SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Version: 9 Mar 2018

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1. NAME OF THE MEDICINAL PRODUCT

Spiriva Respimat 2.5 microgram, inhalation solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The delivered dose is 2.5 microgram tiotropium per puff (2 puffs comprise one medicinal dose) and is equivalent to 3.124 microgram tiotropium bromide monohydrate.
The delivered dose is the dose which is available for the patient after passing the mouthpiece.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation solution
Clear, colourless, inhalation solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

COPD
Tiotropium is indicated as a maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD).

Asthma
Spiriva Respimat is indicated as add-on maintenance bronchodilator treatment in patients aged 6 years and older with severe asthma who experienced one or more severe asthma exacerbations in the preceding year (see sections 4.2 and 5.1).

4.2 Posology and method of administration

Posology
The medicinal product is intended for inhalation use only. The cartridge can only be inserted and used in the Respimat inhaler (see 4.2).
Two puffs from the Respimat inhaler comprise one medicinal dose.
The recommended dose for adults is 5 microgram tiotropium given as two puffs from the Respimat inhaler once daily, at the same time of the day.

The recommended dose should not be exceeded.

In the treatment of asthma the full benefit will be apparent after several doses of the medicinal product. In adult patients with severe asthma, tiotropium should be used in addition to inhaled corticosteroids (≥ 800 µg budesonide/day or equivalent) and at least one controller.

Special populations
Geriatric patients can use tiotropium bromide at the recommended dose.
Renally impaired patients can use tiotropium bromide at the recommended dose. For patients with moderate to severe impairment (creatinine clearance ≤ 50 ml/min, see 4.4 and 5.2).

Hepatically impaired patients can use tiotropium bromide at the recommended dose (see 5.2).

Paediatric population

Asthma

The recommended dose for patients 6 to 17 years of age is 5 microgram tiotropium given as two puffs from the Respimat inhaler once daily, at the same time of the day.

In adolescents (12 - 17 years) with severe asthma, tiotropium should be used in addition to inhaled corticosteroids (> 800 - 1600 µg budesonide/day or equivalent) and one controller or in addition to inhaled corticosteroids (400 - 800 µg budesonide/day or equivalent) with two controllers.

For children (6 - 11 years) with severe asthma, tiotropium should be used in addition to inhaled corticosteroids (> 400 µg budesonide/day or equivalent) and one controller or in addition to inhaled corticosteroids (200 - 400 µg budesonide/day or equivalent) with two controllers.

The safety and efficacy of Spiriva Respimat in children aged 6 - 17 years with moderate asthma has not been established.The safety and efficacy of Spiriva Respimat in children below 6 years of age has not been established. Currently available data are described in sections 5.1 and 5.2 but no recommendation on a posology can be made.

COPD

There is no relevant use of Spiriva Respimat in children and adolescents below 18 years.

Cystic fibrosis

The efficacy and safety of Spiriva Respimat has not been established (see sections 4.4 and 5.1).

Method of administration

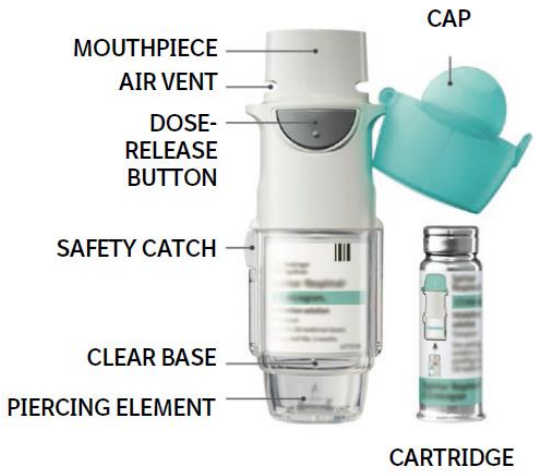
To ensure proper administration of the medicinal product, the patient should be shown how to use the inhaler by a physician or other health professionals.

Patient's instructions for use and handling

Introduction

Spiriva Respimat (tiotropium bromide). Read these Instructions for Use before you start using Spiriva Respimat. Children should use Spiriva Respimat with an adult's assistance.

You will need to use this inhaler only ONCE A DAY. Each time you use it take TWO PUFFS.

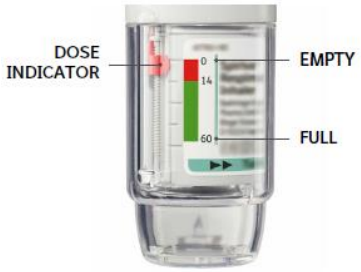


- If Spiriva Respimat has not been used for more than 7 days release one puff towards the ground.
- If Spiriva Respimat has not been used for more than 21 days repeat steps 4 to 6 under 'Prepare for first use' until a cloud is visible. Then repeat steps 4 to 6 three more times.
- Do not touch the piercing element inside the clear base.

How to care for your Spiriva Respimat

Clean the mouthpiece including the metal part inside the mouthpiece with a damp cloth or tissue only, at least once a week.
Any minor discoloration in the mouthpiece does not affect your Spiriva Respimat inhaler performance. If necessary, wipe the outside of your Spiriva Respimat inhaler with a damp cloth.

When to get a new Spiriva Respimat



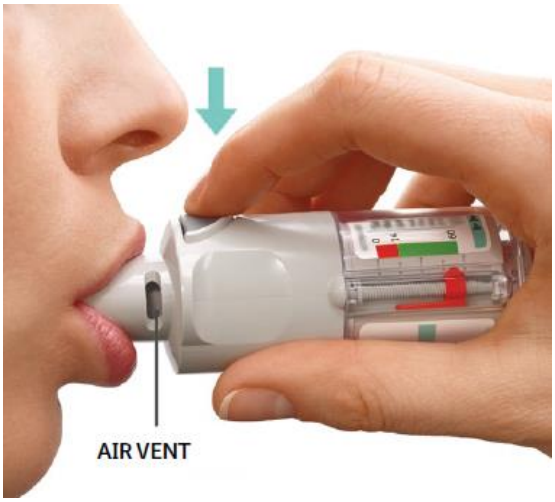
- Your Spiriva Respimat inhaler contains 60 puffs (30 doses) if used as indicated (two puffs/once daily).
- The dose indicator shows approximately how much medication is left.
- When the dose indicator enters the red area of the scale you need to get a new prescription; there is approximately medication for 7 days left (14 puffs).
- Once the dose indicator reaches the end of the red scale, your Spiriva Respimat locks automatically – no more doses can be released. At this point, the clear base cannot be turned any further.
- Spiriva Respimat should be discarded three months after you have prepared it for first use, even if it has not been fully used or used at all.

Prepare for first use

1. Remove clear base • Keep the cap closed. • Press the safety catch while firmly pulling off the clear base with your other hand.	
2. Insert cartridge • Insert the narrow end of the cartridge into the inhaler. • Place the inhaler on a firm surface and push down firmly until it clicks into place. • Do not remove the cartridge once it has been inserted into the inhaler.	
3. Replace clear base • Put the clear base back into place until it clicks. • Do not remove the clear base again.	

4. Turn • Keep the cap closed. • Turn the clear base in the direction of the arrows on the label until it clicks (half a turn).	
5. Open • Open the cap until it snaps fully open.	
6. Press • Point the inhaler toward the ground. • Press the dose-release button. • Close the cap. • Repeat steps 4-6 until a cloud is visible. • **After a cloud is visible**, repeat steps 4-6 three more times. Your inhaler is now ready to use. These steps will not affect the number of doses available. After preparation your inhaler will be able to deliver 60 puffs (30 doses).	

Daily use

TURN • Keep the cap closed. • **TURN** the clear base in the direction of the arrows on the label until it clicks (half a turn).	
OPEN • **OPEN** the cap until it snaps fully open.	
PRESS • Breathe out slowly and fully. • Close your lips around the mouthpiece without covering the air vents. Point your Inhaler to the back of your throat. • While taking a slow, deep breath through your mouth, **PRESS** the dose-release button and continue to breathe in slowly for as long as comfortable. • Hold your breath for 10 seconds or for as long as comfortable. • Repeat Turn, Open, Press for a total of 2 puffs. • Close the cap until you use your inhaler again.	

4.3 Contraindications

Hypersensitivity to tiotropium bromide or to any of the excipients listed in section 6.1 or to atropine or its derivatives, e.g. ipratropium or oxitropium.

4.4 Special warnings and precautions for use

Tiotropium bromide, 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.

Spiriva Respimat should not be used as monotherapy for asthma. Asthma patients must be advised to continue taking anti-inflammatory therapy, i.e. inhaled corticosteroids, unchanged after the introduction of Spiriva Respimat, even when their symptoms improve.

Immediate hypersensitivity reactions may occur after administration of tiotropium bromide inhalation solution.

Consistent with its anticholinergic activity, tiotropium bromide should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction.

Inhaled medicines may cause inhalation-induced bronchospasm.

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 of heart failure (NYHA Class III or IV) within the past year. These patients were excluded from the clinical trials and these conditions may be affected by the anticholinergic mechanism of action.

As plasma concentration increases with decreased renal function in patients with moderate to severe renal impairment (creatinine clearance ≤ 50 ml/min) tiotropium bromide should be used only if the expected benefit outweighs the potential risk. There is no long term experience in patients with severe renal impairment (see 5.2).

Patients should be cautioned to avoid getting the spray into their eyes. They should be advised that this may result in precipitation or worsening of narrow-angle glaucoma, eye pain or discomfort, temporary blurring of vision, visual halos or coloured images in association with red eyes from conjunctival congestion and corneal oedema. Should any combination of these eye symptoms develop, patients should stop using tiotropium bromide and consult a specialist immediately.

Dry mouth, which has been observed with anti-cholinergic treatment, may in the long term be associated with dental caries.

Tiotropium bromide should not be used more frequently than once daily (see 4.9).

Spiriva Respimat is not recommended in cystic fibrosis (CF). If used in patients with CF, Spiriva Respimat may increase the signs and symptoms of CF (e.g. serious adverse events, pulmonary exacerbations, respiratory tract infections).

4.5 Interaction with other medicinal products and other forms of interaction

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 and asthma, including sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids, antihistamines, mucolytics, leukotriene modifiers, cromones, anti-IgE treatment without clinical evidence of drug interactions.

Use of LABA or ICS was not found to alter the exposure to tiotropium.

The co-administration of tiotropium bromide with other anticholinergic containing drugs has not been studied and therefore is not recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is a very 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 at clinically relevant doses (see 5.3). As a precautionary measure, it is preferable to avoid the use of Spiriva Respimat during pregnancy.

Breastfeeding
It is unknown whether tiotropium bromide is excreted in human breast milk. Despite studies in rodents which have demonstrated that excretion of tiotropium bromide in breast milk occurs only in small amounts, use of Spiriva Respimat is not recommended during breast-feeding. Tiotropium bromide is a long-acting compound. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Spiriva Respimat should be made taking into account the benefit of breast-feeding to the child and the benefit of Spiriva Respimat therapy to the woman.

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 5.3).

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

Summary of the safety profile
Many of the listed undesirable effects can be assigned to the anticholinergic properties of tiotropium bromide.

Tabulated summary of adverse reactions
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 pooled from 7 placebo-controlled clinical trials in COPD (3,282 patients) and 12 placebo-controlled clinical trials in adult and paediatric patients with asthma (1,930 patients) with treatment periods ranging from four weeks to one year.

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)

System Organ Class / MedDRA Preferred Term	**Frequency COPD**	**Frequency Asthma**
Metabolism and nutrition disorders		
Dehydration	Not known	Not known
Nervous system disorders		
Dizziness	Uncommon	Uncommon
Headache	Uncommon	Uncommon
Insomnia	Rare	Uncommon
Eye disorders		
Glaucoma	Rare	Not known
Intraocular pressure increased	Rare	Not known

System Organ Class / MedDRA Preferred Term	Frequency COPD	Frequency Asthma
Vision blurred	Rare	Not known
Cardiac disorders		
Atrial fibrillation	Rare	Not known
Palpitations	Rare	Uncommon
Supraventricular tachycardia	Rare	Not known
Tachycardia	Rare	Not known
Respiratory, thoracic and mediastinal disorders		
Cough	Uncommon	Uncommon
Pharyngitis	Uncommon	Uncommon
Dysphonia	Uncommon	Uncommon
Epistaxis	Rare	Rare
Bronchospasm	Rare	Uncommon
Laryngitis	Rare	Not known
Sinusitis	Not known	Not known
Gastrointestinal disorders		
Dry Mouth	Common	Uncommon
Constipation	Uncommon	Rare
Oropharyngeal candidiasis	Uncommon	Uncommon
Dysphagia	Rare	Not known
Gastrooesophageal reflux disease	Rare	Not known
Dental caries	Rare	Not known
Gingivitis	Rare	Rare
Glossitis	Rare	Not known
Stomatitis	Not known	Rare
Intestinal obstruction, including ileus paralytic	Not known	Not known
Nausea	Not known	Not known
Skin and subcutaneous tissue disorders, immune system disorders		
Rash	Uncommon	Uncommon
Pruritus	Uncommon	Rare
Angioneurotic oedema	Rare	Rare
Urticaria	Rare	Rare
Skin infection/skin ulcer	Rare	Not known
Dry skin	Rare	Not known
Hypersensitivity (including immediate reactions)	Not known	Rare
Anaphylactic reaction	Not known	Not known
Musculoskeletal and connective tissue disorders		
Joint swelling	Not known	Not known
Renal and urinary disorders		
Urinary retention	Uncommon	Not known
Dysuria	Uncommon	Not known
Urinary tract infection	Rare	Rare

Description of selected adverse reactions

In controlled clinical studies in COPD, the commonly observed undesirable effects were anticholinergic undesirable effects such as dry mouth which occurred in approximately 2.9 % of patients. In asthma the incidence of dry mouth was 0.83%.

In 7 clinical trials in COPD, dry mouth led to discontinuation in 3 of 3,282 tiotropium treated patients (0.1 %). No discontinuations due to dry mouth were reported in 12 clinical trials in asthma (1,930 patients).

Serious undesirable effects consistent with anticholinergic effects include glaucoma, constipation, intestinal obstruction including ileus paralytic and urinary retention.

Paediatric population
The safety database includes 560 paediatric patients (296 patients aged 1 to 11 and 264 patients aged 12 to 17) from 5 placebo-controlled clinical trials with treatment periods ranging between 12 weeks to one year. The frequency, type and severity of adverse reactions in the paediatric popuation are similar as in adults.

Other special population
An increase in anticholinergic effects may occur with increasing age.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V

4.9 Overdose

High doses of tiotropium bromide may lead to anticholinergic signs and symptoms.

However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 340 microgram tiotropium bromide in healthy volunteers. Additionally, no relevant adverse effects, beyond dry mouth/throat and dry nasal mucosa, were observed following 14-day dosing of up to 40 microgram tiotropium inhalation solution in healthy volunteers with the exception of pronounced reduction in salivary flow from day 7 onwards.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other drugs for obstructive airway diseases, inhalants, anticholinergics
ATC code: R03B B04

Mechanism of action
Tiotropium bromide is a long-acting, specific antagonist at muscarinic receptors. It has similar affinity to the subtypes, M_1 to M_5. In the airways, tiotropium bromide competitively and reversibly binds to the M_3 receptors in the bronchial smooth musculature, antagonising the cholinergic (bronchoconstrictive) effects of acetylcholine, resulting in bronchial smooth muscle relaxation. The effect was dose dependent and lasted longer than 24h. As an N-quaternary anticholinergic, tiotropium bromide is topically (broncho-) selective when administered by inhalation, demonstrating an acceptable therapeutic range before systemic anticholinergic effects may occur.

Pharmacodynamic effects
The dissociation of tiotropium from especially M_3-receptors is very slow, exhibiting a significantly longer dissociation half-life than ipratropium. Dissociation from M_2-receptors is faster than from M_3, which in functional in vitro studies, elicited (kinetically controlled) receptor subtype selectivity of M_3 over M_2. The high potency, very slow receptor dissociation and topical inhaled selectivity found its clinical correlate in significant and long-acting bronchodilation in patients with COPD and asthma.

Clinical efficacy and safety in COPD

The clinical Phase III development programme included two 1-year, two 12-weeks and two 4-weeks randomised, double-blind studies in 2901 COPD patients (1038 receiving the 5 µg tiotropium dose). The 1-year programme consisted of two placebo-controlled trials. The two 12-week trials were both active (ipratropium) - and placebo-controlled. All six studies included lung function measurements. In addition, the two 1-year studies included health outcome measures of dyspnoea, health-related quality of life and effect on exacerbations.

Placebo-controlled studies

Lung function

Tiotropium inhalation solution, administered once daily, provided significant improvement in lung function (forced expiratory volume in one second and forced vital capacity) within 30 minutes following the first dose, compared to placebo (FEV_1 mean improvement at 30 minutes: 0.113 litres; 95% confidence interval (CI): 0.102 to 0.125 litres, $p< 0.0001$). Improvement of lung function was maintained for 24 hours at steady state compared to placebo (FEV_1 mean improvement: 0.122 litres; 95% CI: 0.106 to 0.138 litres, $p< 0.0001$).

Pharmacodynamic steady state was reached within one week.

Spiriva Respimat significantly improved morning and evening PEFR (peak expiratory flow rate) as measured by patient's daily recordings compared to placebo (PEFR mean improvement: mean improvement in the morning 22 L/min; 95% CI: 18 to 55 L/min, $p< 0.0001$; evening 26 L/min; 95% CI: 23 to 30 L/min, $p<0.0001$). The use of Spiriva Respimat resulted in a reduction of rescue bronchodilator use compared to placebo (mean reduction in rescue use 0.66 occasions per day, 95% CI: 0.51 to 0.81 occasions per day, $p<0.0001$).

The bronchodilator effects of Spiriva Respimat were maintained throughout the 1-year period of administration with no evidence of tolerance.

Dyspnoea, Health-related Quality of Life, COPD Exacerbations in long term 1 year studies

Dyspnoea

Spiriva Respimat significantly improved dyspnoea (as evaluated using the Transition Dyspnoea Index) compared to placebo (mean improvement 1.05 units; 95% CI: 0.73 to 1.38 units, $p<0.0001$). An improvement was maintained throughout the treatment period.

Health-related Quality of Life

The improvement in mean total score of patient's evaluation of their Quality of Life (as measured using the St. George's Respiratory Questionnaire) between Spiriva Respimat versus placebo at the end of the two 1-year studies was 3.5 units (95% CI: 2.1 to 4.9, $p<0.0001$). A 4-unit decrease is considered clinically relevant.

COPD Exacerbations

In three one-year, randomised, double-blind, placebo-controlled clinical trials Spiriva Respimat treatment resulted in a significantly reduced risk of a COPD exacerbation in comparison to placebo. Exacerbations of COPD were defined as "a complex of at least two respiratory events/symptoms with a duration of three days or more requiring a change in treatment (prescription of antibiotics and/or systemic corticosteroids and/or a significant change of the prescribed respiratory medication)".

Spiriva Respimat treatment resulted in a reduced risk of a hospitalisation due to a COPD exacerbation (significant in the appropriately powered large exacerbation trial).

The pooled analysis of two Phase III trials and separate analysis of an additional exacerbation trial is displayed in Table 1. All respiratory medications except anticholinergics and long-acting beta-agonists were allowed as concomitant treatment, i.e. rapidly acting beta-agonists, inhaled corticosteroids and xanthines. Long-acting beta-agonists were allowed in addition in the exacerbation trial.

Table 1: Statistical Analysis of Exacerbations of COPD and Hospitalized COPD Exacerbations in Patients with Moderate to Very Severe COPD

Study ($N_{Spiriva}$, $N_{placebo}$)	Endpoint	Spiriva Respimat	Placebo	% Risk Reduction (95% CI)[a]	p-value
1-year Ph III studies, pooled analysis[d] (670, 653)	Days to first COPD exacerbation	160[a]	86[a]	29 (16 to 40)[b]	<0.0001[b]
	Mean exacerbation incidence rate per patient year	0.78[c]	1.00[c]	22 (8 to 33)[c]	0.002[c]
	Time to first hospitalised COPD exacerbation			25 (-16 to 51)[b]	0.20[b]
	Mean hospitalised exacerbation incidence rate per patient year	0.09 [c]	0.11 [c]	20 (-4 to 38) [c]	0.096 [c]
1-year Ph IIIb exacerbation study (1939, 1953)	Days to first COPD exacerbation	169[a]	119[a]	31 (23 to 37)[b]	<0.0001[b]
	Mean exacerbation incidence rate per patient year	0.69[c]	0.87[c]	21 (13 to 28)[c]	<0.0001[c]
	Time to first hospitalised COPD exacerbation			27 (10 to 41)[b]	0.003[b]
	Mean hospitalised exacerbation incidence rate per patient year	0.12[c]	0.15[c]	19 (7 to 30)[c]	0.004[c]

[a] Time to first event: days on treatment by when 25% of patients had at least one exacerbation of COPD / hospitalized COPD exacerbation. *In study A 25% of placebo patients had an exacerbation by day 112, whereas for Spiriva Respimat 25% had an exacerbation by day 173 (p=0.09);in study B 25% of placebo patients had an exacerbation by day 74, whereas for Spiriva Respimat 25% had an exacerbation by day 149 (p<0.0001)*.

[b] Hazard ratios were estimated from a Cox proportional hazard model. The percentage risk reduction is 100(1 - hazard ratio).

[c] Poisson regression. Risk reduction is 100(1 - rate ratio).

[d] Pooling was specified when the studies were designed. The exacerbation endpoints were significantly improved in individual analyses of the two one year studies.

Long-term tiotropium active- controlled study

A long-term large scale randomised, double-blind, active-controlled study with an observation period up to 3 years has been performed to compare the efficacy and safety of Spiriva Respimat and Spiriva HandiHaler (5,711 patients receiving Spiriva Respimat; 5,694 patients receiving Spiriva HandiHaler). The primary endpoints were time to first COPD exacerbation, time to all-cause mortality and in a sub-study (906 patients) trough FEV_1 (pre-dose).

The time to first COPD exacerbation was numerically similar during the study with Spiriva Respimat and Spiriva HandiHaler (hazard ratio (Spiriva Respimat/Spiriva HandiHaler) 0.98 with a 95% CI of 0.93 to 1.03). The median number of days to the first COPD exacerbation was 756 days for Spiriva Respimat and 719 days for Spiriva HandiHaler.

The bronchodilator effect of Spiriva Respimat was sustained over 120 weeks, and was similar to Spiriva HandiHaler. The mean difference in trough FEV1 for Spiriva Respimat versus Spiriva HandiHaler was -0.010 L (95% CI -0.038 to 0.018 L).
In the post-marketing TIOSPIR study comparing Spiriva Respimat and Spiriva HandiHaler, all-cause mortality (including vital status follow up) was similar with hazard ratio (Spiriva Respimat/Spiriva HandiHaler) = 0.96 , 95% CI 0.84 -1.09). Respective treatment exposure was 13,135 and 13,050 patient-years.
In the placebo-controlled studies with vital status follow-up to the end of the intended treatment period, Spiriva Respimat showed a numerical increase in all-cause mortality compared to placebo (rate ratio (95% confidence interval) of 1.33 (0.93, 1.92) with treatment exposure to Spiriva Respimat of

2,574 patient years; the excess in mortality was observed in patients with known rhythm disorders. Spiriva HandiHaler showed a 13 % reduction in the risk of death ((hazard ratio including vital status follow-up (tiotropium/placebo) = 0.87; 95% CI, 0.76 to 0.99)). Treatment exposure to Spiriva HandiHaler was 10,927 patient-years. No excess mortality risk was observed in the subgroup of patients with known rhythm disorders in the placebo controlled Spiriva HandiHaler study as well as in the TIOSPIR Spiriva Respimat to HandiHaler comparison.

Clinical efficacy and safety in asthma

The clinical Phase III programme for persistent asthma in adults included two 1-year randomised, double-blind, placebo-controlled studies in a total of 907 asthma patients (453 receiving Spiriva Respimat) on a combination of ICS (≥ 800 µg budesonide/day or equivalent) with a LABA. The studies included lung function measurements and severe exacerbations as primary endpoints.

PrimoTinA-asthma studies

In the two 1-year studies in patients who were symptomatic on maintenance treatment of at least ICS (≥800 µg budesonide/day or equivalent) plus LABA, Spiriva Respimat showed clinically relevant improvements in lung function over placebo when used as add-on to background treatment.

At week 24, mean improvements in peak and trough FEV_1 were 0.110 litres (95% CI: 0.063 to 0.158 litres, p<0.0001) and 0.093 litres (95% CI: 0.050 to 0.137 litres, p<0.0001), respectively. The improvement of lung function compared to placebo was maintained for 24 hours.

In the PrimoTinA-asthma studies, treatment of symptomatic patients (N=453) with ICS plus LABA plus tiotropium reduced the risk of severe asthma exacerbations by 21% as compared to treatment of symptomatic patients (N=454) with ICS plus LABA plus placebo. The risk reduction in the mean number of severe asthma exacerbations/patient year was 20%.

This was supported by a reduction of 31% in risk for asthma worsening and 24% risk reduction in the mean number of asthma worsenings/patient year (see Table 2).

Table 2: Exacerbations in Patients Symptomatic on ICS (≥800 µg budesonide/day or equivalent) plus LABA (PrimoTinA-asthma studies)

Study	Endpoint	Spiriva Respimat, added-on to at least ICS[a]/LABA (N=453)	Placebo, added-on to at least ICS[a]/LABA (N=454)	% Risk Reduction (95% CI)	p-value
two 1-year Phase III studies, pooled analysis	Days to 1st severe asthma exacerbation	282[c]	226[c]	21[b] (0, 38)	0.0343
	Mean number of severe asthma exacerbations/ patient year	0.530	0.663	20[d] (0, 36)	0.0458
	Days to 1st worsening of asthma	315[c]	181[c]	31[b] (18, 42)	<0.0001
	Mean number of asthma worsenings/ patient year	2.145	2.835	24[d] (9, 37)	0.0031

[a] ≥800 µg budesonide/day or equivalent

[b] Hazard ratio, confidence interval and p-value obtained from a Cox proportional hazards model with only treatment as effect. The percentage risk reduction is 100(1 - hazard ratio).

[c] Time to first event: days on treatment by when 25%/50% of patients had at least one severe asthma exacerbation/worsening of asthma

[d] The rate ratio was obtained from a Poisson regression with log exposure (in years) as offset. The percentage risk reduction is 100 (1-rate ratio).

Paediatric population

COPD

The European Medicines Agency has waived the obligation to submit the results of studies with Spiriva Respimat in all subsets of the paediatric population in COPD (see section 4.2 for information on paediatric use).

Asthma

All studies in the clinical Phase III program for persistent asthma in paediatric patients (1 - 17 years) were randomised, double-blind and placebo-controlled. All patients were on background treatments that include an ICS.

Severe Asthma

Adolescents (12 - 17 years)

In the 12-week PensieTinA-asthma study a total of 392 patients (130 receiving Spiriva Respimat) who were symptomatic on a high dose of ICS with one controller or a medium dose of ICS with 2 controllers were included.

For patients aged 12 - 17 years, a high dose ICS was defined as a dose of > 800 - 1600 µg budesonide/day or equivalent; a medium dose ICS as 400 - 800 µg budesonide/day or equivalent. In addition, patients aged 12 - 14 years could receive an ICS dose > 400 µg budesonide/day or equivalent and at least one controller or ≥ 200 µg budesonide/day or equivalent and at least two controllers.

In this study, Spiriva Respimat showed improvements in lung function over placebo when used as add-on to background treatment, however, the differences in peak and trough FEV_1 were not statistically significant.

- At week 12, mean improvements in peak and trough FEV_1 were 0.090 litres (95% CI: -0.019 to 0.198 litres, p=0.1039) and 0.054 litres (95% CI: -0.061 to 0.168 litres, p=0.3605), respectively.
- At week 12, Spiriva Respimat significantly improved morning and evening PEF (morning 17.4 L/min; 95% CI: 5.1 to 29.6 L/min; evening 17.6 L/min; 95% CI: 5.9 to 29.6 L/min).

Children (6 - 11 years)

In the 12-week VivaTinA-asthma study a total 400 patients (130 receiving Spiriva Respimat) who were symptomatic on a high dose ICS with one controller or a medium dose ICS with 2 controllers were included. A high dose ICS was defined by a dose of > 400 µg budesonide/day or equivalent, a medium dose as 200 - 400 µg budesonide/day or equivalent.
In this study, Spiriva Respimat showed significant improvements in lung function over placebo when used as add-on to background treatment.

- At week 12, mean improvements in peak and trough FEV_1 were 0.139 litres (95% CI: 0.075 to 0.203 litres, p<0.0001) and 0.087 litres (95% CI: 0.019 to 0.154 litres, p=0.0117), respectively.

Moderate Asthma

Adolescents (12 - 17 years)

In the 1-year RubaTinA-asthma study in a total of 397 patients (134 receiving Spiriva Respimat) who were symptomatic on a medium dose ICS (200 - 800 µg budesonide/day or equivalent for patients aged 12 - 14 years or 400 - 800 µg budesonide/day or equivalent for patients aged 15 - 17 years),

Spiriva Respimat showed significant improvements in lung function over placebo when used as add-on to background treatment.

Children (6 - 11 years)
In the 1-year CanoTinA-asthma study in a total of 401 patients (135 receiving Spiriva Respimat) who were symptomatic on a medium dose ICS (200 - 400 µg budesonide/day or equivalent), Spiriva Respimat showed significant improvements in lung function over placebo when used as add-on to background treatment.

Children (1 - 5 years)

One 12-week randomised, double-blind, placebo-controlled, phase II/III clinical study (NinoTinA-asthma) was conducted in a total of 101 children (31 received Spiriva Respimat) with asthma on background treatments that include an ICS. An Aerochamber Plus Flow-Vu® valved holding chamber with face mask was used to administer trial medication in 98 patients.

The primary objective of the study was safety; efficacy assessments were exploratory.

The number and percentage of patients reporting adverse events (AEs) irrespective of relatedness are shown in Table 3. The number of asthma adverse events was lower for Spiriva Respimat compared to placebo. Exploratory efficacy evaluations did not show differences for Spiriva Respimat from placebo.

Table 3: Frequency of patients with AEs reported for ≥ 5 patients in the NinoTinA-asthma study (children aged 1 to 5 years)

	Placebo N (%)	Spiriva Respimat N (%)
Number of patients	34 (100.0)	31 (100.0)
Patients with any AE	25 (73.5)	18 (58.1)
Nasopharyngitis	5 (14.7)	2 (6.5)
Upper respiratory tract infection	1 (2.9)	5 (16.1)
Asthma*	10 (29.4)	2 (6.5)
Pyrexia	6 (17.6)	3 (9.7)

*The MedDRA low level terms under the preferred term "Asthma" were either "Asthma aggravated" or "Exacerbation of asthma"

The European Medicines Agency has waived the obligation to submit the results of studies with Spiriva Respimat in the subset of paediatric patients below 1 year of age. (see section 4.2 for information on paediatric use).

Clinical efficacy and safety in cystic fibrosis (CF):

The clinical development programme in CF included 3 multicentre studies in 959 patients aged 5 months and above. Patients below 5 years used a spacer (AeroChamber Plus®) with face mask and were included for safety assessment only. The two pivotal studies (a dose finding Phase II study and a confirmatory Phase III study) compared lung function effects (percent predicted FEV_1 AUC_{0-4h} and trough FEV_1) of Spiriva Respimat (tiotropium 5 µg: 469 patients) versus placebo (315 patients) in 12-weeks randomised, double-blind periods; the Phase III study also included a long term open label extension, up to 12 months. In these studies, all respiratory medications, except anticholinergics, were allowed as concomitant treatment, e.g. long acting beta agonists, mucolytics and antibiotics.

Effects on lung function are displayed in Table 4. No significant improvement in symptoms and health status (exacerbations by Respiratory and Systemic Symptoms Questionnaire and quality of life by Cystic Fibrosis Questionnaire) have been observed.

Table 4: Adjusted mean difference from placebo for absolute changes from baseline after 12 weeks

	Phase II		**Phase III**			
	All patients ($N_{Spiriva}$ = 176, $N_{placebo}$ = 168)		All patients ($N_{Spiriva}$ = 293, $N_{placebo}$ = 147)		≤11 years ($N_{Spiriva}$ = 95, $N_{placebo}$ = 47)	≥12 years ($N_{Spiriva}$ = 198, $N_{placebo}$ = 100)
	mean (95% CI)	p-value	**mean** (95% CI)	p-value	**mean** (95% CI)	**mean** (95% CI)
FEV_1AUC_{0-4h} (% predicted) [a] *absolute changes*	**3.39** (1.67, 5.12)	<0.001	**1.64** (-0.27, 3.55)	0.092	**-0.63** (-4.58, 3.32)	**2.58** (0.50, 4.65)
FEV_1AUC_{0-4h} (litres) *absolute changes*	**0.09** (0.05, 0.14)	<0.001	**0.07** (0.02, 0.12)	0.010	**0.01** (-0.07, 0.08)	**0.10** (0.03, 0.17)
Trough FEV_1 (% predicted) [a] *absolute changes*	**2.22** (0.38, 4.06)	0.018	**1.40** -0.50, 3.30	0.150	**-1.24** (-5.20, - 271)	**2.56** (0.49, 4.62)
Trough FEV_1 (litres) *absolute changes*	**0.06** (0.01, 0.11)	0.028	**0.07** (0.02, 0.12)	0.012	**-0.01** (-0.08, 0.06)	**0.10** (0.03, 0.17)

[a] Co-primary endpoints

All Adverse Drug Reactions (ADRs) observed in the CF studies are known undesirable effects of tiotropium (see 4.8). The most commonly observed adverse events considered related during the 12 week double blind period were cough (4.1%) and dry mouth (2.8%).

The number and percentage of patients reporting adverse events (AEs) of special interest in cystic fibrosis irrespective of relatedness are shown in Table 5. Signs and symptoms considered to be manifestations of cystic fibrosis increased numerically, although not statistically significantly, with tiotropium, especially in patients ≤11 years old.

Table 5: Percentage of patients with AEs of special interest in cystic fibrosis by age group over 12 weeks of treatment irrespective of relatedness (pooled Phase II and Phase III)

	≤11 years		≥12 years	
	$N_{placebo}$ = 96	$N_{Spiriva}$ = 158	$N_{placebo}$ = 215	$N_{Spiriva}$ = 307
Abdominal pain	7.3	7.0	5.1	6.2
Constipation	1.0	1.9	2.3	2.6
Distal intestinal obstruction syndrome	0.0	0.0	1.4	1.3
Respiratory tract infections	34.4	36.7	28.4	28.3
Sputum increased	1.0	5.1	5.6	6.2
Exacerbations	10.4	14.6	18.6	17.9

"Distal intestinal obstruction syndrome" and "Sputum increased" are MedDRA preferred terms. "Respiratory tract infections" is the MedDRA higher level group term. "Abdominal pain", "Constipation" and "Exacerbations" are collections of MedDRA preferred terms.

Thirty-four (10.9 %) patients randomised to placebo and 56 (12.0%) patients randomised to Spiriva Respimat experienced a serious adverse event.

The European Medicines Agency has waived the obligation to submit the results of studies with Spiriva Respimat in the subset of paediatric patients below 1 year of age.

5.2 Pharmacokinetic properties

a) General Introduction

Tiotropium bromide is a non-chiral quaternary ammonium compound and is sparingly soluble in water. Tiotropium bromide is available as inhalation solution administered by the Respimat inhaler. Approximately 40% of the inhaled dose is deposited in the lungs, the target organ, the remaining amount being deposited in the gastrointestinal tract. Some of the pharmacokinetic data described below were obtained with higher doses than recommended for therapy.

b) General Characteristics of the Active Substance after Administration of the Medicinal Product

Absorption: Following inhalation by young healthy volunteers, urinary excretion data suggests that approximately 33% of the inhaled dose reaches the systemic circulation. Oral solutions of tiotropium bromide have an absolute bioavailability of 2-3%. Food is not expected to influence the absorption of this quaternary ammonium compound.
Maximum tiotropium plasma concentrations were observed 5-7 minutes after inhalation.
At steady state, peak tiotropium plasma levels in COPD patients of 10.5 pg/ml were achieved and decreased rapidly in a multi-compartmental manner. Steady state trough plasma concentrations were 1.60 pg/ml.
A steady state tiotropium peak plasma concentration of 5.15 pg/ml was attained 5 minutes after the administration of the same dose to patients with asthma.
Systemic exposure to tiotropium following the inhalation of tiotropium via the Respimat inhaler was similar to tiotropium inhaled via the HandiHaler device.

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.

Biotransformation: The extent of biotransformation is small. This is evident from a urinary excretion of 74% of unchanged substance after an intravenous dose to young healthy volunteers. The ester tiotropium bromide is nonenzymatically cleaved to the alcohol (N-methylscopine) and acid compound (dithienylglycolic acid) that are inactive on muscarinic receptors. In-vitro experiments with human liver microsomes and human hepatocytes suggest that some further drug (< 20% of dose after intravenous administration) is metabolised by cytochrome P450 (CYP) dependent oxidation and subsequent glutathion conjugation to a variety of Phase II-metabolites.
In vitro studies in liver microsomes reveal that the enzymatic pathway can be inhibited by the CYP 2D6 (and 3A4) inhibitors, quinidine, ketoconazole and gestodene. Thus CYP 2D6 and 3A4 are involved in 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 CYP 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1 or 3A in human liver microsomes.

Elimination: The effective half-life of tiotropium ranges between 27 - 45 h following inhalation by healthy volunteers and COPD patients. The effective half-life was 34 hours in patients with asthma. Total clearance was 880 ml/min after an intravenous dose in young healthy volunteers. Intravenously administered tiotropium is mainly excreted unchanged in urine (74%).
After inhalation of the solution by COPD patients to steady-state, urinary excretion is 18.6 % (0.93 µg) of the dose, the remainder being mainly non-absorbed drug in gut that is eliminated via the faeces.
After inhalation of the solution by healthy volunteers urinary excretion is 20.1-29.4 % of the dose, the remainder being mainly non-absorbed drug in gut that is eliminated via the faeces.
In patients with asthma, 11.9% (0.595 µg) of the dose is excreted unchanged in the urine over 24 hours post dose at steady state. 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.

Linearity / Nonlinearity: Tiotropium demonstrates linear pharmacokinetics in the therapeutic range independent of the formulation.

c) Characteristics in Patients

Geriatric Patients: As expected for all predominantly renally excreted drugs, advancing age was associated with a decrease of tiotropium renal clearance (347 ml/min in COPD patients < 65 years to 275 ml/min in COPD patients ≥65 years). This did not result in a corresponding increase in $AUC_{0-6,ss}$ or $C_{max,ss}$ values. Exposure to tiotropium was not found to differ with age in patients with asthma.

Renally Impaired Patients: Following once daily inhaled administrations of tiotropium to steady-state in COPD patients, mild renal impairment (CL_{CR} 50 - 80 ml/min) resulted in slightly higher $AUC_{0-6,ss}$ (between 1.8 - 30% higher) and similar $C_{max,ss}$ values compared to patients with normal renal function(CL_{CR} >80 ml/min).
In COPD patients with moderate to severe renal impairment (CL_{CR} < 50 ml/min), the intravenous administration of a single dose of tiotropium resulted in doubling of the total exposure (82% higher AUC_{0-4h} and 52% higher C_{max}) compared to COPD patients with normal renal function, which was confirmed by plasma concentrations after dry powder inhalation.
In asthma patients with mild renal impairment (CL_{CR} 50-80 ml/min) inhaled tiotropium did not result in relevant increases in exposure compared to patients with normal renal function.

Hepatically Impaired Patients: Liver insufficiency is not expected to have any relevant influence on tiotropium pharmacokinetics. Tiotropium is predominantly cleared by renal elimination (74% in young healthy volunteers) and simple non-enzymatic ester cleavage to pharmacologically inactive products.

Japanese COPD Patients: In cross trial comparison, mean peak tiotropium plasma concentrations 10 minutes post-dosing at steady-state were 20% to 70% higher in Japanese compared to Caucasian COPD patients following inhalation of tiotropium but there was no signal for higher mortality or cardiac risk in Japanese patients compared to Caucasian patients. Insufficient pharmacokinetic data is available for other ethnicities or races.

Paediatric Patients:
Asthma
The peak and total (AUC and urinary excretion) exposure to tiotropium is comparable between patients with asthma who were 6 - 11 years old, 12 - 17 years old and ≥18 years old. Based on urinary excretion, the total exposure to tiotropium in patients 1 to 5 years of age was 52 to 60% lower than in other older age groups. The total exposure data when adjusted for body surface area were found to be comparable in all age groups. Spiriva Respimat was administered with a valved holding chamber with face mask in patients 1 to 5 years of age.

COPD
There were no paediatric patients in the COPD programme (see 4.2).

Cystic Fibrosis
Following inhalation of 5 µg tiotropium, the tiotropium plasma level in CF patients ≥5 years was 10.1 pg/ml 5 minutes post-dosing at steady-state and decreased rapidly thereafter. The fraction of the dose available in CF patients <5 years old who used the spacer and mask was approximately 3- to 4-fold lower than that observed in CF patients 5 years and older. Tiotropium exposure was related to body-weight in CF patients <5 years.

d) Pharmacokinetic / Pharmacodynamic Relationship(s)

There is no direct relationship between pharmacokinetics and pharmacodynamics.

5.3 Preclinical safety data

Many effects observed in conventional studies of safety pharmacology, repeat-dose toxicity, and reproductive toxicity could be explained by the anticholinergic properties of tiotropium bromide. Typically in animals reduced food consumption, inhibited body weight gain, dry mouth and nose,

reduced lacrimation and salivation, mydriasis and increased heart rate were observed. Other relevant effects noted in repeated dose toxicity studies were: mild irritancy of the respiratory tract in rats and mice evinced by rhinitis and epithelial changes of the nasal cavity and larynx, and prostatitis along with proteinaceous deposits and lithiasis in the bladder in rats.

In juvenile rats exposed from postnatal day 7 to sexual maturity, the same direct and indirect pharmacological changes were observed as in the repeat-dose toxicity studies as well as rhinitis. No systemic toxicity was noted and no toxicologically relevant effects on key developmental parameters, tracheal or key organ development were seen.

Harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development could only be demonstrated at maternally toxic dose levels. Tiotropium bromide was not teratogenic in rats or rabbits. 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 any dosage.
The respiratory (irritation) and urogenital (prostatitis) changes and reproductive toxicity was observed at local or systemic exposures more than five-fold the therapeutic exposure. Studies on genotoxicity and carcinogenic potential revealed no special hazard for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride
Disodium edetate
Water, purified
Hydrochloric acid 3.6 % (for pH adjustment)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years
In-use shelf life: 3 months

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

Type and material of the container in contact with the medicinal product:
Solution filled into a polyethylene/polypropylene cartridge with a polypropylene cap with integrated silicone sealing ring. The cartridge is enclosed within an aluminium cylinder.

Pack sizes and devices supplied:

Single pack: 1 Respimat inhaler and 1 cartridge, providing 60 puffs (30 medicinal doses)

Double pack: 2 single packages, each containing 1 Respimat inhaler and 1 cartridge, providing 60 puffs (30 medicinal doses)

Triple pack: 3 single packages, each containing 1 Respimat inhaler and 1 cartridge, providing 60 puffs (30 medicinal doses)

Eight pack: 8 single packages, each containing 1 Respimat inhaler and 1 cartridge, providing 60 puffs (30 medicinal doses)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
D-55216 Ingelheim am Rhein
Germany

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<{DD/MM/YYYY}> <{DD month YYYY}>

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

<[To be completed nationally]>

LABELLING

Version: 9 Mar 2018

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

FOLDING BOX

1. NAME OF THE MEDICINAL PRODUCT

Spiriva Respimat 2.5 microgram, inhalation solution

Tiotropium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

The delivered dose is 2.5 microgram tiotropium (as bromide monohydrate) per puff
(2 puffs comprise one medicinal dose)

3. LIST OF EXCIPIENTS

Benzalkonium chloride
Disodium edetate
Purified water
Hydrochloric acid 3.6%

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation solution
One cartridge contains 4.0 ml providing 60 puffs (30 medicinal doses)

Single pack: 1 Respimat Inhaler and 1 cartridge
Double pack: 2 single packages, each containing 1 Respimat Inhaler and 1 cartridge
Triple pack: 3 single packages, each containing 1 Respimat Inhaer and 1 cartridge
Eight pack: 8 single packages, each containing 1 Respimat Inhaler and 1 cartridge

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
In-use shelf life: 3 months

9. SPECIAL STORAGE CONDITIONS

Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
D-55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Spiriva Respimat

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number} [product code]
SN: {number} [serial number]
NN: {number} [national reimbursement number or other national number identifying the medicinal product]

Additionally:

Insert cartridge in the Respimat inhaler before use.

Spiriva Respimat Inhaler

Boehringer Ingelheim Pharma GmbH & Co.KG
D-55216 Ingelheim

CE 0123

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

DEVICE – Front label

1. NAME OF THE MEDICINAL PRODUCT

Spiriva Respimat
2.5 microgram, inhalation solution
Tiotropium

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim (Logo)

3. EXPIRY DATE

In-use shelf life: 3 months

4. BATCH NUMBER

5. OTHER

60 puffs (30 medicinal doses)

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

DEVICE – BACK LABEL (Requirements according to Medical Device Directive)

1. NAME OF THE MEDICINAL PRODUCT

Spiriva Respimat Inhaler

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch:

5. OTHER

Scale for dose indicator
▷▷ Turn ▷▷

Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Strasse 173
D-55216 Ingelheim

CE 0123

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CARTRIDGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Spiriva Respimat
2.5 microgram, inhalation solution
Tiotropium
Inhalation use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP
In-use shelf life: 3 months

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

One cartridge contains 4.0 ml providing 60 puffs (30 medicinal doses)

6. OTHER

PACKAGE LEAFLET

Version: 9 Mar 2018

Package leaflet: Information for the user

Spiriva Respimat 2.5 microgram, inhalation solution
tiotropium

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Spiriva Respimat is and what it is used for

Spiriva Respimat helps people who have chronic obstructive pulmonary disease (COPD) or asthma to breathe more easily. COPD is a long-term lung disease that causes shortness of breath and coughing. The term COPD is associated with the conditions chronic bronchitis and emphysema. Asthma is a long-term disease characterised by airway inflammation and narrowing of the airways.
As COPD and asthma are long-term diseases you should use Spiriva Respimat every day and not only when you have breathing problems or other symptoms. When used to treat asthma you should use Spiriva Respimat in addition to so-called inhaled corticosteroids and long-acting $ß_2$ agonists.

Spiriva Respimat is a long-acting bronchodilator that helps to open your airways and makes it easier to get air in and out of the lungs. Regular use of Spiriva Respimat can also help you when you have on-going shortness of breath related to your disease, and will help to minimise the effects of the disease on your everyday life. Daily use of Spiriva Respimat will also help to prevent any sudden, short-term worsening of your COPD symptoms which may last for several days.

For correct dosing of Spiriva Respimat please see section 3. How to use Spiriva Respimat and the instructions for use provided on the other side of the leaflet.

2. What you need to know before you use Spiriva Respimat

Do not use Spiriva Respimat

- if you are allergic (hypersensitive) to tiotropium or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic (hypersensitive) to atropine or substances related to it, e.g. ipratropium or oxitropium.

Warnings and precautions

Talk to your doctor or pharmacist before using Spiriva Respimat.

Talk to your doctor if you suffer from narrow angle glaucoma, prostate problems or have difficulty passing urine.

If you have problems with your kidneys, please consult your doctor.

When taking Spiriva Respimat take care not to let any spray enter your eyes. This may result in eye pain or discomfort, blurred vision, seeing halos around lights or coloured images in association with red eyes (i.e. narrow angle glaucoma). Eye symptoms may be accompanied by headache, nausea or vomiting. Wash your eyes in warm water, stop using tiotropium bromide and immediately consult your doctor for further advice.

If your breathing has got worse or if you experience rash, swelling or itching directly after using your inhaler, stop using it and tell your doctor immediately.

Dry mouth which has been observed with anti-cholinergic treatment may in the long term be associated with dental caries. Therefore, please remember to pay attention to oral hygiene.

Spiriva Respimat is indicated for the maintenance treatment of your chronic obstructive pulmonary disease or asthma. Do not use this medicine to treat a sudden attack of breathlessness or wheezing. Your doctor should have given you another inhaler ("rescue medication") for this. Please follow the instructions you doctor has given you.

If you have been prescribed Spiriva Respimat for your asthma it should be added on to your treatments that include an inhaled corticosteroid and long-acting $ß_2$ agonists. Continue taking the inhaled corticosteroid as prescribed by your doctor, even if you feel better.

In case you have suffered from a myocardial infarction during the last 6 months or from any unstable or life threatening irregular heart beat or severe heart failure within the past year, please, inform your doctor.This is important to decide if Spiriva is the right medicine for you to take.

Do not take Spiriva Respimat more frequently than once daily.

You should also contact your doctor if you feel that your breathing is worsening.

If you have cystic fibrosis, tell your doctor because Spiriva Respimat could make your cystic fibrosis symptoms worse.

Children and adolescents

Spiriva Respimat is not recommended for children under 6 years.

Other medicines and Spiriva Respimat

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines, including medicines obtained without a prescription.

In particular, please tell your doctor or pharmacist if you are using/have used anticholinergic drugs, e.g. ipratropium or oxitropium.

No interaction side effects have been reported when Spiriva Respimat has been used with other products used to treat COPD such as reliever inhalers (e.g. salbutamol), methylxanthines (e.g. theophylline), antihistamines, mucolytics (e.g. ambroxol), leukotriene modifiers (e.g. montelukast),

cromones, anti-IgE treatment (e.g. omalizumab) and/or inhaled or oral steroids (e.g. budesonide, prednisolone).

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
You should not use this medicine unless specifically recommended by your doctor.

Driving and using machines

No studies on the effects and the ability to drive and use machines have been performed. In case dizziness or blurred vision occurs the ability to drive and use machinery may be influenced.

3. How to use Spiriva Respimat

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Spiriva Respimat is for inhalation use only.

The recommended dose for patients 6 years and older is:

Spiriva Respimat is effective for 24 hours so you will need to use Spiriva Respimat only **ONCE A DAY**, if possible at the same time of the day. Each time you use it take TWO PUFFS.

As COPD and asthma are long-term diseases use Spiriva Respimat every day and not only when you experience breathing problems. Do not use more than the recommended dose.

Spiriva Respimat is not recommended for use in children below 6 years due to lack of data on safety and efficacy.

Make sure that you know how to use your Spiriva Respimat inhaler properly. The instructions for use of the Spiriva Respimat inhaler are provided on the other side of this leaflet.

If you use more Spiriva Respimat than you should
If you use more Spiriva Respimat than two puffs in one day talk to your doctor immediately. You may be at a higher risk of experiencing a side effect such as dry mouth, constipation, difficulties passing urine, increased heart beat or blurred vision.

If you forget to use Spiriva Respimat
If you forget to take a dose (TWO PUFFS ONCE A DAY), take it as soon as you remember but do not take two doses at the same time or on the same day. Then take your next dose as usual.

If you stop using Spiriva Respimat
Before you stop using Spiriva Respimat, you should talk to your doctor or your pharmacist. If you stop using Spiriva Respimat the signs and symptoms of COPD and asthma may worsen.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Evaluation of the side effects is based on the following frequencies:

Common:	may affect up to 1 in 10 people
Uncommon:	may affect up to 1 in 100 people
Rare:	may affect up to 1 in 1,000 people
Not known:	frequency cannot be estimated from the available data

The side effects described below have been experienced by people taking this medicine and they are listed according to frequency as either common, uncommon, rare or not known.

Side effect	**Frequency COPD**	**Frequency Asthma**
Dry mouth	Common	Uncommon
Hoarseness (dysphonia)	Uncommon	Uncommon
Cough	Uncommon	Uncommon
Headache	Uncommon	Uncommon
Inflammation of the throat (pharyngitis)	Uncommon	Uncommon
Painful urination (dysuria)	Uncommon	Not known
Dizziness	Uncommon	Uncommon
Fungal infections of the oral cavity and throat (oropharyngeal candidiasis)	Uncommon	Uncommon
Difficulties passing urine (urinary retention)	Uncommon	Not known
Constipation	Uncommon	Rare
Rash	Uncommon	Uncommon
Itching (pruritus)	Uncommon	Rare
Increase of the measured eye pressure	Rare	Not known
Serious allergic reaction which causes swelling of the mouth and face or throat (angioneurotic oedema)	Rare	Rare
Difficulty in sleeping (insomnia)	Rare	Uncommon
Irregular heart beat (atrial fibrillation, supraventricular tachycardia)	Rare	Not known
Feeling your hearbeat (palpitations)	Rare	Uncommon
Nosebleed (epistaxis)	Rare	Rare
Inflammation of the tongue (glossitis)	Rare	Not known
Faster heart beat (tachycardia)	Rare	Not known
Tightness of the chest, associated with coughing, wheezing or breathlessness immediately after inhalation (bronchospasm)	Rare	Uncommon
Difficulties swallowing (dysphagia)	Rare	Not known
Seeing halos around lights or coloured images in association with red eyes (glaucoma)	Rare	Not known
Blurred vision	Rare	Not known
Inflammation of the larynx (laryngitis)	Rare	Not known
Dental caries	Rare	Not known
Inflammation of the gums (gingivitis)	Rare	Rare
Nettle rash (urticaria)	Rare	Rare
Infections or ulcerations of the skin	Rare	Not known
Dryness of the skin	Rare	Not known
Infections of the urinary tract	Rare	Rare
Heart burn (gastrooesophageal reflux disease)	Rare	Not known
Hypersensitivity, including immediate reactions	Not known	Rare
Inflammation of the mouth (stomatitis)	Not known	Rare

Side effect	Frequency COPD	Frequency Asthma
Depletion of body water (dehydration)	Not known	Not known
Inflammation in sinuses (sinusitis)	Not known	Not known
Blockage of intestines or absence of bowel movements (intestinal obstruction, including ileus paralytic)	Not known	Not known
Feeling sick (nausea)	Not known	Not known
Severe allergic reaction (anaphylactic reaction)	Not known	Not known
Swelling of joint	Not known	Not known

Immediate allergic reactions such as rash, nettle rash (urticaria), swelling of the mouth and face or sudden difficulties in breathing (angioneurotic oedema) or other hypersensitivity reactions (such as sudden reduction of your blood pressure or dizziness) may occur individually or as part of severe allergic reaction (anaphylactic reaction) after administration of Spiriva Respimat.

In addition, in common with all inhaled medicines, some patients may experience an unexpected tightness of the chest, coughing, wheezing or breathlessness immediately after inhalation (bronchospasm).
If any of these occur, please consult your doctor immediately.

Reporting of side effects
If you get any side effects , talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Spiriva Respimat

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the inhaler label. The expiry date refers to the last day of that month. Spiriva Respimat inhaler should be discarded at the latest 3 months after first use (see Instructions for use overleaf).

Do not freeze.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Spiriva Respimat contains

The active substance is tiotropium. The delivered dose is 2.5 microgram tiotropium per puff (2 puffs comprise one medicinal dose) and is equivalent to 3.124 microgram tiotropium bromide monohydrate. The delivered dose is the dose which is available for the patient after passing the mouthpiece.

The other ingredients are benzalkonium chloride, disodium edetate, purified water, and hydrochloric acid 3.6 % for pH adjustment.

What Spiriva Respimat looks like and contents of the pack

Spirva Respimat 2.5 microgram is composed of one cartridge with inhalation solution and one Respimat inhaler. The cartridge has to be inserted into the inhaler before the first use.

Single pack: 1 Respimat inhaler and 1 cartridge, providing 60 puffs (30 medicinal doses)

Double pack: 2 single packages, each containing 1 Respimat inhaler and 1 cartridge, providing 60 puffs (30 medicinal doses)

Triple pack: 3 single packages, each containing 1 Respimat inhaler and 1 cartridge, providing 60 puffs (30 medicinal doses)

Eight pack: 8 single packages, each containing 1 Respimat inhaler and 1 cartridge, providing 60 puffs (30 medicinal doses)

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

The marketing authorisation holder for Spiriva Respimat is:

Boehringer Ingelheim International GmbH
Binger Straße 173
D-55216 Ingelheim am Rhein
Germany

The manufacturer for Spiriva Respimat is:

Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Straße 173
D-55216 Ingelheim am Rhein
Germany

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria, Liechtenstein:	Spiriva Respimat 2,5 Mikrogramm - Lösung zur Inhalation
Belgium, Luxembourg:	Spiriva Respimat 2,5 microgrammes, solution à inhaler
Bulgaria:	Спирива Респимат 2,5 микрограма, разтвор за инхалация
Cyprus, Greece:	Spiriva Respimat 2.5 μικρογραμμάρια, εισπνεόμενο διάλυμα
Czech Republic:	Spiriva Respimat 2,5 mikrogramu, roztok k inhalaci
Denmark:	Spiriva Respimat Inhalationsvæske, opløsning 2,5 microgram
Estonia:	SPIRIVA RESPIMAT inhalatsioonilahus 2,5µg/annuses
Finland:	SPIRIVA RESPIMAT 2.5 mikrog inhalaationeste, liuos
France:	Spiriva Respimat 2,5 microgrammes/dose, solution pour inhalation
Germany:	Spiriva Respimat 2,5 Mikrogramm Lösung zur Inhalation
Hungary:	Spiriva Respimat 2,5 mikrogramm inhalációs oldat
Iceland:	Spiriva Respimat 2.5 mikróg/skammt
Ireland, Malta, UK:	Spiriva Respimat 2.5 microgram, inhalation solution
Italy:	Spiriva Respimat 2.5 mcg soluzione per inalazione
Latvia:	Spiriva Respimat 2,5 mikrogrami šķīdums inhalācijām
Lithuania:	Spiriva Respimat 2,5 mikrogramo/išpurškime įkvepiamasis tirpalas
Netherlands:	Spiriva Respimat 2,5 microgram, inhalatieoplossing
Norway:	Spiriva Respimat 2,5 mikrogram inhalasjonsvæske, oppløsning
Poland:	Spiriva Respimat 2,5 mikrograma/dawkę odmierzoną, roztwór do inhalacji
Portugal:	Spiriva Respimat 2.5 mg/dose, Solução para inhalção por nebulizaão
Romania:	SPIRIVA RESPIMAT 2,5 microgram soluţie de inhalat

Slovakia:	Spiriva Respimat sol ihl 2,5 µg/1 dávka
Slovenia:	Spiriva Respimat 2,5 mikrogramov raztopina za inhaliranje
Spain:	Spiriva Respimat 2,5 microgramos, solución para inhalación
Sweden:	Spiriva Respimat 2,5 mikrogram, inhalationsvätska, lösning

This leaflet was last revised in {MM/YYYY}.

To be completed nationally

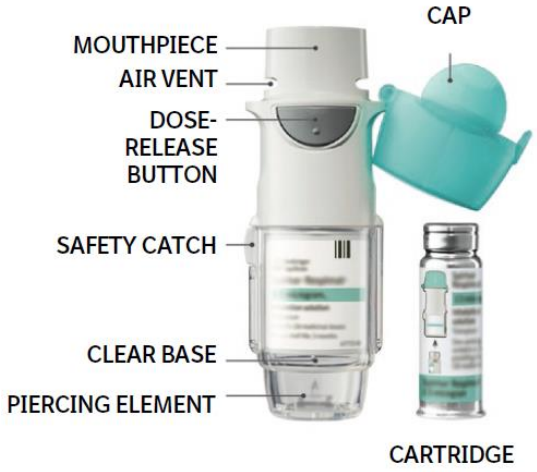
Instructions for Use
Spiriva Respimat inhaler

Introduction

Spiriva Respimat (tiotropium bromide). Read these Instructions for Use before you start using Spiriva Respimat.

Children should use Spiriva Respimat with an adult's assistance.

You will need to use this inhaler only ONCE A DAY. Each time you use it take TWO PUFFS.

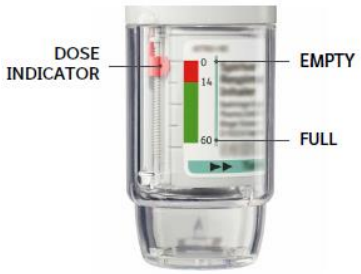


- If Spiriva Respimat has not been used for more than 7 days release one puff towards the ground.
- If Spiriva Respimat has not been used for more than 21 days repeat steps 4 to 6 under 'Prepare for first use' until a cloud is visible. Then repeat steps 4 to 6 three more times.
- Do not touch the piercing element inside the clear base.

How to care for your Spiriva Respimat

Clean the mouthpiece including the metal part inside the mouthpiece with a damp cloth or tissue only, at least once a week.
Any minor discoloration in the mouthpiece does not affect your Spiriva Respimat inhaler performance. If necessary, wipe the outside of your Spiriva Respimat inhaler with a damp cloth.

When to get a new Spiriva Respimat



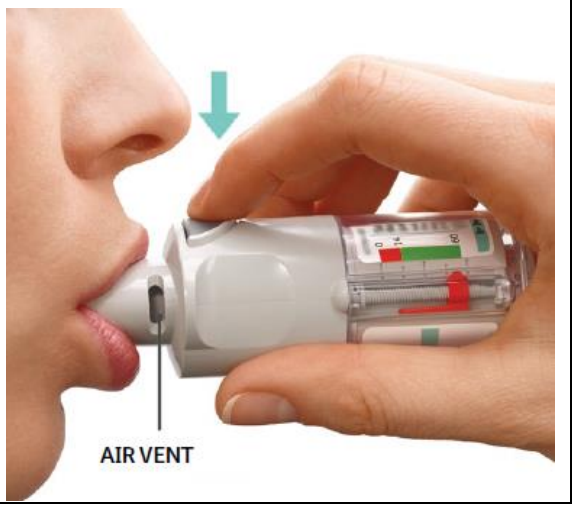
- Your Spiriva Respimat inhaler contains 60 puffs (30 doses) if used as indicated (two puffs/once daily).
- The dose indicator shows approximately how much medication is left.
- When the dose indicator enters the red area of the scale you need to get a new prescription; there is approximately medication for 7 days left (14 puffs).
- Once the dose indicator reaches the end of the red scale, your Spiriva Respimat locks automatically – no more doses can be released. At this point, the clear base cannot be turned any further.
- Spiriva Respimat should be discarded three months after you have prepared it for first use, even if it has not been fully used or used at all.

Prepare for first use

1. Remove clear base • Keep the cap closed. • Press the safety catch while firmly pulling off the clear base with your other hand.	
2. Insert cartridge • Insert the narrow end of the cartridge into the inhaler. • Place the inhaler on a firm surface and push down firmly until it clicks into place.	
3. Replace clear base • Put the clear base back into place until it clicks.	
4. Turn • Keep the cap closed. • Turn the clear base in the direction of the arrows on the label until it clicks (half a turn).	

5. Open • Open the cap until it snaps fully open.	
6. Press • Point the inhaler toward the ground. • Press the dose-release button. • Close the cap. • Repeat steps 4-6 until a cloud is visible. • **After a cloud is visible**, repeat steps 4-6 three more times. Your inhaler is now ready to use. These steps will not affect the number of doses available. After preparation your inhaler will be able to deliver 60 puffs (30 doses).	

Daily use

TURN • Keep the cap closed. • **TURN** the clear base in the direction of the arrows on the label until it clicks (half a turn).	
OPEN • **OPEN** the cap until it snaps fully open.	
PRESS • Breathe out slowly and fully. • Close your lips around the mouthpiece without covering the air vents. Point your Inhaler to the back of your throat. • While taking a slow, deep breath through your mouth, **PRESS** the dose-release button and continue to breathe in slowly for as long as comfortable. • Hold your breath for 10 seconds or for as long as comfortable. • Repeat Turn, Open, Press for a total of 2 puffs. • Close the cap until you use your inhaler again.	

Answers to Common Questions

<u>It is difficult to insert the cartridge deep enough.</u>

Did you accidentally turn the clear base before inserting the cartridge? Open the cap, press the dose-release button, then insert the cartridge.
Did you insert the cartridge with the wide end first? Insert the cartridge with the narrow end first.

I cannot press the dose-release button.

Did you turn the clear base? If not, turn the clear base in a continuous movement until it clicks (half a turn).
Is the dose indicator on the Spiriva Respimat pointing to zero? The Spiriva Respimat inhaler is locked after 60 puffs (30 medicinal doses). Prepare and use your new Spiriva Respimat inhaler.

I cannot turn the clear base.

Did you turn the clear base already?
If the clear base has already been turned, follow steps "OPEN" and "PRESS" under "Daily Use" to get your medicine.
Is the dose indicator on the Spiriva Respimat pointing to zero? The Spiriva Respimat inhaler is locked after 60 puffs (30 medicinal doses). Prepare and use your new Spiriva Respimat inhaler.

The dose indicator on the Spiriva Respimat reaches zero too soon.
Did you use Spiriva Respimat as indicated (two puffs/once daily)? Spiriva Respimat will last 30 days if used at two puffs once daily.
Did you turn the clear base before you inserted the cartridge? The dose indicator counts each turn of the clear base regardless whether a cartridge has been inserted or not.
Did you spray in the air often to check whether the Spiriva Respimat is working? Once you have prepared Spiriva Respimat, no test-spraying is required if used daily.
Did you insert the cartridge into a used Spiriva Respimat? Always insert a new cartridge into a **NEW** Spiriva Respimat.

My Spiriva Respimat sprays automatically.

Was the cap open when you turned the clear base? Close the cap, then turn the clear base.
Did you press the dose-release button when turning the clear base? Close the cap, so the dose-release button is covered, then turn the clear base.
Did you stop when turning the clear base before it clicked? Turn the clear base in a continuous movement until it clicks (half a turn).

My Spiriva Respimat doesn't spray.

Did you insert a cartridge? If not, insert a cartridge.
Did you repeat Turn, Open, Press less than three times after inserting the cartridge? Repeat Turn, Open, Press three times after inserting the cartridge as shown in the steps 4 to 6 under "Prepare for first use".
Is the dose indicator on the Spiriva Respimat pointing to 0? If the dose indicator points to 0, you have used up all your medication and the inhaler is locked.
Once your Spiriva Respimat is assembled, do not remove the clear base or the cartridge. Always insert a new cartridge into a **NEW** Spiriva Respimat.

Further Information

Boehringer Ingelheim Pharma GmbH & Co. KG
D - 55216 Ingelheim
Germany

CE 0123