receptor antagonists (see 8 ADVERSE REACTIONS).

Tiotropium should be used with caution in patients with recent myocardial infarction < 6 months; any unstable or life threatening cardiac arrhythmia or cardiac arrhythmia requiring intervention or a change in drug therapy in the past year; hospitalisation due to heart failure within the past year. These patients were excluded from the clinical trials and these conditions may be affected by the anticholinergic mechanism of action.

Driving and Operating Machinery

No studies on the effects on the ability to drive and use machines have been performed. The occurrence of dizziness or blurred vision may influence the ability to drive and use machinery.

Immune

Hypersensitivity

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

There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder products containing lactose (with probable traces of milk protein); therefore, SPIRIVA should be used with caution in patients with severe milk protein allergy.

Ophthalmologic

Worsening of Narrow-Angle Glaucoma (see Anticholinergic Effects).

SPIRIVA should be used with caution in patients with narrow-angle glaucoma. Patients should be cautioned to avoid getting the drug powder into their eyes. They should be advised that this may result in precipitation or worsening of narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician

immediately should any of these signs or symptoms develop. Miotic drops alone are not considered to be effective treatment.

Renal

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

Worsening of Urinary Retention (see Anticholinergic Effects).

SPIRIVA 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.

Reproductive Health: Female and Male Potential

- **Fertility**

Clinical data on fertility are not available for tiotropium. A non-clinical study performed with tiotropium showed no indication of any adverse effect on fertility (see 16 NON-CLINICAL TOXICOLOGY).

Respiratory

Paradoxical bronchospasm

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

7.1 Special Populations

7.1.1 Pregnant Women

Pregnant Women: There is a limited amount of data from the use of tiotropium in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see 16 NON-CLINICAL TOXICOLOGY). Because animal reproduction studies are not always predictive of human response, SPIRIVA should be used during pregnancy only if the benefits outweigh any possible risk to the unborn child.

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

7.1.2 Breast-feeding

Based on lactating rodent studies, a small amount of tiotropium (1.9%) is excreted in milk over two days. Clinical data from nursing women exposed to SPIRIVA are not available. SPIRIVA should not be used in nursing women unless the expected benefit outweighs any possible risk to the infant.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

No dose adjustment is required in patients 65 years of age and older.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adverse reactions to SPIRIVA are similar in nature to reactions to other anticholinergic bronchodilators. Many of the listed undesirable effects can be assigned to the anticholinergic properties of SPIRIVA.

In controlled clinical studies, the commonly observed undesirable effects were anticholinergic undesirable effects such as dry mouth which occurred in approximately 4% of patients. In 28 clinical trials, dry mouth led to discontinuation in 18 of 9647 tiotropium treated patients (0.2 %).

Other undesirable effects consistent with anticholinergic effects include palpitations, supraventricular tachycardia, atrial fibrillation, blurred vision, glaucoma, constipation and intestinal obstruction including ileus paralytic as well as urinary retention.

An increase in anticholinergic effects may occur with increasing age.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Of the 1456 patients in the four one-year controlled clinical trials, 1207 patients in the two six-month controlled clinical trials and 5993 patients in the four year trial, 906, 402 and 2986 patients, respectively, were treated with SPIRIVA at the recommended dose of 18 mcg once a day.

One-year studies

Four multi-centre, one-year, controlled studies have evaluated once daily doses of SPIRIVA in patients with COPD. The following table shows adverse events that occurred with a frequency of ≥ 3% in the SPIRIVA group in the placebo-controlled trials, and where the rates in the

SPIRIVA group exceeded placebo by ≥ 1%. The frequency of corresponding events in the ipratropium-controlled trials are included for comparison.

Table 2 Adverse event incidence (% patients) in one-year COPD clinical trials

	Placebo Controlled Studies Combined Data (Trials 205.114/117 & 205.115/208)		Ipratropium Controlled Studies Combined Data (Trials 205.122A/126A & 205.122B/126B)	
Body System Event	**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	5	3	6	6
Abdominal Pain	4	2	1	1
Constipation	16	3	12	6
Dry Mouth*	6	5	1	1
Dyspepsia	4	2	1	2
Vomiting				
Musculo-skeletal System				
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				
Urinary Tract Infection	7	5	4	2

* Dry mouth was usually mild and led to discontinuation of therapy in 0.3% of SPIRIVA treated patients.

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

Six month studies

Two multi-centre, six-month, salmeterol and placebo-controlled studies have evaluated once daily doses of SPIRIVA in patients with COPD. The following table shows adverse events where the frequency was ≥ 3% in the SPIRIVA 18 mcg once daily group and where the rates in the SPIRIVA group exceeded placebo by at least 1%.

Table 3 Adverse event incidence (% patients*) in six-month COPD clinical trials

	Combined Data (Trials 205.130 & 205.137)		
Body System Event	**SPIRIVA [n=402]**	**SALMETEROL [n=405]**	**PLACEBO [n=400]**
Body as a Whole			
Accidents	4.2	5.2	2.5
Back Pain	4.0	4.0	3.0
Headache	6.5	6.9	4.5
Influenza Like Symptoms	6.7	5.2	4.0
Gastrointestinal System Disorders			
Dry Mouth	8.2	1.7	2.3
Respiratory System (upper)			
Pharyngitis	4.5	3.5	3.0
Upper Respiratory Tract Infection	19.4	17.0	16.0
Respiratory System (lower)			
Coughing	5.2	5.9	3.5

* Percentages are calculated using total number of patients treated as the denominator.

Long-Term (4-year) Study

The long term effects of treatment with SPIRIVA was assessed in a four-year, multi-national, placebo-controlled trial (205.235) involving 5,993 patients with COPD, during which all patients were permitted to use all respiratory medications as prescribed by their health care providers other than inhaled anticholinergics. In total, there were 9,468 person-years of exposure to tiotropium and 8,746 person-years of exposure to placebo, which includes the 30 day follow-up period.

Adverse events were experienced by 93% of the tiotropium group and 92% of the placebo group. The proportion of patients who experienced serious adverse events was 52% in the tiotropium group and 50% in the placebo group. Fatal events during the treatment period occurred in 381 patients (12.8%) in the tiotropium group and 411 (13.7%) in the placebo group.

Given the duration of the trial and differences in discontinuation rates, comparisons between study drugs are most appropriately assessed by examination of exposure adjusted rates (i.e. incidence rates). Incidence rates of selected events are computed as the number of patients experiencing an event divided by the person years at risk. Time at risk is time of exposure + 30 days for subjects who did not experience a specific event, and time from start of treatment to onset of a specific event for subjects who experienced this event. Rates are presented per 100 person-years of time at risk to tiotropium or placebo.

The most common adverse events were COPD exacerbations (65% of patients), pneumonia (14% of patients), and dyspnea (14% of patients). The incidence rate per 100 person years for COPD exacerbation was 45.5 and 38.1 for placebo and tiotropium, respectively. The rate per 100 person years for pneumonia was 5.14 in placebo and 4.94 in tiotropium group (Table 4).

Table 4 Frequency [N (%)] of patients with adverse events occurring with incidence of preferred term > 3% – using collapsed tiotropium preferred terms[1] - treated set (Trial 205.235)

	Tiotropium N=2986		Placebo N=3006	
	N (%)	IR[2]	N (%)	IR[2]
Total with adverse events	2764 (92.6)		2774 (92.3)	
COPD exacerbations	1934 (64.8)	38.1	1986 (66.1)	45.5
Pneumonia	433 (14.5)	4.94	418 (13.9)	5.14
Dyspnoea	364 (12.2)	4.09	443 (14.7)	5.49
Nasopharyngitis	373 (12.5)	4.33	324 (10.8)	4.06
Upper respiratory tract infection	298 (10.0)	3.38	290 (9.6)	3.57
Hypertension	275 (9.2)	3.08	284 (9.4)	3.45
Bronchitis	232 (7.8)	2.57	233 (7.8)	2.82
Cough	238 (8.0)	2.64	213 (7.1)	2.57
Back pain	198 (6.6)	2.18	188 (6.3)	2.25
Urinary tract infections	190 (6.4)	2.08	169 (5.6)	2.00
Sinusitis	194 (6.5)	2.14	160 (5.3)	1.90
Influenza	158 (5.3)	1.73	158 (5.3)	1.87
Headache	171 (5.7)	1.88	136 (4.5)	1.61
Oedema	145 (4.9)	1.57	130 (4.3)	1.52
Constipation	151 (5.1)	1.63	111 (3.7)	1.29
Diarrhoea	138 (4.6)	1.50	122 (4.1)	1.43
Cataract	120 (4.0)	1.30	123 (4.1)	1.45
Atrial Fibrillation	119 (4.0)	1.28	113 (3.8)	1.32
Mouth dry	152 (5.1)	1.68	80 (2.7)	0.93
Depression	131 (4.4)	1.42	98 (3.3)	1.14
Insomnia	131 (4.4)	1.42	91 (3.0)	1.06
Arthralgia	125 (4.2)	1.36	94 (3.1)	1.10
Benign prostatic hyperplasia	122 (4.1)	1.32	96 (3.2)	1.12
Rhinitis	101 (3.4)	1.09	112 (3.7)	1.32
Abdominal pain	113 (3.8)	1.22	96 (3.2)	1.12
Respiratory failure	88 (2.9)	0.94	120 (4.0)	1.39
Hypercholesterolaemia	104 (3.5)	1.12	97 (3.2)	1.13
Nausea	93 (3.1)	1.00	94 (3.1)	1.09
Dizziness	103 (3.4)	1.11	81 (2.7)	0.94

[1] tiotropium preferred terms include multiple MedDRA preferred terms, [2] incidence rate per 100 person years

Other than lung cancer, serious adverse events reported by >1% of patients in either treatment group were either cardiac or respiratory in nature and are displayed in Table 5.

The most common reason for discontinuation from treatment was due to an exacerbation of a patient's underlying respiratory disease.

Table 5 Frequency [n (%)] and incidence rate (per 100 person years) of patients experiencing serious adverse events[1] reported by >1% of patients in any treatment group according to system organ (SOC) class during the treatment period (from first to last day of study drug + 30 days). (Trials 205.235)

	Tiotropium N = 2986		Placebo N = 3006	
	N (%)	IR	N (%)	IR
Cardiac SOC	322 (10.8)	3.56	350 (11.6)	4.22
Angina	48 (1.6)	0.51	31 (1.0)	0.36
Atrial fibrillation	69 (2.3)	0.74	67 (2.2)	0.77
Cardiac failure	57 (1.9)	0.61	42 (1.4)	0.48
Cardiac failure congestive	27 (0.9)	0.29	42 (1.4)	0.48
Coronary artery disease	20 (0.7)	0.21	32 (1.1)	0.37
Myocardial infarction	65 (2.2)	0.69	84 (2.8)	0.97
Respiratory (lower) SOC	911 (30.5)	11.32	985 (32.8)	13.47
Bronchitis	35 (1.2)	0.37	27 (0.9)	0.31
COPD exacerbation	688 (23.0)	8.19	742 (24.7)	9.70
Dyspnea	36 (1.2)	0.38	54 (1.8)	0.62
Pneumonia	296 (9.9)	3.28	290 (9.6)	3.46
Respiratory failure	85 (2.8)	0.90	113 (3.8)	1.31

[1] excluding lung cancer (multiple different terms)

Consolidated Safety Database

Pooled analysis of Tiotropium / HANDIHALER (Tio/HH) vs. Placebo studies

1) Clinical trial evidence. All Trial Participants.

Data included in this section are based on pooled data from 28 randomized placebo-controlled parallel group clinical trials in phase III and IV with treatment periods ranging between four weeks and four years. The cutoff date for these analyses was December 17, 2010. Adverse drug reactions were identified from data obtained in clinical trials. The clinical trial database includes 9,647 tiotropium patients, contributing 12,469 person years of exposure to tiotropium. Under each treatment, 'N with event' is the number of patients with the selected adverse drug reaction or adverse event.

The frequencies assigned to the undesirable effects listed below are based on crude incidence rates of adverse drug reactions (i.e. events attributed to tiotropium) observed in the tiotropium group (9,647 patients) from 28 pooled placebo-controlled clinical trials with treatment periods ranging from four weeks to four years.

Frequency is defined using the following convention:
Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

Table 6 Adverse drug reactions

MedDRA Preferred Term	**Frequency**
Metabolism and nutrition disorders	
Dehydration	Not known*
Nervous system disorders	
Dizziness	Uncommon
Insomnia	Rare
Eye disorders	
Vision blurred	Uncommon
Glaucoma	Rare
Intraocular pressure increased	Rare
Cardiac disorders	
Atrial fibrillation	Uncommon
Supraventricular tachycardia	Rare
Tachycardia	Rare
Palpitations	Rare
Respiratory, thoracic and mediastinal disorders	
Pharyngitis	Uncommon
Dysphonia	Uncommon
Cough	Uncommon
Bronchospasm	Rare
Epistaxis	Rare
Laryngitis	Rare
Sinusitis	Rare
Gastrointestinal disorders	
Dry mouth, usually mild	Common
Stomatitis	Rare
Gastrooesophageal reflux disease	Uncommon
Constipation	Uncommon

MedDRA Preferred Term	Frequency
Intestinal obstruction, including ileus paralytic	Rare
Gingivitis	Rare
Glossitis	Rare
Oropharyngeal candidiasis	Uncommon
Dysphagia	Rare
Skin and subcutaneous tissue disorders, Immune system disorders	
Rash	Uncommon
Urticaria	Rare
Pruritus	Rare
Hypersensitivity (including immediate reactions)	Rare
Angioedema	Rare
Skin infection, skin ulcer	Not known*
Dry skin	Not known*
Musculoskeletal and connective tissue disorders	
Joint swelling	Not known*
Renal and urinary disorders	
Dysuria	Uncommon
Urinary retention (usually in men with predisposing factors)	Uncommon
Urinary tract infection	Rare

*no events attributed to tiotropium in 9,647 tiotropium treated patients; however, events are considered adverse drug reactions associated with tiotropium

8.3 Less Common Clinical Trial Adverse Reactions

One-year studies

Other events that occurred in the SPIRIVA group at a frequency of 1 - 3% in the placebo-controlled trials and where the rates exceeded that in the placebo group include:

Body as a Whole: allergic reaction, leg pain;
Central and Peripheral Nervous System: dysphonia, paraesthesia;
Gastro-intestinal System Disorders: gastro-intestinal disorder not otherwise specified (NOS), gastroesophageal reflux, stomatitis (including ulcerative stomatitis);
Metabolic and Nutritional Disorders: hypercholesterolemia, hyperglycemia;
Musculo-Skeletal System Disorders: skeletal pain;
Myo Endo Pericardial and Valve Disorders: angina pectoris (including aggravated angina pectoris);

Psychiatric Disorder: depression;

Resistance Mechanism Disorders: herpes zoster;

Respiratory System Disorder (Upper): laryngitis;

Vision Disorder: cataract.

Adverse reactions with incidences > 0.1% and < 1% in excess of placebo include:

Cardiovascular system: tachycardia

Urinary system: difficulty urinating and urinary retention (in men with predisposing factors)

Hypersensitivity reactions: angio-oedema (1 of 906 patients in the four one-year trials).

As with other orally inhaled drugs, pharyngo-oral irritation and paradoxical bronchospasm were observed.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified primarily by reporting in the worldwide post-marketing experience of SPIRIVA: dysphonia, epistaxis, palpitations, dizziness, rash, urticaria, pruritus, atrial fibrillation, tachycardia.

Post-marketing adverse experiences also include rare reports of syncope/loss of consciousness, chest pain, myocardial infarction, angina pectoris, arrhythmia, and cardiac failure. 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.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Tiotropium is mainly excreted renally (approximately 74% of the intravenously administered dose). The remaining dose is mainly nonenzymatically cleared with a minor portion (<20% of intravenous dose) being metabolized by CYP2D6 and CYP3A4 (see 10.3 Pharmacokinetics Metabolism). Tiotropium does not inhibit cytochrome P450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, 3A4 even in supratherapeutic concentrations, which makes clinically relevant metabolic interactions with tiotropium unlikely.

9.4 Drug-Drug Interactions

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

Anticholinergics

The chronic co-administration of tiotropium bromide with other anticholinergic-containing

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

9.5 Drug-Food Interactions

Food is not expected to influence the absorption of tiotropium.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Tiotropium is a long acting muscarinic receptor antagonist (LAMA), also known as an anticholinergic. It has a similar affinity to the subtypes of muscarinic receptors M1 to M5. In the lungs, inhibition of M3-receptors at the smooth muscle results in relaxation of the airways. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. The M_3-receptor is the main muscarinic receptor subtype involved in the bronchoconstriction induced by acetylcholine. Among the other muscarinic receptor subtypes of known physiological relevance, M_2-receptors are responsible for the effects of parasympathetic inhibition of heart rate.

Tiotropium bromide is a quaternary ammonium molecule with duration of action sufficient to provide 24 hours of bronchoprotection with once-a-day inhalational administration.

The long duration of action of tiotropium is thought to be due to its slow dissociation kinetics from the muscarinic M_3-receptor subtype. Dissociation from M2-receptors is faster than from M3, which in functional in vitro studies, elicited (kinetically controlled) receptor subtype selectivity of M3 over M2. As an N-quaternary anticholinergic, tiotropium is topically selective when administered by inhalation to the lung. Pharmacological in vitro and in vivo studies profiled tiotropium as a potent, long acting bronchodilator suitable for a once-daily dose regimen.

10.2 Pharmacodynamics

Primary Pharmacodynamic Effects

The primary pharmacodynamic effect in subjects with COPD following inhalation of tiotropium is bronchodilation, which is primarily a site-specific, rather than a systemic effect. Tiotropium bromide, administered once daily in the COPD population, provided significant improvement

in lung function (forced expiratory volume in one second, FEV1 and forced vital capacity, FVC) within 30 minutes following the first dose which was maintained for 24 hours.

The time course of the effect of SPIRIVA was determined in a randomized, placebo-controlled 6-week clinical study that included spirometry measurements every 3 hours in 105 COPD patients.

SPIRIVA administered once daily provided significant improvement in lung function (forced expiratory volume in one second, FEV_1; and forced vital capacity, FVC) within 30 minutes following the first dose and was maintained for 24 hours whether SPIRIVA was administered in the morning or in the evening.

Repeated inhalation of SPIRIVA has not been linked with tolerance towards bronchodilatory effects of the drug.

Onset of Pharmacodynamic Steady State

Study results supported that pharmacodynamic steady state was attained within the first week of dosing with the majority of bronchodilation observed by the third day; additionally, the multiple dose studies supported the once daily dosing regimen for tiotropium administered by inhalation of a dry powder formulation.

Dose-ranging - Multiple-dose

A 9 mcg dose provided 75%, the 18 mcg dose provided 85%, and the 36 mcg dose provided 92% of the maximum effect. The data suggested that a dose of approximately 18 mcg was superior to lower doses and nearly as effective as a dose of approximately 36 mcg. The increased incidence of dry mouth at and above 36 mcg suggested that a lower dose would be preferable; thereby supporting the proposed dose of 18 mcg. The data also suggested that since the differences between the trough FEV_1 and average $FEV_{1(0\text{-}6\ hr)}$ response are minimal, a once a day dosing regimen for tiotropium appears to be appropriate.

Secondary Pharmacodynamic Effects

Studies with supratherapeutic doses have confirmed that reduced salivation is among the most sensitive effects. This clinical physiologic effect is mirrored by reports of dry mouth.

Cardiac Electrophysiology

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

The effect of tiotropium dry powder for inhalation on QT interval was also evaluated in a randomized, placebo- and positive-controlled crossover study in 53 healthy volunteers. Subjects received tiotropium inhalation powder 18 mcg, 54 mcg (3 times the recommended

dose), or placebo for 12 days. ECG assessments were performed at baseline and throughout the dosing interval following the first and last dose of study medication. Relative to placebo, the maximum mean change from baseline in study-specific QTc interval was 3.2 msec and 0.8 msec for tiotropium inhalation powder 18 mcg and 54 mcg, respectively. No subject showed a new onset of QTc >500 msec or QTc changes from baseline of ≥60 msec.

4-year Long Term Efficacy and Safety Study

The long term efficacy and safety of treatment with SPIRIVA was assessed in a four-year multi-centre, multi-national, double-blind, randomized, placebo-controlled, parallel-group clinical trial (205.235), involving 5,993 patients with moderate-severe COPD. The mean age of the patients was 65 ± 8 years (range 40 - 88 years) with a post bronchodilator FEV_1 of ≤ 70% of predicted at baseline.

The effect of SPIRIVA on the rate of decline in FEV_1 was investigated in patients with COPD who were permitted all therapy (including short-acting beta-agonists, long-acting beta-agonists, inhaled steroids, or theophyllines) other than inhaled anticholinergics drugs. Long-term outcomes of health-related quality of life, exacerbations, related hospitalizations and mortality were also evaluated.

Study results

SPIRIVA maintained improvements in FEV_1 throughout 4 years but did not alter the annualized rate of decline of FEV_1. There were no significant differences between treatment groups in the mean annual rate of decline for both of the co-primary efficacy endpoints (either pre-bronchodilator or post-bronchodilator FEV1) and FVC from day 30 to the end of treatment.

For mean pre-bronchodilator FEV_1, the estimated mean difference between tiotropium and control groups ranged from 87 to 103 ml (p-value<0.0001), Day 30 to Month 48, with an overall mean difference of 94 ml (p-value<0.0001).

Mortality data were captured as a safety endpoint. During treatment, there was a 16% reduction in the risk of death on SPIRIVA compared to control. The incidence rate of death was 4.10 per 100 patient years in the tiotropium group vs. 4.79 per 100 patient years in the control group. [Hazard Ratio (tiotropium/control) = 0.84, 95% CI = 0.73, 0.97]. The overall incidence of adverse events, including cardiac and respiratory AEs, was similar between SPIRIVA and placebo during the 4 year treatment period (Table 4 & 5).

SPIRIVA statistically significantly delayed the time to the first exacerbation (p <0.0001) and the time to first hospitalization for an exacerbation (p<0.0025). Based on the Kaplan-Meier estimates, median time to the first exacerbation was estimated to be 12.5 months and 16.7 months in placebo and tiotropium treated patients, respectively. The estimated number of COPD exacerbations per patient year was 0.85 (95% CI 0.81, 0.88) in the placebo group and 0.73 (95% CI 0.69, 0.76) in the tiotropium group. There was no difference in the number of COPD exacerbations leading to hospitalization per patient year between two treatment groups.

There was no treatment difference in the rate of decline of SGRQ scores. Statistically significant differences in favour of tiotropium were observed at all time points for the St. George's Respiratory Questionnaire (SGRQ) total score, activity score, impact score and symptom score (all p-value <0.015). A statistically significantly higher proportion of patients in the tiotropium compared to control groups achieved ≥ 4 unit improvements in the SGRQ total scores from baseline at years 1 (49.1% vs. 41.2%), 2 (47.5% vs. 39.0%), 3 (46.2% vs. 36.5%), and 4 years (44.9% vs. 36.3%) (p<0.001 for all).

HANDIHALER Flow Rate Characteristics in Patients with COPD

Twenty-six COPD patients with disease severity ranging from 16% to 65% of predicted normal FEV_1 participated in this study. Each patient used the HANDIHALER device containing a placebo capsule after being given the standard instructions to inhale slowly and deeply, but at a rate rapid enough to hear the capsule vibrate. Based on *in vitro* observations that capsule vibration and evacuation occurs at a rate of 20 L/min or greater, this was regarded as the minimal critical flow rate for patients to achieve. All 26 patients were able to achieve this flow rate and hear the capsule vibrate. The median inspiratory flow rate for all patients was 30 L/min with a range of 20.4 - 45.6 L/min. As such, the results indicate that COPD patients with a wide range of disease severity based on FEV_1, can generate the minimal required inspiratory flow rate (20 L/min) through the HANDIHALER necessary to vibrate the capsule and evacuate the powder from the capsules.

Evaluation of Mucociliary Clearance

As a class, systemically absorbed anticholinergic drugs have been reported to decrease mucociliary clearance. A study was conducted to investigate the effect of three (3) weeks of once daily inhaled tiotropium 18 mcg on tracheobronchial clearance (TBC) as assessed by radioaerosol technique in patients with COPD (n=37).

The data showed that once daily inhaled tiotropium resulted in improved penetration of radioaerosol but did not change TBC compared to baseline; however, TBC following tiotropium was apparently delayed compared to placebo. This difference however, was within the pre-specified limit for non-inferiority of tiotropium compared to placebo. The deeper penetration of radioaerosol is attributable to the effectiveness of tiotropium as a bronchodilator in patients with COPD. The deeper penetration of the aerosol particles influenced by the increased airway patency is the likely cause of the apparent slower TBC in the tiotropium group.

Severity of COPD

In COPD patients, disease severity is likely to be confounded with age effects and seems to have no relevant influence on tiotropium absorption.

10.3 Pharmacokinetics

Tiotropium bromide is a non-chiral quaternary ammonium compound and is sparingly soluble in water. It is administered via inhaler by dry powder inhalation. Generally with the inhaled route of administration, the majority of the delivered dose is deposited in the gastrointestinal

tract, and to a lesser extent in the intended organ of the lung. Some 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. Oral solutions of tiotropium have an absolute bioavailability of 2 - 3%. Food is not expected to influence the absorption of tiotropium. Maximum tiotropium plasma concentrations were observed 5 – 7 minutes after inhalation. At steady state, peak tiotropium plasma concentrations in COPD patients were 12.9 pg/mL and decreased rapidly in a multi-compartmental manner. Steady state trough plasma concentrations were 1.71 pg/mL and were reached by day 7, with no accumulation thereafter.

Distribution

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

Metabolism

The extent of biotransformation is small. This is evident from urinary excretion of approximately 74% of unchanged substance after an intravenous dose to young healthy volunteers. Tiotropium, an ester, is nonenzymatically cleaved to the alcohol N-methylscopine and dithienylglycolic acid, both of which do not bind muscarinic receptors.

In-vitro experiments with human liver microsomes and human hepatocytes suggest that some further drug (<20% of dose after intravenous administration) is metabolized by cytochrome P450 dependent oxidation and subsequent glutathione conjugation to a variety of Phase II-metabolites. This enzymatic pathway can be inhibited by the CYP450 2D6 (and 3A4) inhibitors, quinidine, ketoconazole and gestodene. Thus CYP450 2D6 and 3A4 are involved in the metabolic pathway that is responsible for the elimination of a smaller part of the dose. Tiotropium bromide even in supra-therapeutic concentrations does not inhibit cytochrome P450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1 or 3A in human liver microsomes.

Elimination

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

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

After dry powder inhalation to COPD patients to steady state, urinary excretion is 7% (1.3 mcg) of the unchanged dose over 24 hours, the remainder being mainly non-absorbed drug in gut that is eliminated via the faeces.

The renal clearance of tiotropium exceeds the creatinine clearance indicating secretion into

the urine. After chronic once daily inhalation by COPD patients, pharmacokinetic steady state was reached by day 7 with no accumulation thereafter.

Special Populations and Conditions

- **Pediatrics:** Pharmacokinetics in children were not investigated as tiotropium development is currently restricted to therapy for COPD in adults.
- **Geriatrics:** As expected for all predominantly renally excreted drugs, advanced age (≥ 65 years) was associated with a decrease of tiotropium renal clearance from 365 mL/min in COPD patients < 65 years to 271 mL/min in COPD patients ≥ 65 years. This did not result in a corresponding increase in $AUC_{0-6,ss}$ or $C_{max,ss}$ values.
- **Sex:** Based on a pooled analysis of pharmacokinetic data, the exposure to tiotropium was not found to differ by sex.
- **Hepatic Insufficiency:** The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied. However, impaired liver function is not expected to have any clinically relevant influence on tiotropium pharmacokinetics since tiotropium is predominantly cleared by renal elimination and by non-enzymatic ester cleavage to products that do not bind to muscarinic receptors.
- **Renal Insufficiency:** Once daily inhaled administrations of tiotropium to steady-state in COPD patients with mild renal impairment (creatinine clearance 60-< 90 ml/min) resulted in similar $AUC_{0-6,ss}$ and $C_{max,ss}$ values compared to patients with normal renal function. Moderate renal impairment (creatinine clearance 30- <60 mL/min) resulted in modestly higher $AUC_{0-6,ss}$ (approximately 54% higher) and $C_{max,ss}$ (approximately 15% higher) values compared to patients with COPD with normal renal function (creatinine clearance ≥ 90 mL/min).

  In patients with severe renal impairment (creatinine clearance <30 mL/min), a single intravenous administration of tiotropium bromide resulted in approximately 94% higher AUC_{0-4} and 52% higher C_{max} compared to patients with normal renal function.

Animal Pharmacology

Systemic effects of tiotropium are very limited as observed in safety pharmacology studies. Tiotropium induced, after parenteral administration (s.c. or i.v.), typical systemic peripheral anticholinergic effects: inhibition of salivary, lacrimal and gastric acid excretions, mydriasis, tachycardia and delayed intestinal transit. This was expected since most of the affected functions are controlled through muscarinic M_3- (salivary and lacrimal secretions, intestinal transit), and/or M_1- (gastric acid secretion, pupillary diameter) or M_2- (heart rate) receptor subtypes. At the parenteral dosages used, sufficient plasma concentrations of tiotropium are obtained that can block all three subtypes of muscarinic receptors. After inhalation administration, however, pharmacologically effective doses were shown to be devoid of systemic anticholinergic effects in both guinea pigs and dogs. The therapeutic window between bronchoprotection and inhibition of salivation is maintained even after repeated administration of tiotropium up to 14 days.

Similar peripheral anticholinergic effects were also observed after oral administration of tiotropium although equipotent oral doses were approximately 100-fold higher than parenteral doses. This indicates an extremely low absorption of tiotropium from the gastrointestinal tract.

A clear dissociation between bronchoprotective effects and the above mentioned systemic anticholinergic effects was observed after an administration by inhalation, demonstrating that a lung-selective cholinergic blockade can be obtained through this route of administration.

Pharmacodynamic interaction studies in anesthetized dogs revealed that the treatment with glucocorticoids did not interfere with the bronchodilatory action of tiotropium. Investigations with i.v. theophylline revealed a slight enhancement of the bronchodilatory effect of tiotropium. The bronchodilatory effect of tiotropium and salbutamol were additive in anesthetized dogs. In pregnant rats, excision studies at 10 mg/kg i.v. on day 12 or day 18 of pregnancy showed that while drug-related radioactivity crossed the placenta, the tissue and organ concentrations in the fetus were lower than in maternal tissue. The radioactivity in the fetus was eliminated rapidly. A single 10 mg/kg i.v. dose of [^{14}C] tiotropium administered to lactating rats resulted in milk: plasma radioactivity ratios of 0.4 (0.5 hour, first sampling time) to 18 at 24 hours and approximately 1.9 % of the dose was estimated to be excreted in the milk over two days. At least four metabolites were detected in milk, one of them identified as N-methylscopine.

11 STORAGE, STABILITY AND DISPOSAL

After opening a strip, the in-use shelf life of the remaining capsules in the strip is 5 days. If more than one capsule is exposed to air inadvertently, the exposed unused capsules must be discarded.

Temperature

Store capsules and HANDIHALER device between 15-25°C. Do not freeze.

Moisture

Protect from moisture.

12 SPECIAL HANDLING INSTRUCTIONS

SPIRIVA capsules should be used with the HANDIHALER inhalation device only. The HANDIHALER inhalation device should not be used with any other capsules.

The capsules should always be stored in the blister and only removed from the blister immediately before use.

Do not store SPIRIVA capsules in the HANDIHALER device.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

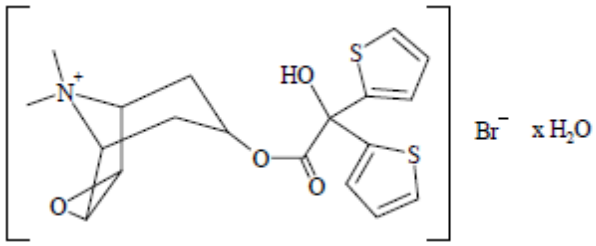
Drug Substance

Proper name: tiotropium bromide monohydrate

Chemical name: (1α,2β,4β,5α,7β)-7-[Hydroxydi-2-thienylacetyl)oxy]-9,9dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane bromide monohydrate

Molecular formula and molecular mass: $C_{19}H_{22}NO_4S_2Br \bullet H_2O$; 490.4

Structural formula:



Physicochemical properties:

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

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Chronic Obstructive Pulmonary Disease (COPD)

Table 7 - Summary of patient demographics for clinical trials in COPD

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
205.114/117, 205.115/208	Multi-centre, placebo-controlled, randomized, double-blind, parallel group	Tiotropium 18 mcg, once-daily oral inhalation, 1 year duration	Tiotropium n = 550 Placebo n = 371	65 years (39-87)	m&f
205.122A/126A, 205.122B/126B	Multi-centre, active controlled, randomized, double-blind, parallel group	Tiotropium 18 mcg, once-daily oral inhalation, 1 year duration	Tiotropium n = 356 Ipratropium n = 179	64 years (41-82)	m&f
205.130, 205.137	Multi-centre, active and placebo-controlled, randomized, double-blind, parallel group	Tiotropium 18 mcg, once-daily oral inhalation, six months duration	Tiotropium n = 402 Salmeterol n = 405 Placebo n = 400	64 years (39-87)	m&f

Long-term clinical trials (6 Months to 1 Year Trials)

Study demographics and trial design

The efficacy and safety of SPIRIVA were evaluated in six (6) Phase 3 studies in 2663 COPD patients with moderate to severe airway obstruction, 1308 receiving SPIRIVA: two 1-year, placebo-controlled studies, two 6-month, placebo-controlled studies and two 1-year, ipratropium-controlled studies. All studies were randomized, double-blind, (double-dummy-active control), controlled, parallel group studies which followed nearly identical protocols with identical patient inclusion and exclusion criteria. In all studies, tiotropium was administered as a once-daily inhaled dose of 18 mcg via the HANDIHALER inhalation device.

The main inclusion criteria were patients 40 years of age or older, diagnosis of COPD with screening $FEV_1 \leq 65\%$ of predicted normal, and a history of smoking of 10-pack years or more. The main exclusion criterion was significant disease other than COPD which in the opinion of

the investigator, precluded the patient's participation in this study.

Lung Function

For all 6 clinical trials, the primary efficacy parameter was trough FEV_1 as an index of bronchodilator efficacy.

In all studies, a single 18 mcg dose of SPIRIVA provided significant improvement in pulmonary function (mean FEV_1 increase of 11% or more) within 30 minutes following administration; the response reached a peak within 3 hours and was maintained for 24 hours.

Following one year treatment, SPIRIVA induced a sustained increase (> 120 mL) over baseline in trough FEV_1 (23 - 24 hrs post dose) with no evidence of tolerance. The difference in trough FEV_1 at the end of one year with SPIRIVA was 150 mL ($p < 0.001$).

In the two six-month studies, SPIRIVA performed consistently better than salmeterol in trough response over the 24 weeks of the study. The difference between SPIRIVA and salmeterol for trough response was not statistically significant in one of the six-month studies while in the other the difference was statistically significant.

A similar pattern of response was observed for FVC over the six-month and one-year treatment periods.

SPIRIVA improved morning and evening peak expiratory flow rate (PEFR) as measured by patients' daily recordings.

Use of SPIRIVA was associated with a reduced requirement for rescue bronchodilator medications. No age or sex-related differences in efficacy were observed.

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

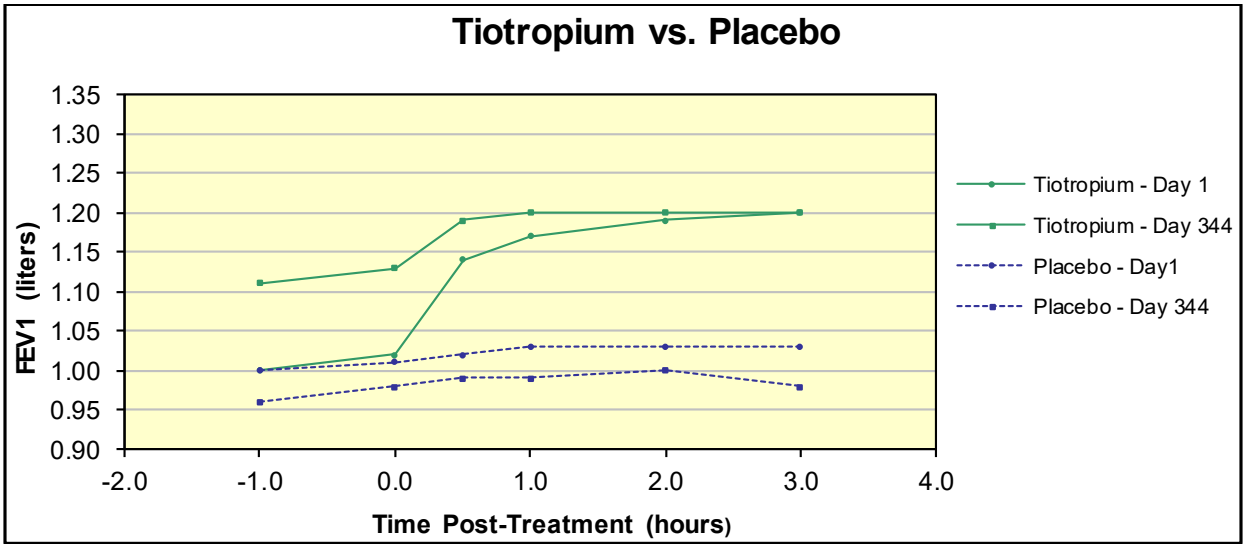


Figure 2 - Mean FEV_1 Over Time (prior to and after administration of study drug) on Days 1 and 364 in Two 1-Year Ipratropium-Controlled Trials

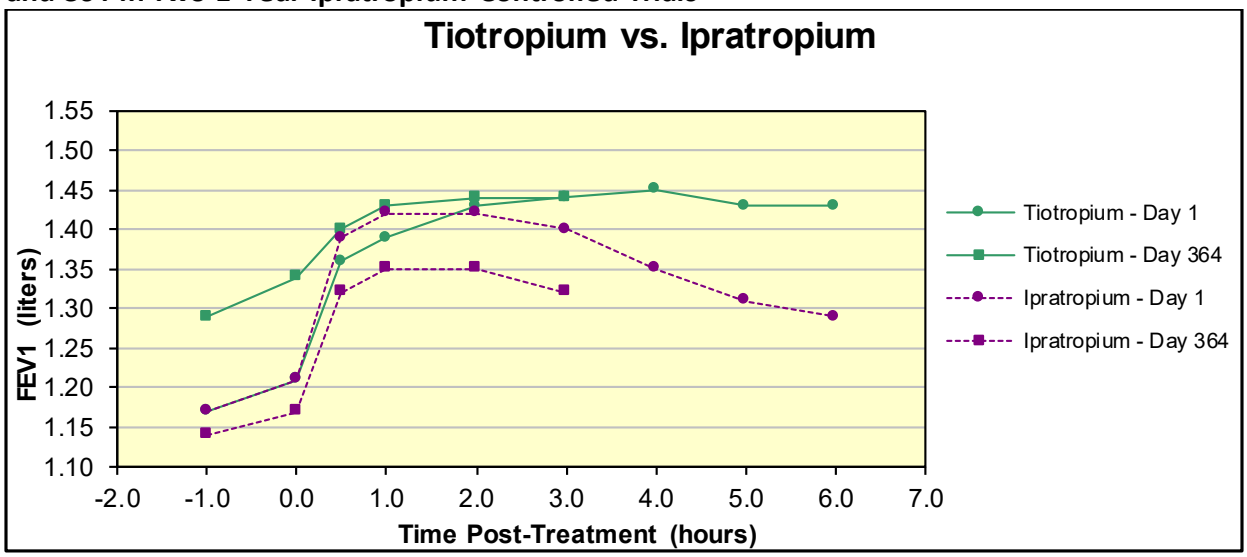
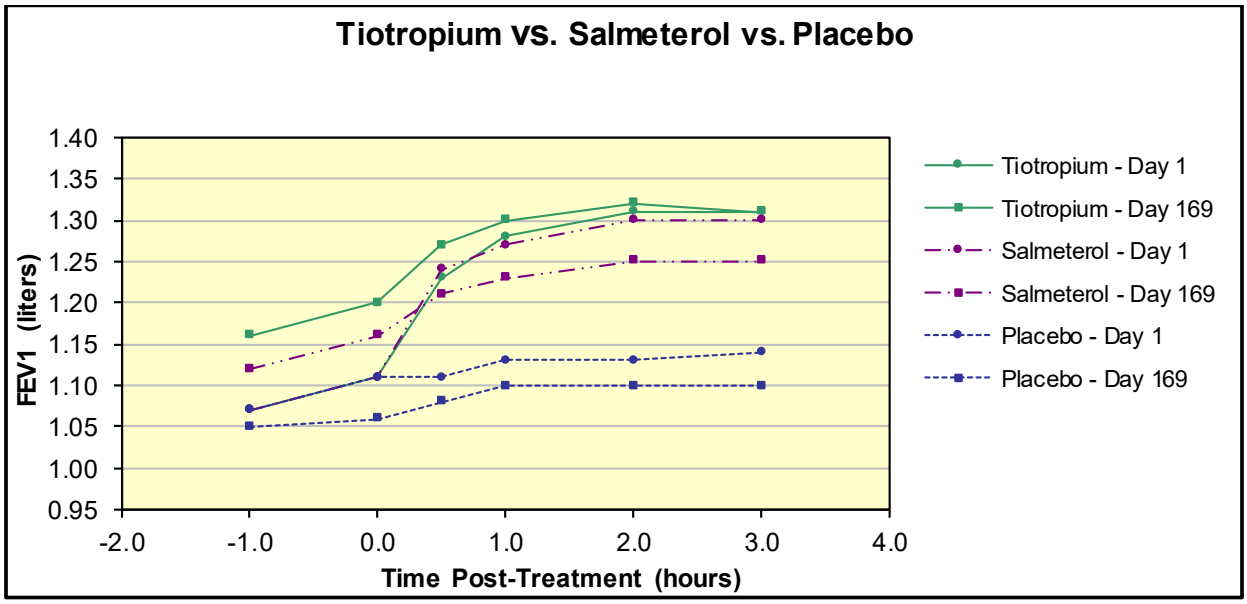


Figure 3 - Mean FEV_1 Over Time (prior to and after administration of study drug) on Days 1 and 169 in Two 6-Month Salmeterol- and Placebo-Controlled Trials



Dyspnea and Health-related Quality of Life

In addition to lung function, Transition Dyspnea Index (TDI), as an index of dyspnea, was measured in all six trials. TDI was a secondary variable in the four 1 year studies; the protocols of the two six-month studies were amended to include TDI as a co-primary variable after the trials were completed, but before the blind was broken. TDI focal score ≥ 1 was considered to

be clinically significant. The proportion of patients achieving a clinically meaningful response (responders) was compared.

Improvement in dyspnea as measured by TDI occurred within the first 8 days of treatment and was sustained over the one-year treatment period. In both the one-year and six-month trials, the proportion of patients achieving a clinically meaningful response (TDI focal score ≥ 1 was considered to be clinically significant and such patients were considered responders) was 46.0% and 43.1% for SPIRIVA, and 28.6% and 29.8% for placebo, respectively.

Improvement in disease-specific quality of life was assessed using the St. George's Respiratory Questionnaire. SPIRIVA improved health-related quality of life which was maintained over the treatment period.

Exercise Tolerance

Two multi-centre, double-blind, placebo-controlled trials were conducted to evaluate the efficacy and safety of 6 weeks of treatment with SPIRIVA in 459 patients with COPD. The primary efficacy endpoint was submaximal exercise tolerance as measured by endurance time (ET) to symptom limitation during constant work rate cycle exercise at 75% of maximal work capacity on day 42 of the randomized treatment phase.

Table 8 - Summary of patient demographics for clinical trials in exercise tolerance programme

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
205.131	Multi-centre, placebo-controlled, randomized, double-blind, parallel group	Tiotropium 18 mcg, once-daily oral inhalation, 6 weeks duration	Tiotropium n = 98 Placebo n = 100	60.5 (40-71)	m&f
205.223	Multi-centre, placebo-controlled, randomized, double-blind, parallel group	Tiotropium 18 mcg, once-daily oral inhalation, 6 weeks duration	Tiotropium n = 131 Placebo n = 130	62.6 (41-75)	m&f

Study results

The results of these trials showed that SPIRIVA significantly improved symptom-limited exercise tolerance by 102 seconds (geometric mean ET compared with placebo adjusted for baseline, p=0.0012) in Trial 205.131, and 100 seconds (median ET change from baseline compared with placebo, p=0.0003) in Trial 205.223. The increased endurance time was associated with a reduction in lung hyperinflation and dyspnea during exercise.

COPD Exacerbations

The effect of SPIRIVA on COPD exacerbations was investigated in a randomized, double-blind, placebo-controlled trial of 1,829 patients with COPD over a 6 month period. The study enrolled patients from one health care system (US Veterans Affairs). The mean age of these patients was 68 years and about 98.5% were male. At baseline, the mean FEV_1 was 1.04L and the mean predicted FEV_1 was 35.6%. About 29% of patients were using home oxygen at the entry of this study.

In this six month trial, a COPD exacerbation was defined as a complex of respiratory symptoms (increased or new onset) of more than one of the following: cough, sputum, wheezing, dyspnea or chest tightness with a duration of at least three days requiring treatment with antibiotics and/or systemic steroids and/or hospital admission (including ER visits greater than 24 hours). Although there is no consensus with respect to a definition of COPD exacerbation and its classification, the definition used in this trial has been used in a number of large clinical trials.

Study results

The results of this trial showed that SPIRIVA reduced the proportion of patients who experienced at least one COPD exacerbation (27.9% vs. 32.3%, p=0.0368) and reduced the number of exacerbations by 18.8% (0.853 vs. 1.051 events per patient year of exposure, p=0.0028) compared to placebo. Seven percent of patients in the SPIRIVA group and 9.5% of patients in the placebo group were hospitalized due to a COPD exacerbation (p=0.056).

Table 9 - Efficacy endpoint results of study 205.266 in COPD exacerbations

	Tiotropium N=914	Placebo N=915	P-value	Absolute difference and 95%CI
The percent of patients with a COPD exacerbation	27.9%	32.3%	0.0368	-4.4% (-0.1%, -8.7%)
Mean number of COPD exacerbations/patient-year	0.853	1.051	0.0028	-0.198 events per patient year of exposure

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity

The acute inhalation toxicity in mice, rats and dogs was low and independent of the formulation type used (aqueous aerosol, lactose powder). Non-lethal dosages produced clinical signs characteristic of the pharmacodynamic activity of tiotropium (mydriasis, dry mouth and nose) as well as non-specific signs of toxicity (dyspnea, tremor, ataxia, convulsions,

loss of motility and body weight). In mice, deaths occurred at 131 mg/kg tiotropium when administered as an aqueous aerosol through nose only exposure (the LD_{50}-value could not be established). No lethal dosage was achieved by the inhalation of either formulation in rats (LD_{50} > 334.5 mg/kg) or dogs (LD_{50} > 3.6 and > 0.7 mg/kg). Necropsy of decedents revealed pulmonary emphysema and/or congestion of liver and kidneys. No gross lesions were detected among survivors. The oral LD_{50} for mice and rats are 219,099 and 1,279,279 times respectively the maximum recommended human dose on a mg/m^2 basis.

Chronic Toxicity

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

Even low dosages induced signs characteristic of the anticholinergic activity of tiotropium; therefore, a No Observed Toxic Effect Level (NOTEL) could only be established in a limited number of studies. In the rat, the inhalation NOTEL was < 0.013 mg/kg and the inhalation NOTEL in the dog was > 0.010 mg/kg. The few changes that were perhaps unexpected include urogenital tract changes and cataracts in rats. The urogenital changes are nevertheless considered as sequelae to pharmacological effects and as such are part of a syndrome that includes the prostate. In view of the species-specificity of the syndrome and its harmless nature, it is unlikely to have any influence on human safety assessment. Similarly, although the precise mechanism remains unknown, cataract formation appears to be specific to Wistar rats and to the mode of administration. As the method of administration to the patient avoids direct eye exposure to tiotropium, any risk to patients is negligible.

Carcinogenicity:

Inhalation carcinogenicity studies in mice and rats have revealed no carcinogenic potential at target tiotropium doses up to 2.54, 180 and 75 mcg/kg/day (male mice, female mice and rats, respectively). These doses correspond to about 0.45, 92 and 27 times the maximum recommended human dose (MRHD) on a mg/m^2 basis.

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

Reproductive and Developmental Toxicology:

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

The NOTEL for maternal/paternal toxicity in the rat and rabbit was < 0.01 mg/kg Ba 679 BR and for developmental toxicity 0.01 mg/kg in all three segments when administered by inhalation.

In a general reproduction and fertility study in rats, there was no indication of any adverse effect on fertility or mating performance of either treated parents or their offspring at clinically relevant dosages.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]Spiriva®

Tiotropium Inhalation Powder Capsules

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

What is SPIRIVA used for?

SPIRIVA is used long-term in adults to manage airway blockage from chronic obstructive pulmonary disease (COPD; a lung disease that makes it hard to breathe). This can include chronic bronchitis (inflammation of the lungs) and emphysema (damage to parts of the lung known as alveoli).

SPIRIVA is **not** a rescue medicine and should **not** be used on an as needed basis for treating sudden severe symptoms of COPD (e.g., sudden breathing problems). Your healthcare professional may give you other medicines to use for sudden breathing problems.

How does SPIRIVA work?

SPIRIVA belongs to a class of medications known as long-acting muscarinic antagonist (LAMA) bronchodilators, also known as an anticholinergic. It works by relaxing the muscles around the airways in your lungs for 24 hours. When you inhale it, it makes it easier for you to breathe.

What are the ingredients in SPIRIVA?

Medicinal ingredient: Tiotropium bromide monohydrate.

Non-medicinal ingredients: Gelatin, and lactose monohydrate (which contains milk protein).

SPIRIVA comes in the following dosage forms:

Inhalation powder capsules: 18 mcg of tiotropium (as tiotropium bromide monohydrate).

Do not use SPIRIVA if:

- you are allergic to tiotropium bromide, atropine or its derivatives (such as ipratropium), or to other ingredients in SPIRIVA. If you are unsure ask your healthcare professional.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take SPIRIVA. Talk about any health conditions or problems you may have, including if you:

- are pregnant or plan to become pregnant;
- are breastfeeding or plan to breastfeed;
- are taking any medications including eye drops, this includes those you can buy without prescription;
- have difficulty urinating, which can include problems caused by an enlarged prostate;
- have eye pain caused by increased pressure in the eyes (narrow-angle glaucoma);
- have problems digesting certain milk sugars (e.g., galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption). SPIRIVA capsules contain lactose, a milk sugar. If you are unsure ask your healthcare professional;
- have kidney problems;
- have or have had heart problems.

Other warnings you should know about:

Eye problems: Avoid getting the SPIRIVA powder into your eyes. This may cause eye pain, discomfort, temporary blurring of vision, and/or coloured images in association with red eyes. These may be signs of acute narrow-angle glaucoma (eye pain caused by increased pressure in the eyes). If you develop any of these symptoms, consult a healthcare professional right away.

Driving and using machines: SPIRIVA can cause dizziness or blurred vision. Before you drive or do tasks that require special attention, wait until you know how you respond to SPIRIVA.

Monitoring: Your healthcare professional might monitor your health throughout your treatment with SPIRIVA. This can include monitoring your kidney and the development of sudden or worsening COPD symptoms.

Contact your healthcare professional immediately if:

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

See the **Serious side effects and what to do about them** table below for more information on these and other serious side effects.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with SPIRIVA:

- medicines similar to SPIRIVA (other short- or long-acting muscarinic antagonists) used for your lung disease may interact with SPIRIVA and increase the risk of experiencing possible side effects.

How to take SPIRIVA:

- SPIRIVA has been prescribed for you and should not be given to other people. Take SPIRIVA capsules exactly as your healthcare professional tells you to. Do not take more than once a day or exceed the prescribed dose. You should check with your healthcare professional if you are not sure.
- Your healthcare professional may also provide you with an inhaled short-acting bronchodilator for the treatment of COPD symptoms that may occur suddenly.
- The contents of the capsule must be inhaled once daily through the mouthpiece of the HANDIHALER inhalation device only. **Do NOT swallow the capsule!** The HANDIHALER device is especially designed for SPIRIVA and must **not** be used with any other capsules. Likewise, you should not take your SPIRIVA capsules with any inhalation device other than the HANDIHALER.
- Before starting your treatment with SPIRIVA, be certain that you are completely familiar with the use and proper care of the HANDIHALER device.

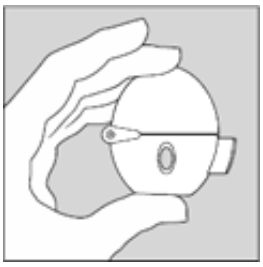
HANDIHALER Inhalation Device:

- The HANDIHALER inhalation device enables you to inhale the medicine contained in the SPIRIVA capsule that your healthcare professional has prescribed for your breathing problems.
- After first use, you can use your HANDIHALER device for up to one-year to take your medication before needing a replacement.
- If you are unable to inspire through the HANDIHALER device to make the SPIRIVA capsule vibrate, consult your healthcare professional.

How to Use the HANDIHALER Inhalation Device and SPIRIVA:

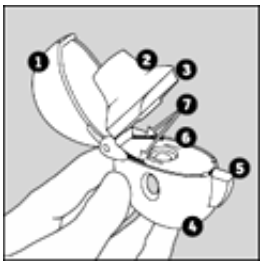
Preparation:

1. Become familiar with the HANDIHALER device.



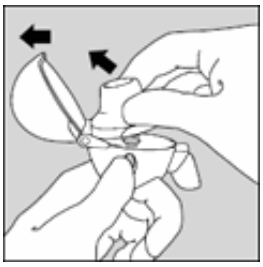
HANDIHALER device parts:

❶ Dust cap
❷ Mouthpiece
❸ Mouthpiece ridge
❹ Base
❺ Piercing button
❻ Centre chamber
❼ Air intake vents



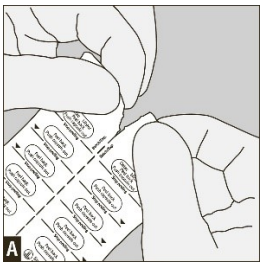
2. To release the dust cap, press the green piercing button completely in and let go.

3. Open the dust cap completely by pulling it upwards, then open the mouthpiece by pulling it upwards.

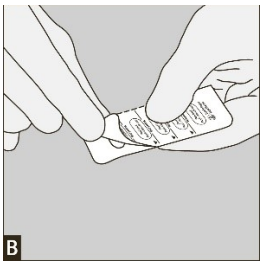


Blister Handling:

4A. The blister card contains two blister strips (5 capsules each) joined along a perforated line. Prior to removing the first capsule from the blister card, separate the SPIRIVA blister strips by tearing along the perforation.

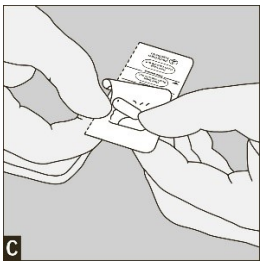


4B. **Immediately** before use, peel the aluminum back foil until **one** capsule is fully visible. After opening a strip, the in-use shelf life of the remaining capsules in the strip is 5 days.



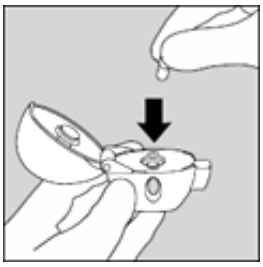
4C. Remove **one** SPIRIVA capsule from the blister. Do not expose more than one capsule. If more than one capsule is exposed, you should discard the exposed unused capsules. Do **not** store the capsule in the HANDIHALER device.

SPIRIVA capsules are partially filled but contain exact amount of medication as declared on the label.

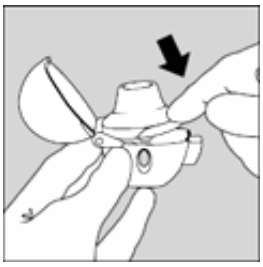


Administration:

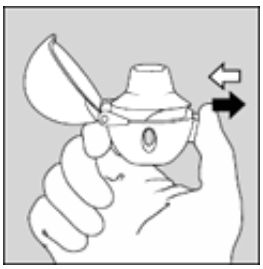
5. Place the capsule in the centre chamber. It does not matter which end of the capsule is placed in the chamber.



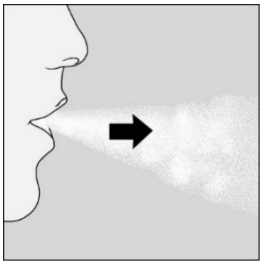
6. Close the mouthpiece **firmly until you hear a click**, leaving the dust cap open.



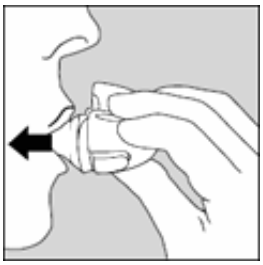
7. **Hold the HANDIHALER with the mouthpiece upwards and press the green piercing button completely in only once, and release**. This makes holes in the capsule and allows the medication to be released when you breathe in. The piercing of the SPIRIVA capsule may produce small gelatin pieces. Some of 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.



8. If you feel that your chest is congested with mucus, try to cough to clear your lungs before you inhale SPIRIVA. Breathe out completely.
Important: Do not breathe into the mouthpiece at any time.



9. Hold the HANDIHALER by the grey base. **Do not block the air intake vents**. Raise the HANDIHALER to your mouth and close your lips tightly around the mouthpiece. Keep your head in an upright position and breathe in slowly and deeply but at a rate **sufficient to hear or feel the capsule vibrate**. Breathe in until your lungs are full; then hold your breath as long as comfortable (try counting to 10) and at the same time take the HANDIHALER out of your mouth. Resume normal breathing.



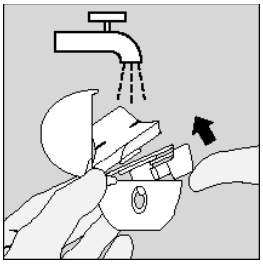
10. **To ensure complete inhalation of capsule contents, you must repeat steps 8 and 9 once again.**

11. Open the mouthpiece again. Tip out the used capsule and dispose. Do not touch the used capsules. If the dry powder gets on your hands, make sure you wash your hands thoroughly.

12. Close the mouthpiece and dust cap for storage of your HANDIHALER device.

Cleaning:
It is important to clean the HANDIHALER once a month as follows:

1. Open the dust cap and mouthpiece.
2. Open the base by lifting the piercing button.
3. Rinse the complete inhaler with warm water to remove any powder.
4. Dry the HANDIHALER device thoroughly by tipping excess of water out on a paper towel and air-dry afterwards, leaving the dust cap, mouthpiece and base open. It takes 24 hours to air dry, so clean it right after you used it and it will be ready for your next dose. The outside of the mouthpiece may be cleaned with a moist but not wet tissue if needed.



Do **not** place the HANDIHALER device in the dishwasher.

If you have any questions about SPIRIVA or the HANDIHALER device, contact your healthcare professional.

Usual dose:

One (1) SPIRIVA capsule is to be inhaled once daily, preferably at the same time each day, only with the HANDIHALER inhalation device.

Overdose:

Symptoms of an overdose with SPIRIVA include:

- constipation,
- difficulty urinating,
- dry mouth,
- increased eye pressure or pain,
- eye redness,
- vision changes.

If you think you, or a person you are caring for, have taken too much SPIRIVA, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss or forget to take a dose, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and take the next dose at your regularly scheduled time. Do not take 2 doses at the same time or on the same day.

What are possible side effects from using SPIRIVA?

These are not all the possible side effects you may have when taking SPIRIVA. If you experience any side effects not listed here, tell your healthcare professional.

Side effects of SPIRIVA may include:

- coughing;
- dry mouth or throat. Check with your healthcare professional if the dry mouth persists;
- bad taste. Check with your healthcare professional if the bad taste persists;
- dizziness;
- hoarse voice;
- itching;
- difficulty in sleeping;
- heartburn;

- constipation. If you experience constipation for a prolonged period of time, tell your healthcare professional;
- sore throat;
- sinus infection;
- inflammation of the mouth, gums and/or tongue;
- nosebleed;
- infections or ulcerations of the skin;
- dry skin;
- swelling of joints;
- dehydration.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON (< 1/100 patients)			
Oropharyngeal candidiasis (a fungal infection of the oral cavity and throat).		✓	
Fast or irregular heartbeat			✓
Urinary retention (inability to pass urine or to empty the bladder): difficulty and pain when passing urine, urinating frequently, or urination in a weak stream or drips.		✓	
RARE (< 1/1000 patients)			
Eye disorders: new or worsened pressure in your eyes, eye pain or discomfort, blurred vision, seeing halos or rainbows around items, or red eyes.			✓
Paradoxical bronchospasm (sudden narrowing of the airway after taking medicines known as bronchodilators): tightness of the chest associated with coughing, wheezing, or breathlessness immediately after inhalation (bronchospasm).			✓
Intestinal obstruction (blockage that stops or impairs passage of contents of intestines): absence of bowel movements, cramping pain in abdomen that may begin			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
suddenly, bloating, loss of appetite, pain that comes and goes but will then last, nausea and vomiting, or diarrhea.			
Urinary tract infection (infection in urinary system including kidneys, ureters, bladder and urethra): pain or burning sensation while urinating, frequent urination, blood in urine, pain in the pelvis, strong smelling urine, or cloudy urine.		✓	
Serious allergic reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing, wheezing, feeling sick to your stomach, or throwing up.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

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

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

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

Storage:

- Store your SPIRIVA capsules and HANDIHALER inhalation device between 15°C to 25°C. Protect from freezing, moisture, heat, and sunlight.
- Your capsules should always be stored in the blister strips and only removed from the blister immediately before use. After opening a blister strip, use within 5 days. If more

than one capsule is accidently exposed to air, discard the exposed unused capsule.
- Do not store SPIRIVA capsules inside the HANDIHALER device.
- Keep out of reach and sight of children.

If you want more information about SPIRIVA:

- Talk to your healthcare professional.
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's, Boehringer Ingelheim (Canada) Ltd., website (https://www.boehringer-ingelheim.ca), or by calling 1-800-263-5103, ext. 84633.

This leaflet was prepared by Boehringer Ingelheim (Canada) Ltd.

This information is current up to the time of the last revision date shown below, but more current information may be available from the manufacturer.

Last Revised: APR 22, 2022