

1 **ATTENTION PHARMACISTS: Detach "Patient's Instructions for Use" and dispense with**
2 **the product.**
3



4
5 **Spiriva® HandiHaler®**
6 (tiotropium bromide inhalation powder)
7

8 **For Oral Inhalation Only**
9

10 **Prescribing Information**

11 **DESCRIPTION**

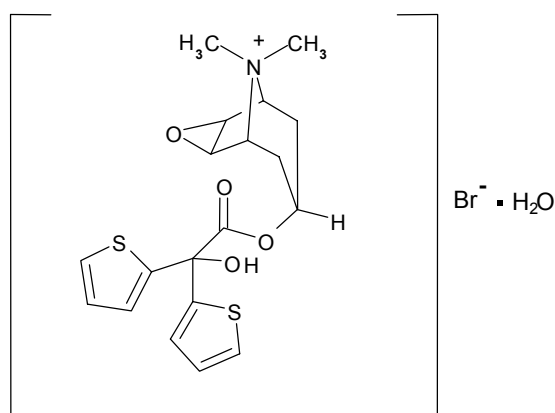
12 Spiriva HandiHaler consists of a capsule dosage form containing a dry powder formulation of
13 Spiriva (tiotropium bromide) intended for oral inhalation only with the HandiHaler inhalation
14 device.
15

16 Each light green, hard gelatin capsule contains 18 mcg tiotropium (equivalent to 22.5 mcg
17 tiotropium bromide monohydrate) blended with lactose monohydrate as the carrier.
18

19 The dry powder formulation within the capsule is intended for oral inhalation only.
20

21 The active component of Spiriva is tiotropium. The drug substance, tiotropium bromide
22 monohydrate, is an anticholinergic with specificity for muscarinic receptors. It is chemically
23 described as (1 α ,2 β ,4 β ,5 α ,7 β)-7-[(Hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-
24 azoniatricyclo[3.3.1.0^{2,4}]nonane bromide monohydrate. It is a synthetic, non-chiral, quaternary
25 ammonium compound. Tiotropium bromide is a white or yellowish white powder. It is
26 sparingly soluble in water and soluble in methanol.
27

28 The structural formula is:



29
30

31 Tiotropium bromide (monohydrate) has a molecular mass of 490.4 and a molecular formula of
32 $C_{19}H_{22}NO_4S_2Br \cdot H_2O$.

33

34 The HandiHaler is an inhalation device used to inhale the dry powder contained in the Spiriva
35 capsule. The dry powder is delivered from the HandiHaler device at flow rates as low as
36 20 L/min. Under standardized *in vitro* testing, the HandiHaler device delivers a mean of
37 10.4 mcg tiotropium when tested at a flow rate of 39 L/min for 3.1 seconds (2L total). In a
38 study of 26 adult patients with chronic obstructive pulmonary disease (COPD) and severely
39 compromised lung function [mean FEV₁ 1.02 L (range 0.45 to 2.24 L); 37.6% of predicted
40 (range 16%-65%)], the median peak inspiratory flow (PIF) through the HandiHaler device was
41 30.0 L/min (range 20.4 to 45.6 L/min). The amount of drug delivered to the lungs will vary
42 depending on patient factors such as inspiratory flow and peak inspiratory flow through the
43 HandiHaler device, which may vary from patient to patient, and may vary with the exposure
44 time of the capsule outside the blister pack.

45

46 For administration of Spiriva, a capsule is placed into the center chamber of the HandiHaler
47 device. The capsule is pierced by pressing and releasing the button on the side of the inhalation
48 device. The tiotropium formulation is dispersed into the air stream when the patient inhales
49 through the mouthpiece. (See **Patient's Instructions For Use**)

50 **CLINICAL PHARMACOLOGY**

51 **Mechanism of Action**

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

60 **Pharmacokinetics**

61 Tiotropium is administered by dry powder inhalation. In common with other inhaled drugs, the
62 majority of the delivered dose is deposited in the gastrointestinal tract and, to a lesser extent, in
63 the lung, the intended organ. Many of the pharmacokinetic data described below were obtained
64 with higher doses than recommended for therapy.

65 Absorption:

66 Following dry powder inhalation by young healthy volunteers, the absolute bioavailability of
67 19.5% suggests that the fraction reaching the lung is highly bioavailable. It is expected from
68 the chemical structure of the compound (quaternary ammonium compound) that tiotropium is
69 poorly absorbed from the gastrointestinal tract. Food is not expected to influence the
70 absorption of tiotropium for the same reason. Oral solutions of tiotropium have an absolute
71 bioavailability of 2-3%. Maximum tiotropium plasma concentrations were observed five
72 minutes after inhalation.

73 Distribution:

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

82 Biotransformation:

83 The extent of biotransformation appears to be small. This is evident from a urinary excretion
84 of 74% of unchanged substance after an intravenous dose to young healthy volunteers.
85 Tiotropium, an ester, is nonenzymatically cleaved to the alcohol *N*-methylscopine and
86 dithienylglycolic acid, neither of which bind to muscarinic receptors.

87

88 *In vitro* experiments with human liver microsomes and human hepatocytes suggest that a
89 fraction of the administered dose (74% of an intravenous dose is excreted unchanged in the
90 urine, leaving 25% for metabolism) is metabolized by cytochrome P450-dependent oxidation
91 and subsequent glutathione conjugation to a variety of Phase II metabolites. This enzymatic
92 pathway can be inhibited by CYP450 2D6 and 3A4 inhibitors, such as quinidine, ketoconazole,
93 and gestodene. Thus, CYP450 2D6 and 3A4 are involved in the metabolic pathway that is
94 responsible for the elimination of a small part of the administered dose. *In vitro* studies using
95 human liver microsomes showed that tiotropium in supra-therapeutic concentrations does not
96 inhibit CYP450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4.

97 Elimination:

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

106

107 Drug Interactions:

108 An interaction study with tiotropium (14.4 mcg intravenous infusion over 15 minutes) and
109 cimetidine 400 mg three times daily or ranitidine 300 mg once daily was conducted.
110 Concomitant administration of cimetidine with tiotropium resulted in a 20% increase in the
111 AUC_{0-4h}, a 28% decrease in the renal clearance of tiotropium and no significant change in the
112 C_{max} and amount excreted in urine over 96 hours. Co-administration of tiotropium with
113 ranitidine did not affect the pharmacokinetics of tiotropium. Therefore, no clinically significant
114 interaction occurred between tiotropium and cimetidine or ranitidine.

115 Electrophysiology:

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

123 Special Populations:

124 *Elderly Patients:*

125 As expected for drugs predominantly excreted renally, advanced age was associated with a
126 decrease of tiotropium renal clearance (326 mL/min in COPD patients <58 years to
127 163 mL/min in COPD patients >70 years), which may be explained by decreased renal
128 function. Tiotropium excretion in urine after inhalation decreased from 14% (young healthy
129 volunteers) to about 7% (COPD patients). Plasma concentrations were numerically increased
130 with advancing age within COPD patients (43% increase in AUC₀₋₄ after dry powder
131 inhalation), which was not significant when considered in relation to inter- and intra-individual
132 variability. (See **DOSAGE AND ADMINISTRATION SECTION**)

133 *Hepatically-impaired Patients:*

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

139 *Renally-impaired Patients:*

140 Since tiotropium is predominantly renally excreted, renal impairment was associated with
141 increased plasma drug concentrations and reduced drug clearance after both intravenous
142 infusion and dry powder inhalation. Mild renal impairment (CrCl 50-80 mL/min), which is
143 often seen in elderly patients, increased tiotropium plasma concentrations (39% increase in
144 AUC₀₋₄ after intravenous infusion). In COPD patients with moderate to severe renal
145 impairment (CrCl <50 mL/min), the intravenous administration of tiotropium resulted in
146 doubling of the plasma concentrations (82% increase in AUC₀₋₄), which was confirmed by

147 plasma concentrations after dry powder inhalation. (See **DOSAGE AND ADMINISTRATION**
148 and **PRECAUTIONS** Sections)
149

150 **CLINICAL STUDIES**

151 The Spiriva HandiHaler clinical development program consisted of six phase 3 studies in 2,663
152 patients with COPD (1,308 receiving Spiriva): two 1-year, placebo-controlled studies, two 6-
153 month, placebo-controlled studies and two 1-year, ipratropium-controlled studies. These
154 studies enrolled patients who had a clinical diagnosis of COPD, were 40 years of age or older,
155 had a history of smoking greater than 10 pack-years, had an FEV₁ less than or equal to 60 or
156 65% of predicted, and a ratio of FEV₁/FVC of less than or equal to 0.7.

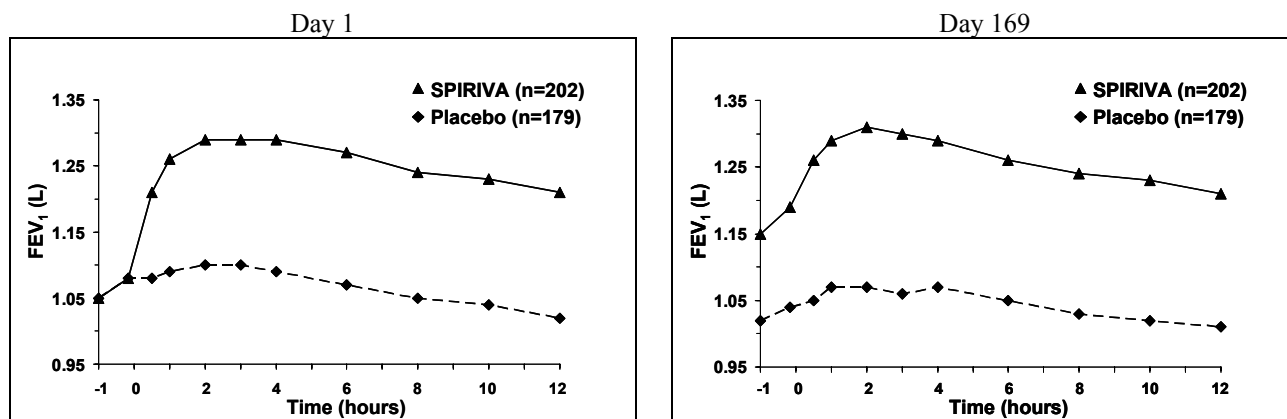
157
158 In these studies, Spiriva, administered once-daily in the morning, provided improvement in
159 lung function (forced expiratory volume in one second, FEV₁), with peak effect occurring
160 within 3 hours following the first dose.

161
162 In the 1-year, placebo controlled trials, the mean improvement in FEV₁ at 30 minutes was
163 0.13 liters (13%) with a peak improvement of 0.24 liters (24%) relative to baseline after the
164 first dose (day 1). Further improvements in FEV₁ and FVC were observed with
165 pharmacodynamic steady state reached by day 8 with once-daily treatment. The mean peak
166 improvement in FEV₁, relative to baseline, was 0.28 to 0.31 liters (28% to 31%), after 1 week
167 (day 8) of once-daily treatment. Improvement of lung function was maintained for 24 hours
168 after a single dose and consistently maintained over the 1-year treatment period with no
169 evidence of tolerance.

170
171 In the two 6-month, placebo-controlled trials, serial spirometric evaluations were performed
172 throughout daytime hours in Trial A (12 hours) and limited to 3 hours in Trial B. The serial
173 FEV₁ values over 12 hours (Trial A) are displayed in Figure 1. These trials further support the
174 improvement in pulmonary function (FEV₁) with Spiriva, which persisted over the spirometric
175 observational period. Effectiveness was maintained for 24 hours after administration over the
176 6-month treatment period.

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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)*

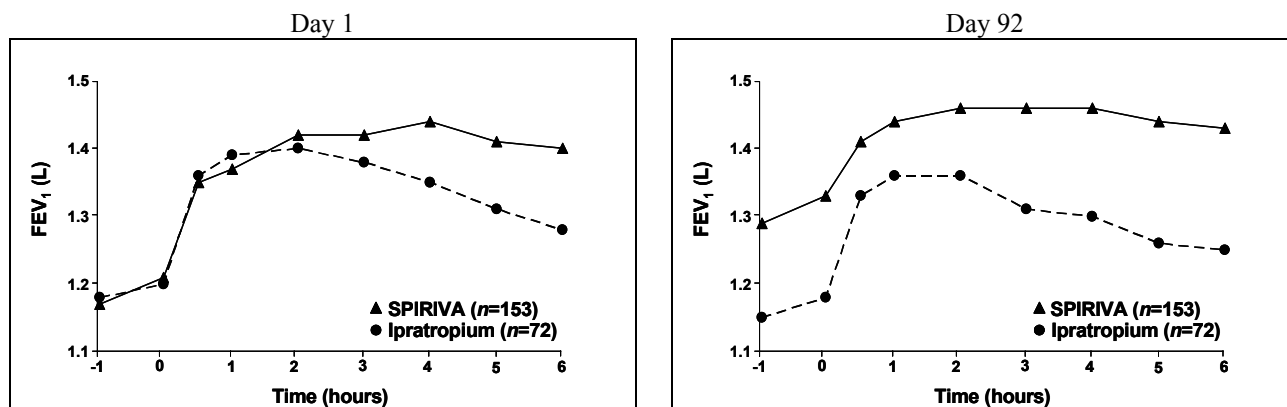


181 *Means adjusted for center, treatment, and baseline effect. On Day 169, a total of 183 and 149 patients in the
182 Spiriva and placebo groups, respectively, completed the trial. The data for the remaining patients were imputed
183 using last observation or least favorable observation carried forward.

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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.

188 **Figure 2: Mean FEV₁ Over Time (0 to 6 hours postdose) on Days 1 and 92, respectively**
189 **for one of the two Ipratropium-Controlled Studies***
190



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

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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 was administered in the morning or in the evening.

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

203 **INDICATIONS AND USAGE**

204 Spiriva HandiHaler is indicated for the long-term, once-daily, maintenance treatment of
205 bronchospasm associated with chronic obstructive pulmonary disease (COPD), including
206 chronic bronchitis and emphysema.

207 **CONTRAINDICATIONS**

208 Spiriva HandiHaler is contraindicated in patients with a history of hypersensitivity to atropine
209 or its derivatives, including ipratropium, or to any component of this product.
210

211 **WARNINGS**

212 Spiriva HandiHaler is intended as a once-daily maintenance treatment for COPD and is not
213 indicated for the initial treatment of acute episodes of bronchospasm, i.e., rescue therapy.
214

215 Immediate hypersensitivity reactions, including angioedema, may occur after administration of
216 Spiriva. If such a reaction occurs, therapy with Spiriva should be stopped at once and
217 alternative treatments should be considered.
218

219 Inhaled medicines, including Spiriva, may cause paradoxical bronchospasm. If this occurs,
220 treatment with Spiriva should be stopped and other treatments considered.
221

222 **PRECAUTIONS**

223 **General**

224 As an anticholinergic drug, Spiriva may potentially worsen symptoms and signs associated
225 with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction and should be
226 used with caution in patients with any of these conditions.
227

228 As a predominantly renally excreted drug, patients with moderate to severe renal impairment
229 (creatinine clearance of ≤ 50 mL/min) treated with Spiriva should be monitored closely. (See

230 **CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations:**
231 **Renally-impaired Patients**)

232 **Information for Patients**

233 It is important for patients to understand how to correctly administer Spiriva capsules using the
234 HandiHaler inhalation device. (See **Patient's Instructions for Use**) Spiriva capsules
235 should only be administered via the HandiHaler device and the HandiHaler device should not
236 be used for administering other medications.
237

238 Capsules should always be stored in sealed blisters and only removed immediately before use.
239 The blister strip should be carefully opened to expose only one capsule at a time. Open the
240 blister foil as far as the *STOP* line to remove only one capsule at a time. The drug should be
241 used immediately after the packaging over an individual capsule is opened, or else its
242 effectiveness may be reduced. Capsules that are inadvertently exposed to air (i.e., not intended
243 for immediate use) should be discarded.

244
245 Eye pain or discomfort, blurred vision, visual halos or colored images in association with red
246 eyes from conjunctival congestion and corneal edema may be signs of acute narrow-angle
247 glaucoma. Should any of these signs and symptoms develop, consult a physician immediately.
248 Miotic eye drops alone are not considered to be effective treatment.

249
250 Care must be taken not to allow the powder to enter into the eyes as this may cause blurring of
251 vision and pupil dilation.

252
253 Spiriva HandiHaler is a once-daily maintenance bronchodilator and should not be used for
254 immediate relief of breathing problems, i.e., as a rescue medication.

255

256 **Drug Interactions**

257 Spiriva has been used concomitantly with other drugs commonly used in COPD without
258 increases in adverse drug reactions. These include sympathomimetic bronchodilators,
259 methylxanthines, and oral and inhaled steroids. However, the co-administration of Spiriva with
260 other anticholinergic-containing drugs (e.g., ipratropium) has not been studied and is therefore
261 not recommended.

262 **Drug/Laboratory Test Interactions**

263 None known.

264 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

265 No evidence of tumorigenicity was observed in a 104-week inhalation study in rats at
266 tiotropium doses up to 0.059 mg/kg/day, in an 83-week inhalation study in female mice at
267 doses up to 0.145 mg/kg/day, and in a 101-week inhalation study in male mice at doses up to
268 0.002 mg/kg/day. These doses correspond to 25, 35, and 0.5 times the Recommended Human
269 Daily Dose (RHDD) on a mg/m² basis, respectively. These dose multiples may be
270 overestimated due to difficulties in measuring deposited doses in animal inhalation studies.

271

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

277

278 In rats, decreases in the number of corpora lutea and the percentage of implants were noted at
279 inhalation tiotropium doses of 0.078 mg/kg/day or greater (approximately 35 times the RHDD
280 on a mg/m² basis). No such effects were observed at 0.009 mg/kg/day (approximately 4 times
281 than the RHDD on a mg/m² basis). The fertility index, however, was not affected at inhalation
282 doses up to 1.689 mg/kg/day (approximately 760 times the RHDD on a mg/m² basis). These
283 dose multiples may be overestimated due to difficulties in measuring deposited doses in animal
284 inhalation studies.

285 **Pregnancy**

286 *Pregnancy Category C*

287 No evidence of structural alterations was observed in rats and rabbits at inhalation tiotropium
288 doses of up to 1.471 and 0.007 mg/kg/day, respectively. These doses correspond to
289 approximately 660 and 6 times the recommended human daily dose (RHDD) on a mg/m² basis.
290 However, in rats, fetal resorption, litter loss, decreases in the number of live pups at birth and
291 the mean pup weights, and a delay in pup sexual maturation were observed at inhalation
292 tiotropium doses of ≥ 0.078 mg/kg (approximately 35 times the RHDD on a mg/m² basis). In
293 rabbits, an increase in post-implantation loss was observed at an inhalation dose of 0.4
294 mg/kg/day (approximately 360 times the RHDD on a mg/m² basis). Such effects were not
295 observed at inhalation doses of 0.009 and up to 0.088 mg/kg/day in rats and rabbits,
296 respectively. These doses correspond to approximately 4 and 80 times the RHDD on a mg/m²
297 basis, respectively. These dose multiples may be overestimated due to difficulties in measuring
298 deposited doses in animal inhalation studies.
299

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

302 **Use in Labor and Delivery**

303 The safety and effectiveness of Spiriva has not been studied during labor and delivery.

304 **Nursing Mothers**

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

309 **Pediatric Use**

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

314 **Geriatric Use**

315 Of the total number of patients who received Spiriva in the 1-year clinical trials, 426 were
316 <65 years, 375 were 65-74 years and 105 were ≥75 years of age. Within each age subgroup,
317 there were no differences between the proportion of patients with adverse events in the Spiriva
318 and the comparator groups for most events. Dry mouth increased with age in the Spiriva group
319 (differences from placebo were 9.0%, 17.1%, and 16.2% in the aforementioned age subgroups).
320 A higher frequency of constipation and urinary tract infections with increasing age was
321 observed in the Spiriva group in the placebo-controlled studies. The differences from placebo
322 for constipation were 0%, 1.8%, and 7.8% for each of the age groups. The differences from
323 placebo for urinary tract infections were -0.6%, 4.6% and 4.5%. No overall differences in
324 effectiveness were observed among these groups. Based on available data, no adjustment of
325 Spiriva dosage in geriatric patients is warranted.

326 **ADVERSE REACTIONS**

327 Of the 2,663 patients in the four 1-year and two 6-month controlled clinical trials, 1,308 were
 328 treated with Spiriva at the recommended dose of 18 mcg once a day. Patients with narrow
 329 angle glaucoma, or symptomatic prostatic hypertrophy or bladder outlet obstruction were
 330 excluded from these trials.

331
 332 The most commonly reported adverse drug reaction was dry mouth. Dry mouth was usually
 333 mild and often resolved during continued treatment. Other reactions reported in individual
 334 patients and consistent with possible anticholinergic effects included constipation, increased
 335 heart rate, blurred vision, glaucoma, urinary difficulty, and urinary retention.

336
 337 Four multicenter, 1-year, controlled studies evaluated Spiriva in patients with COPD. Table 1
 338 shows all adverse events that occurred with a frequency of $\geq 3\%$ in the Spiriva group in the
 339 1-year placebo-controlled trials where the rates in the Spiriva group exceeded placebo by $\geq 1\%$.
 340 The frequency of corresponding events in the ipratropium-controlled trials is included for
 341 comparison.
 342

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				
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

343
 344 Arthritis, coughing, and influenza-like symptoms occurred at a rate of $\geq 3\%$ in the Spiriva
 345 treatment group, but were $< 1\%$ in excess of the placebo group.
 346

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

358
359 In the 1-year trials, the incidence of dry mouth, constipation, and urinary tract infection
360 increased with age. (see **PRECAUTIONS, Geriatric Use**)

361
362 Two multicenter, 6-month, controlled studies evaluated Spiriva in patients with COPD. The
363 adverse events and the incidence rates were similar to those seen in the 1-year controlled trials.

364
365 In addition to adverse events identified during clinical trials, the following adverse reactions
366 have been reported in the worldwide post-marketing experience: epistaxis, palpitations,
367 pruritus, and urticaria.

369 **OVERDOSAGE**

370 High doses of tiotropium may lead to anticholinergic signs and symptoms. However, there
371 were no systemic anticholinergic adverse effects following a single inhaled dose of up to
372 282 mcg tiotropium in 6 healthy volunteers. In a study of 12 healthy volunteers, bilateral
373 conjunctivitis and dry mouth were seen following repeated once-daily inhalation of 141 mcg of
374 tiotropium.

375
376 Acute intoxication by inadvertent oral ingestion of Spiriva capsules is unlikely since it is not
377 well-absorbed systemically.

378
379 A case of overdose has been reported from post-marketing experience. A female patient was
380 reported to have inhaled 30 capsules over a 2.5 day period, and developed altered mental status,
381 tremors, abdominal pain, and severe constipation. The patient was hospitalized, Spiriva was
382 discontinued, and the constipation was treated with an enema. The patient recovered and was
383 discharged on the same day.

384
385 No mortality was observed at inhalation tiotropium doses up to 32.4 mg/kg in mice, 267.7
386 mg/kg in rats, and 0.6 mg/kg in dogs. These doses correspond to 7,300, 120,000, and 850 times
387 the recommended human daily dose on a mg/m² basis, respectively. These dose multiples may
388 be overestimated due to difficulties in measuring deposited doses in animal inhalation studies..

389

390 **DOSAGE AND ADMINISTRATION**

391 The recommended dosage of Spiriva HandiHaler is the inhalation of the contents of one Spiriva
392 capsule, once-daily, with the HandiHaler inhalation device. (See **Patient's Instructions for**
393 **Use**)

394
395 No dosage adjustment is required for geriatric, hepatically-impaired, or renally-impaired
396 patients. However, patients with moderate to severe renal impairment given Spiriva should be
397 monitored closely (See CLINICAL PHARMACOLOGY, Pharmacokinetics, Special
398 Populations and PRECAUTIONS)

399
400 Spiriva capsules are for inhalation only and must not be swallowed.

401 **HOW SUPPLIED**

402 Spiriva capsules, containing 18 mcg tiotropium, are light green, with TI 01 printed on one side
403 of the capsule and the Boehringer Ingelheim company logo on the other side.

404
405 The HandiHaler inhalation device is gray colored with a green button. It is imprinted with
406 Spiriva HandiHaler (tiotropium bromide inhalation powder), the Boehringer Ingelheim
407 company logo, and the Pfizer company logo. It is also imprinted to indicate that Spiriva
408 capsules should not be stored in the HandiHaler device and that the HandiHaler device is only
409 to be used with Spiriva capsules.

410
411 Six Spiriva capsules are packaged in an aluminum / PVC / aluminum blister card. One blister
412 card consists of two blister strips, each containing 3 capsules and joined along a perforated-cut
413 line. After using the first capsule, the 2 remaining capsules should be used over the next 2
414 consecutive days. Capsules should always be stored in the blister and only removed
415 immediately before use. The foil lidding should only be peeled back as far as the *STOP* line
416 printed on the blister foil to prevent exposure of more than one capsule. The drug should be
417 used immediately after the packaging over an individual capsule is opened.

418
419 The following packages are available:

- 420
421 carton containing 6 Spiriva capsules (1 blister card) and 1 HandiHaler inhalation device
422 (NDC 0597-0075-06)
423 carton containing 30 Spiriva capsules (5 blister cards) and 1 HandiHaler inhalation device
424 (NDC 0597-0075-37)

425 **Storage**

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

428
429 The capsules should not be exposed to extreme temperature or moisture. Do not store capsules
430 in the HandiHaler device.

431
432 **Rx only**

433

434 Manufactured by:
435 Boehringer Ingelheim Pharma GmbH & Co. KG
436 Ingelheim, Germany

437
438 Marketed by:
439 Boehringer Ingelheim Pharmaceuticals, Inc.
440 Ridgefield, CT 06877 USA
441 and
442 Pfizer Inc.
443 New York, NY 10017 USA

444
445 Address Medical Inquiries to:
446 www.spiriva.com or (800) 542-6257

447
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454
455 Tiotropium bromide is covered by U.S. Patent No. 5,610,163, with other Patents Pending. The
456 HandiHaler inhalation device is covered by U.S. Design Patent No. 355,029.

457
458 Date
459 Identification Number



1
2 **Patient's Instructions For Use**

3
4 **Spiriva® HandiHaler®**
5 (tiotropium bromide inhalation powder)

6
7 FOR ORAL INHALATION ONLY

8
9 Read all instructions before use.

10
11 This leaflet provides summary information about Spiriva capsules and the HandiHaler
12 inhalation device. Before you start to take Spiriva or use the HandiHaler, read this leaflet
13 carefully and keep it for future use. You should read the leaflet that comes with your
14 prescription every time you refill it because there may be new information.

15
16 For more information, ask your health-care provider or pharmacist.

17 ***What should you know about Spiriva and the HandiHaler?***

18 Each Spiriva capsule contains a dry powder blend of active drug (18 mcg tiotropium) and
19 lactose monohydrate as the carrier. The dry powder in the capsule is inhaled from the
20 HandiHaler inhalation device. Spiriva capsules contain only a small amount of powder
21 and as a result the capsule is only partially filled. When disposing of the capsule, you
22 may notice that a tiny amount of this powder is left in the capsule. This is normal.

23
24 Spiriva is a once daily maintenance bronchodilator medicine that opens narrowed airways
25 and helps keep them open for 24 hours. Spiriva HandiHaler should not be used for
26 immediate relief of breathing problems, i.e., as a rescue medication.

27
28 **SPIRIVA CAPSULES ARE INTENDED FOR ORAL INHALATION ONLY AND**
29 **ARE TO BE USED ONLY WITH THE HANDIHALER INHALATION DEVICE.**

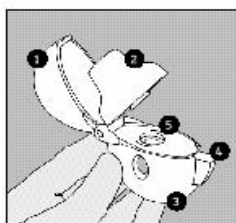
30
31 **SPIRIVA CAPSULES SHOULD NOT BE SWALLOWED.**

32
33 The HandiHaler is an inhalation device that has been specially designed for use with
34 Spiriva capsules. It must not be used to take any other medication.

35
36 Care must be taken not to allow the powder to enter into the eyes. If symptoms of eye
37 pain, eye discomfort, blurred vision, visual halos, or colored images in association with
38 red eyes occur, consult a physician immediately.

40 **How do you take your dose of Spiriva using the HandiHaler?**

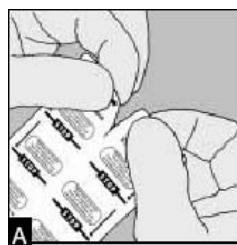
Taking your dose of Spiriva, requires four main steps: Open the blister and the HandiHaler device, insert the Spiriva capsule, press the HandiHaler button, and inhale your medication. (See below for details.)



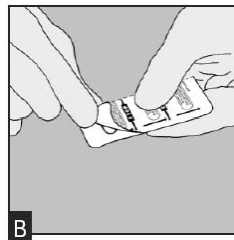
Become familiar with the components of the HandiHaler inhalation device:

1. dust cap
2. mouthpiece
3. base
4. piercing button
5. center chamber

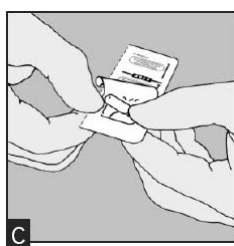
Removing the Spiriva capsule from the blister.



A) Spiriva capsules are packaged in a blister card. Each blister card consists of two blister strips, each containing 3 capsules and joined along a perforated-cut line. Prior to removing the first capsule from the blister card, separate the blister strips by tearing along the perforation. (Figure A)



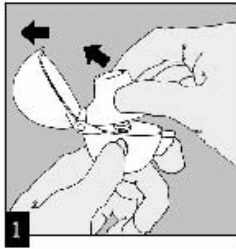
B) The blister should be carefully opened to expose only one capsule at a time. Immediately before you are ready to use your dose of Spiriva, peel back the aluminum foil using the tab until one capsule is fully visible. The foil lidding should only be peeled back as far as the **STOP** line printed on the blister foil to prevent exposure of more than one capsule. (Figure B)



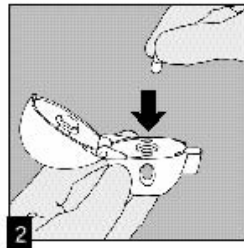
C) **Capsules should always be stored in the sealed blisters and only removed immediately before use. The drug should be used immediately after the packaging over an individual capsule is opened, or else its effectiveness may be reduced.** The blister strip should be carefully opened to expose one capsule at a time. After using the first capsule, the 2 remaining capsules should be used over the next 2 consecutive days. Spiriva capsules should always be stored in the blister. The blister should only be opened and the capsule removed immediately before use. If additional capsules are inadvertently exposed to air, they should not be used and should be discarded. (Figure C)

Do not store capsules in the HandiHaler device.

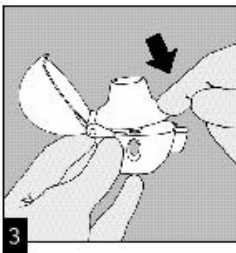
Opening the HandiHaler device and inserting the Spiriva capsule.



1) OPEN: Open the dust cap by pulling it upwards. Then open the mouthpiece. (Figure 1)



2) INSERT: Place the capsule in the center chamber. It does not matter which end of the capsule is placed in the chamber. (Figure 2)

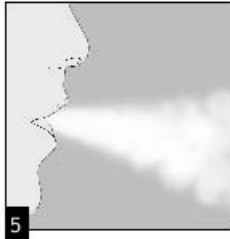


3) Close the mouthpiece **firmly until you hear a click**, leaving the dust cap open. (Figure 3)

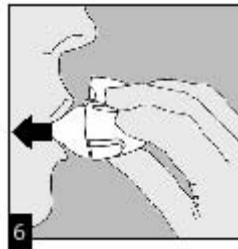
Taking your dose of Spiriva.



4) PRESS: Hold the HandiHaler device with the mouthpiece upwards and press the piercing button completely in once, and release. This makes holes in the capsule and allows the medication to be released when you breathe in. (Figure 4)

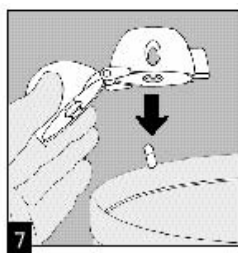


5) Breathe out completely. (Figure 5)
Important: Do not breathe into the mouthpiece at any time.

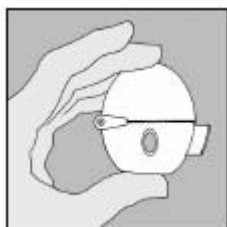


6) INHALE: Raise the HandiHaler device to your mouth and close your lips tightly around the mouthpiece. Keep your head in an upright position and breathe in slowly and deeply but at a rate **sufficient to hear the capsule vibrate**. Breathe in until your lungs are full; then hold your breath as long as is comfortable and at the same time take the HandiHaler device out of your mouth. Resume normal breathing. (Figure 6)

To ensure you get the full dose of Spiriva, you must repeat steps 5 and 6 once again.

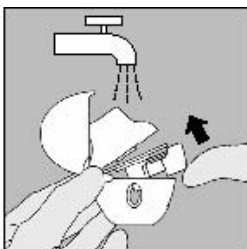


7) After you have finished taking your daily dose of Spiriva, open the mouthpiece again. Tip out the used capsule and dispose. (Figure 7)



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

41 **When and how should you clean your HandiHaler Device?**



Normally, during a one-month period of use, the HandiHaler device does not need to be cleaned. However, if cleaning is needed the HandiHaler device can be cleaned as described below:

Open the dust cap and mouthpiece. Open the base by lifting the piercing button. Rinse the complete inhaler with warm water to remove any powder. Do not use cleaning agents or detergents.

Dry the HandiHaler device thoroughly by tipping the excess 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 use it and it will be ready for your next dose.** Do not use the HandiHaler device when it is wet.

If needed, the outside of the mouthpiece may be cleaned with a moist, but not wet tissue.

The HandiHaler device should not be placed in the dishwasher for cleaning.

42

43 **Where should you store Spiriva capsules and the HandiHaler Device?**

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

46

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

49

50 As with all prescription medications, keep this out of the reach of children.

51

52 **Tell your doctor before you use Spiriva HandiHaler:**

53 if you may be pregnant or wish to become pregnant;

54 if you are a breastfeeding mother;

55 if you are taking any medications including eye drops, this includes those you can buy
56 without a prescription;

57 if you have any other medical problems such as difficulty urinating or an enlarged
58 prostate;

59 if you are allergic to any medications.

60

61 **USE THIS PRODUCT AS DIRECTED, UNLESS INSTRUCTED TO DO OTHERWISE BY**
62 **YOUR PHYSICIAN.**

63

64 Manufactured by:
65 Boehringer Ingelheim Pharma GmbH & Co. KG
66 Ingelheim, Germany

67
68 Marketed by:
69 Boehringer Ingelheim Pharmaceuticals, Inc.
70 Ridgefield, CT 06877 USA
71 and
72 Pfizer Inc.
73 New York, NY 10017 USA

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81
82 Tiotropium bromide is covered by U.S. Patent No. 5,610,163 with other Patents Pending. The
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84
85 Date
86 Identification number