SPIRIVA RESPIMAT re-usable
2.5 microgram,
Solution for Inhalation

1. NAME OF THE MEDICINAL PRODUCT

SPIRIVA RESPIMAT re-usable 2.5 microgram, solution for inhalation

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 a full list of excipients, see section 6.1.

3. PRODUCT DESCRIPTION

SPIRIVA RESPIMAT re-usable Solution for Inhalation is a clear, colourless solution of tiotropium bromide monohydrate filled into a 4.5ml cartridge. Each cartridge providing 60 puffs (30 medicinal doses). The solution is to be used with a Respimat Inhaler.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

COPD

SPIRIVA RESPIMAT re-usable is indicated as a maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD).

Asthma

SPIRIVA RESPIMAT re-usable is indicated as add-on maintenance bronchodilator treatment in patients aged 6 years and older with moderate to severe asthma.

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.

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

COPD

SPIRIVA RESPIMAT re-usable is not recommended for use in children and adolescents below 18 years due to lack of data on safety and efficacy (see 5.1 and 5.2).

Asthma

In asthma, the recommended dosage of tiotropium using the SPIRIVA RESPIMAT re-usable in patients 6 to 17 years of age is 5 micrograms. This is administered as two puffs once daily from the RESPIMAT inhaler, at the same time each day (see RESPIMAT inhaler Instructions for Use).

SPIRIVA RESPIMAT re-usable has not been studied in children less than 1 year old

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.

4.3 Contraindications

SPIRIVA RESPIMAT re-usable is contraindicated in patients with hypersensitivity to tiotropium bromide, atropine or its derivatives, e.g. ipratropium or oxitropium or to any of the excipients (see 6.1).

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 re-usable should not be used as (first-line) 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 re-usable, even when their symptoms improve.
Immediate hypersensitivity reactions may occur after administration of tiotropium bromide solution for inhalation.

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. SPIRIVA RESPIMAT re-usable should be used with caution in patients with known cardiac rhythm disorders (see 5.1).

As plasma concentration increases with decreased renal function in patients with moderate to severe renal impairment (creatinine clearance $\leq$ 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).

Benzalkonium chloride:
This medicine contains 0.0011 mg benzalkonium chloride in each actuation.
Benzalkonium chloride may cause wheezing and breathing difficulties. Patients with asthma are at an increased risk for these adverse events.

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.
Tiotropium bromide has been used concomitantly with other drugs commonly used in the treatment of COPD, including sympathomimetic bronchodilators and oral and inhaled steroids without clinical evidence of drug interactions.

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. Pre-clinical 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 re-usable during pregnancy.

Breast-feeding

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 re-usable is not recommended during breast-feeding. Tiotropium bromide is a long-acting compound. A decision on whether to continue/discontinue breast-feeding or to continues/discontinue therapy with SPIRIVA RESPIMAT re-usable should be made taking into account the benefit of breast-feeding to the child and the benefit of SPIRIVA RESPIMAT re-usable therapy to the woman.

Fertility

Clinical data on fertility are not available for tiotropium. A pre-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 occurence 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 asthma (1930 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 (≥1/10,000to <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
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
Epistaxis	Uncommon	Rare
Pharyngitis	Uncommon	Uncommon
Dysphonia	Uncommon	Uncommon
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 1.2%.

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 6 clinical trials in asthma (1,256 patients).

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

Paedriatic population

The frequency, type and severity of adverse reactions in the paediatric population are similar as in adults

Other special population

An increase in anticholinergic effects may occur with increasing age.

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 solution for inhalation in healthy volunteers with the exception of pronounced reduction in salivary flow from day 7 onwards. No significant undesirable effects have been observed in four long term-studies in COPD patients with a daily dose of 10 microgram tiotropium solution for inhalation over 4-48 weeks.

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

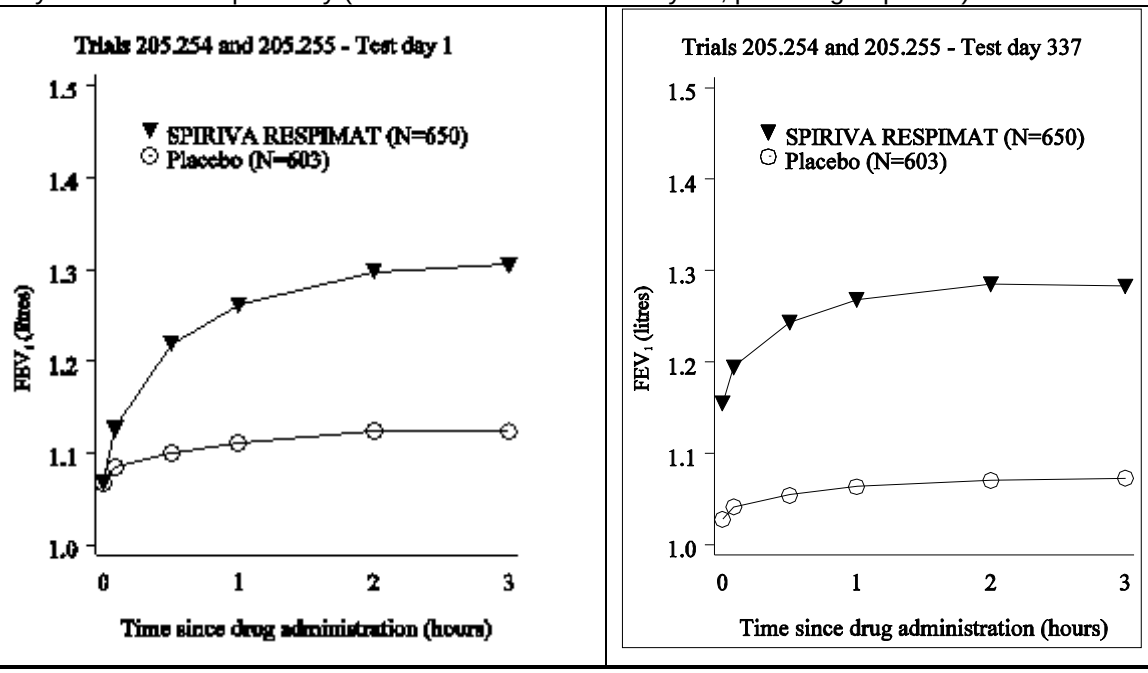
Lung function

Tiotropium solution for inhalation, 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 re-usable 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 re-usable 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 re-usable were maintained throughout the 1-year period of administration with no evidence of tolerance.

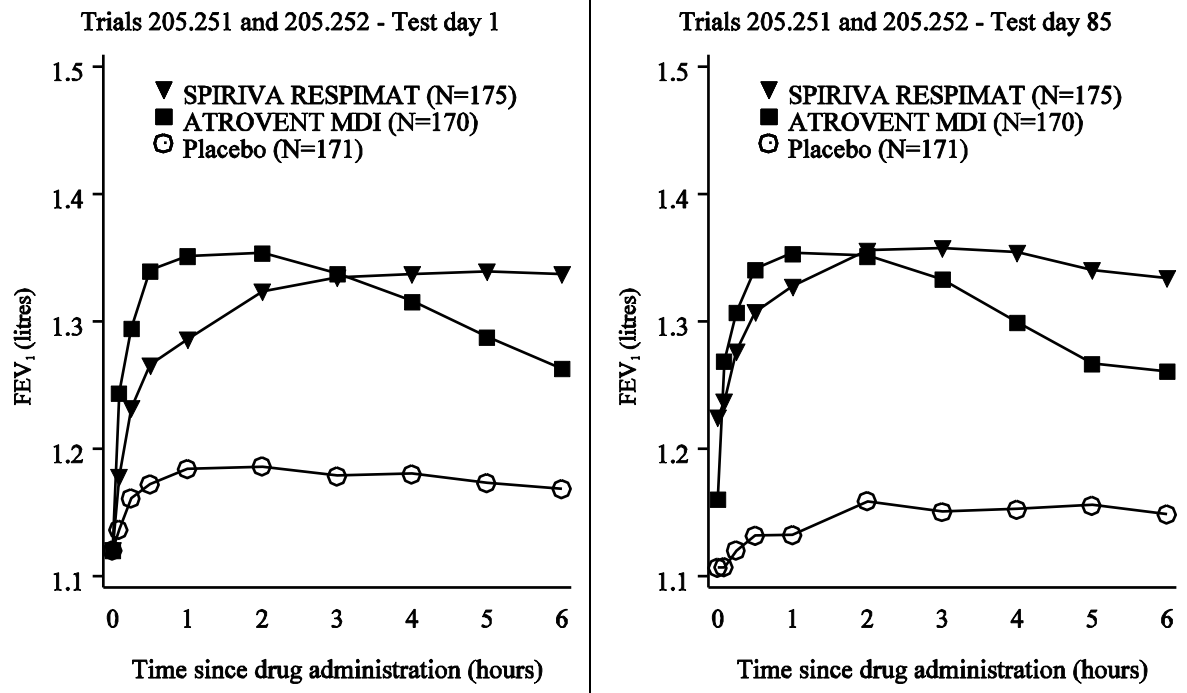
Figure 1: Mean FEV_1 (litres) at each time point (prior to and after administration of study drug) on Days 1 and 337 respectively (combined data from two 1-year, parallel-group trials)*



*Means adjusted for center, smoking status and baseline effect. A total of 545 and 434 patients in the SPIRIVA® and placebo groups, respectively completed test day 337. The data for the remaining

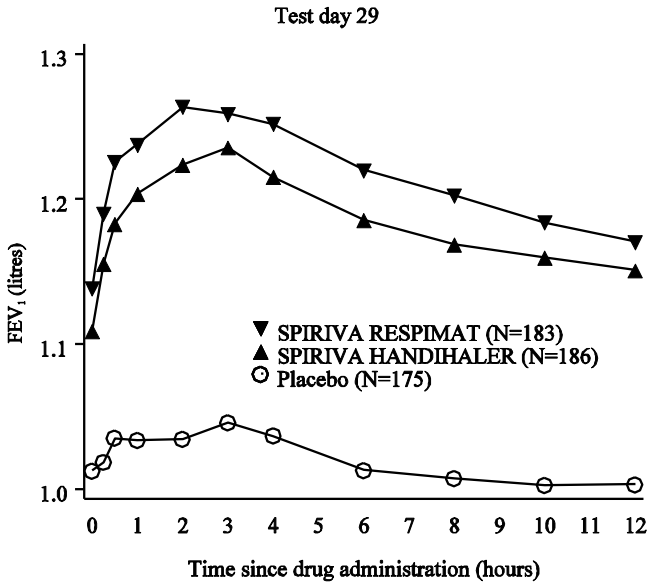
patients were imputed using last observation or least favourable observation carried forward.

Figure 2: Mean FEV_1 (litres) at each time point (prior to and after administration of study drug) on Days 1 and 85 respectively (combined data from two 12-week, parallel-group trials)



*Day 85, a total of 155, 142 and 152 patients in the SPIRIVA®, ATROVENT® MDI and placebo groups, respectively completed test day 85. The data for the remaining patients were imputed using last observation or least favourable observation carried forward.

Figure 3: Mean FEV_1 (litres) at each time point (prior to and after administration of study drug) on Day 29 (combined data from two 4-week cross-over studies 205.249 and 205.250)*



*Means adjusted for center, patient (within center), period and baseline effect. The data for patients who discontinued a test day early were imputed using last observation or least favourable observation

carried forward. Patients who completed the trials took all 3 treatments.

A combined analysis of two randomised, placebo-controlled, crossover, clinical studies demonstrated that the bronchodilator response for SPIRIVA RESPIMAT re-usable (5 µg) was numerically higher compared to SPIRIVA HandiHaler (18 µg) inhalation powder after a 4-week treatment period.

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

(a) Dypsnoea
SPIRIVA RESPIMAT re-usable 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.

(b) 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 re-usable 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.

(c) COPD Exacerbations
In three one-year, randomised, double-blind, placebo-controlled clinical trials SPIRIVA RESPIMAT re-usable 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 re-usable 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	NA[e]	NA[e]	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	NA[e]	NA[e]	27 (10 to 41)[b]	0.003[b]
	Mean hospitalised exacerbation	0.12[c]	0.15[c]	19	0.004[c]

Study ($N_{Spiriva}$, $N_{placebo}$)	Endpoint	Spiriva Respimat	Placebo	% Risk Reduction (95% CI)[a]	p-value
	incidence rate per patient year			(7 to 30)[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.

[e] Less than 25% of patients had a COPD exacerbation leading to hospitalisation

Long-term tiotropium active- controlled study

A long term, large scale, randomised, double-blind, active-controlled study with a treatment period up to 3 years has been performed to compare the efficacy and safety of SPIRIVA RESPIMAT re-usable and SPIRIVA HANDIHALER (5,711 patients receiving SPIRIVA® RESPIMAT 2.5 microgram (5 microgram medicinal dose); 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 similar during the study with SPIRIVA RESPIMAT re-usable and SPIRIVA HANDIHALER (hazard ratio (SPIRIVA RESPIMAT re-usable / 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 re-usable and 719 days for SPIRIVA HANDIHALER

The bronchodilator effect of SPIRIVA RESPIMAT re-usable was sustained over 120 weeks, and was similar to SPIRIVA HANDIHALER. The mean difference in trough FEV_1 for SPIRIVA RESPIMAT re-usable versus SPIRIVA HANDIHALER was -0.010 L (95% CI -0.038 to 0.018 mL).

In the post-marketing TIOSPIR study comparing SPIRIVA RESPIMAT re-usable and Spiriva HandiHaler, all-cause mortality (including vital status follow up) was similar with hazard ratio (SPIRIVA RESPIMAT re-usable/Spiriva HandiHaler) = 0.96 , 95% CI 0.84 -1.09). Respective treatment exposure was 13,135 and 13,050 patient-years.

The COPD exacerbation hospitalisation rate (per patient year) was 0.12 for SPIRIVA RESPIMAT re-usable and 0.20 for placebo, which was a numerical improvement (p=0.26). The combined data of the two 1-year trials did not have sufficient statistical power to detect a difference in this secondary endpoint.

The incidence of angina was numerically higher in the SPIRIVA RESPIMAT re-usable 5 mcg groups (1.4%) than in placebo groups (0.5%). However, the number of serious ischaemic events including myocardial infarction, which may be seen as a marker of flow limitation in the coronary circulation, were the same or lower for SPIRIVA RESPIMAT re-usable 5 mcg groups. Therefore, no consistent pattern of events indicative of myocardial ischaemia was found.

The incidence of pneumonia was numerically higher in the SPIRIVA RESPIMAT re-usable 5 mcg groups (2.6%) than in the placebo groups (1.6%). Events coded as “lower respiratory tract infections” were balanced across treatment groups. These events which include COPD exacerbations, bronchitis, lower respiratory tract infections, as well as pneumonia are all lower respiratory tract infections having

similar signs and symptoms. Therefore, it can be inferred that the observed differences are in reporting terminology only and, as such, do not reflect any real clinically significant difference between groups.

The incidence rate of fatal events per 100 patient-years in the SPIRIVA RESPIMAT re-usable 5 mcg groups (669 patient-years) was comparable to that observed with SPIRIVA HandiHaler 18 mcg groups (2957 patient-years), being 1.79 and 2.13 respectively. The incidence rate of fatal events in the Respimat placebo groups (583 patient-years) was unusually low, being 0.86 compared with 2.53 in the SPIRIVA HandiHaler placebo groups (2175 patient-years). In the two 12 month trials, there was a higher incidence of premature discontinuations of patients with more severe COPD from the Respimat placebo groups. No causality for fatal events was attributable to any treatment assignment.

Clinical efficacy and safety in asthma

Adult Patients

The clinical Phase III programme for persistent asthma included two 1-year randomised, double-blind, placebo-controlled studies in a total of 907 asthma patients (453 receiving SPIRIVA RESPIMAT re-usable) 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 re-usable 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 FEV1 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).

In the two 6-month MezzoTinA-asthma studies in patients who were symptomatic on maintenance treatment of medium-dose ICS, SPIRIVA RESPIMAT re-usable showed significant improvements in lung function over placebo when used as add-on to background treatment.

- At week 24, mean improvements in peak and trough FEV1 were 0.185 litres (95% CI: 0.146 to 0.223 litres, p<0.0001) and 0.146 litres (0.105 to 0.188 litres, p<0.0001), respectively. The peak and trough FEV1 values for salmeterol were 0.196 litres (95% CI: 0.158 to 0.234 litres) and 0.114 litres (95% CI: 0.073 to 0.155 litres), respectively.

- SPIRIVA RESPIMAT re-usable significantly improved morning and evening PEF (morning 24 L/min; 95% CI: 18 to 31 L/min, p< 0.0001; evening 23 L/min; 95% CI: 17 to 30 L/min, p<0.0001). The morning and evening PEF for salmeterol compared to placebo were 25 L/min (95% CI: 19 to 31 L/min) and 21 L/min (95% CI: 15 to 27 L/min), respectively.

- Patients who took SPIRIVA RESPIMAT re-usable had a significantly higher ACQ responder rate at week 24 compared to patients taking placebo (Table 3).

Table 3: ACQ Responders in Patients symptomatic on ICS (Mezzo TinA-asthma studies)

Study	**Treatment**	**ACQ responder (%)**	**p-value***
24 week Ph III studies, pooled analysis	Placebo, added-on to ICS (N=518)	57.7	
	SPIRIVA RESPIMAT ,	64.3	0.0348

	added-on to ICS (N=513)		
	Salmeterol, added-on to ICS (N=535)	66.5	0.0039

* calculated as 2*one−sided−p−value in the direction corresponding to testing the null hypothesis

Paediatric Patients

The clinical Phase III program for persistent asthma in paediatric patients (1-17 years) was based on the following clinical trials and a partial extrapolation of data from adults:

- Adolescents (12-17 years): one 1-year and one 12-week randomised, double-blind, placebo-controlled studies in a total of 789 asthma patients (264 receiving SPIRIVA RESPIMAT re-usable)

- Children (6-11 years): one 1-year and one 12-week randomised, double-blind, placebo-controlled studies in a total of 801 asthma patients (265 receiving SPIRIVA RESPIMAT re-usable)

- Children (1-5 years): one 12-week randomised, double-blind placebo-controlled study in a total of 101 asthma patients (31 receiving SPIRIVA RESPIMAT re-usable)

In all these studies, patients were on background treatment of at least ICS.

Adolescents (12-17 years)

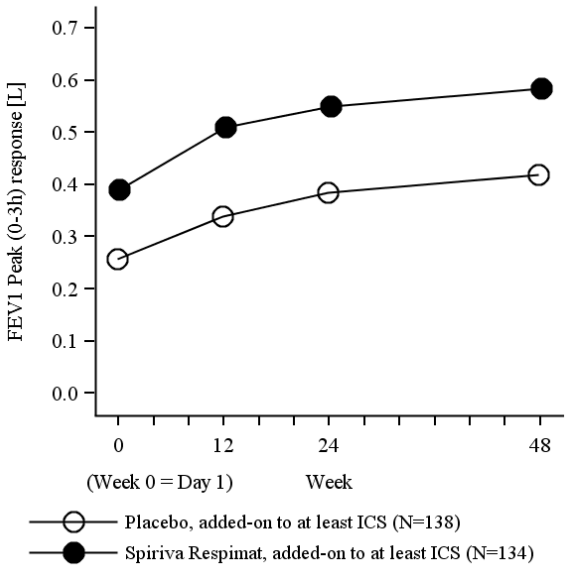
In the 1-year RubaTinA-asthma study in patients who were symptomatic on maintenance treatment of at least medium-dose ICS, SPIRIVA RESPIMAT re-usable showed significant improvements in lung function over placebo when used as add-on to background treatment.

- At week 24, mean improvements in peak and trough FEV1 were 0.174 litres (95% CI: 0.076 to 0.272 litres, p=0.0005) and 0.117 litres (95% CI: 0.010 to 0.223 litres, p=0.0320), respectively.

- At week 24, SPIRIVA RESPIMAT re-usable significantly improved morning and evening PEF (morning 15.8 L/min; 95% CI: 2.3, 29.3 L/min, p=0.0214; evening 16.7 L/min; 95% CI: 3.4, 30.0 L/min, p=0.0137).

- The bronchodilator effects of SPIRIVA RESPIMAT re-usable were maintained throughout the 1 year period of administration with no evidence of tachyphylaxis (Figure 4).

Figure 4: Peak FEV1 response over 48 weeks in the RubaTinA-asthma study



In the 12-week PensieTinA-asthma study in patients who were symptomatic on maintenance treatment of at least medium dose ICS in combination with 1 or more controller medication, SPIRIVA RESPIMAT re-usable showed improvements in lung function over placebo when used as add-on to background treatment, however, the differences in peak and trough FEV1 were not statistically significant.

- At week 12, mean improvements in peak and trough FEV1 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 re-usable 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).

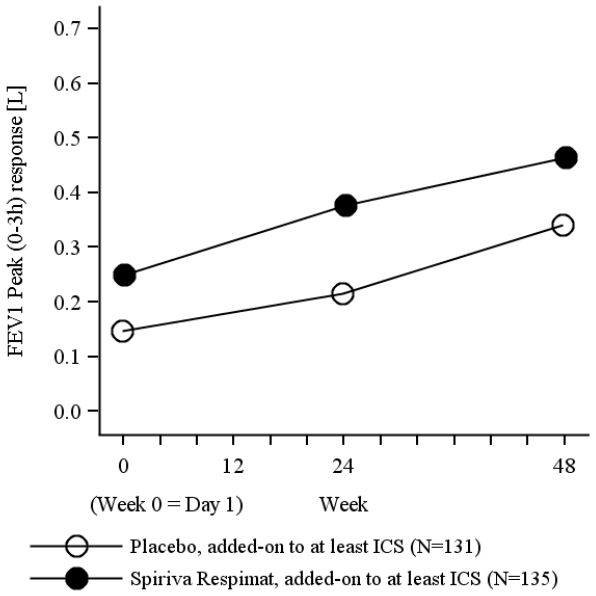
Children (6-11 years)

In the 1-year CanoTinA-asthma study in patients who were symptomatic on maintenance treatment of at least medium-dose ICS, SPIRIVA RESPIMAT re-usableshowed significant improvements in lung function and asthma control over placebo when used as add-on to background treatment.

- At week 24, mean improvements in peak and trough FEV1 were 0.164 litres (95% CI: 0.103 to 0.225 litres, p<0.0001) and 0.118 litres (95% CI: 0.048 to 0.188 litres, p=0.0010), respectively.

- The bronchodilator effects of SPIRIVA RESPIMAT re-usable were maintained throughout the 1 year period of administration with no evidence of tachyphylaxis (Figure 5).

Figure 5: Peak FEV1 response over 48 weeks in the CanoTinA-asthma study



In the 12-week VivaTinA-asthma study in patients who were symptomatic on maintenance treatment of at least medium dose ICS in combination with 1 or more controller medication, SPIRIVA RESPIMAT re-usable 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 FEV1 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.

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 re-usable) with asthma on background treatment of at least ICS.
An Aerochamber Plus Flow-Vu valved holding chamber with facemask was used to administer SPIRIVA RESPIMAT re-usable in 98 patients.

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

The number of asthma adverse events was lower for SPIRIVA RESPIMAT re-usablecompared to placebo. Exploratory efficacy evaluations did not show differences for SPIRIVA RESPIMAT re-usable from placebo.

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 solution for inhalation 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 suggest 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.

At steady state, peak tiotropium plasma concentrations of 10.5 pg/ml were achieved in COPD patients 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.

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 bromide 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 to 45 hr 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 bromide is mainly excreted unchanged in urine (74%). After inhalation of the inhalation solution by COPD patients, 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. 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, 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, advanceing age was associated with a decrease of tiotropium renal clearance from 347 mL/min in COPD patients < 65 years to 275mL/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.

Paediatric Patients:

The peak and total exposure to tiotropium was not found to differ between paediatric patients (aged 6 to 17 years) and adults with asthma. In patients 1 to 5 years old with asthma, the total exposure as measured by urinary excretion was 52 to 60% lower than that observed in patients 6 years and older with asthma; 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 facemask in patients 1 to 5 years of age.

Renally Impaired Patients:

Following once daily inhaled administration of tiotropium to steady-state in COPD patients with mild renal impairment (CL_{CR} 50-80 ml/min) resulted in slightly higher $AUC_{0-6,ss}$ (between 1.8 to 30% higher) and similar $C_{max,ss}$ compared to patients with normal renal function (CLcr >80 mL/min). In COPD patients with moderate to severe renal impairment (CL_{CR} < 50 ml/min) the intravenous administration of tiotropium bromide resulted in doubling of the total exposure (82% higher in 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 and also by inhalation of the solution via the Respimat inhaler. 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.

Paediatric Patients: There were no paediatric patients in the COPD programme (see 4.2)

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 Special precautions for storage

Do not freeze.
Do not store above 30°C

6.3 Availability

Pack sizes and devices supplied:

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

Please refer to packaging for information on shelf life.
Discard cartridge 3 months after insertion

Recommended use: 6 cartridges per inhaler
(Note: The functioning of the Respimat re-usable inhaler has been demonstrated in tests for 540 actuations (corresponding to 9 cartridges).

6.4 Name and address of Manufacturer

Manufactured by:
Boehringer Ingelheim Pharma GmbH & Co. KG
Ingelheim am Rhein
Germany
Or
Boehringer Ingelheim España, S.A.
c/ Prat de la Riba, 50
08174 Sant Cugat del Vallès
(Barcelona)
Spain

for
Boehringer Ingelheim International GmbH
Ingelheim am Rhein
Germany

Date of revision: 21 February 2022

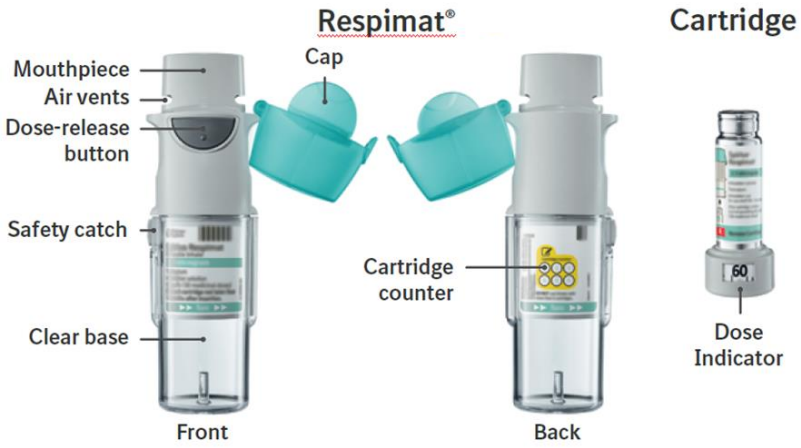
Store in a safe place out of reach of children!

Instructions For Use

SPIRIVA RESPIMAT re-usable (tiotropium bromide).
Read these Instructions for Use before you start using SPIRIVA RESPIMAT re-usable.

Children should use SPIRIVA RESPIMAT re-usable 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 not been used for more than 7 days release one puff towards the ground.
- If not been used for more than 21 days repeat steps 4 to 6 until a cloud is visible. Then repeat steps 4 to 6 three more times.

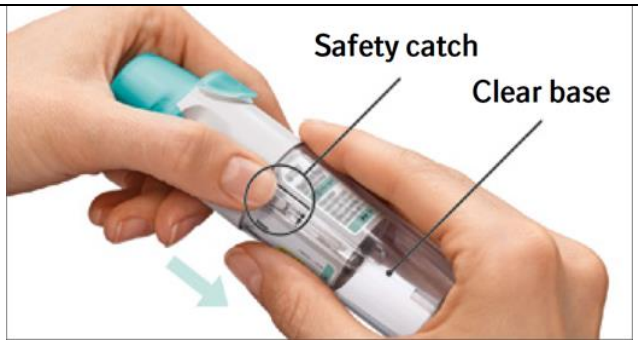
How to care for your SPIRIVA RESPIMAT re-usable

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 re-usable inhaler performance. If necessary, wipe the outside of your SPIRIVA RESPIMAT re-usable inhaler with a damp cloth.

When to replace the inhaler

When you have used an inhaler with 6 cartridges, get a new SPIRIVA RESPIMAT re-usable pack containing an inhaler.

Prepare for use

1. Remove clear base • Keep the cap closed. • Press the safety catch while pulling off the clear base with your other hand	
2. Insert cartridge • Insert the cartridge into the inhaler. • Place the inhaler on a firm surface and push down firmly until it clicks into place.	
3. **Track cartridge and put clear base back** • Mark the check-box on inhaler's label to track the number of cartridges. • 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 and will 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. • Repeat Turn, Open, Press for a total of 2 puffs. • Close the cap until you use your inhaler again.	

When to replace the SPIRIVA RESPIMAT re-usable Cartridge

The dose indicator shows how many puffs remain in the cartridge.

	60 Puffs remaining
	Less than 10 puffs remaining. Obtain a new cartridge
	Your cartridge is used up. Turn the clear base to loosen it. Your inhaler is now in a locked position. Pull off the cartridge from the inhaler. Insert a new cartridge until it clicks (refer to step 2). The new cartridge will stick out more than the very first cartridge (continue with step 3). Remember to put the clear base back to unlock the inhaler.

Answers to Common Questions

It is difficult to insert the cartridge deep enough.

Did you accidentally turn the clear base before inserting the cartridge? Open the cap, press the dose-release button, then insert the cartridge.

Are you replacing the cartridge? The new cartridge will stick out more than the very first cartridge. Insert it until it clicks, then replace the clear base.

I cannot press the dose-release button.

Did you put the clear base back? If not, put the clear base back to unlock the inhaler. The Respimat re-usable only functions with the clear base in place.

Did you turn the clear base? If not, turn the clear base in a continuous movement until it clicks (half a turn).

Does the dose indicator on your cartridge display a white arrow on a red background? Your cartridge is used up. Insert a new cartridge.

It is difficult to remove the cartridge after it is used up.

Pull and turn the cartridge at the same time.

I cannot turn or replace the clear base back.

Is the clear base loose and does the dose indicator on your cartridge display a white arrow on a red background? Your cartridge is used up. Insert a new cartridge.

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.

My RESPIMAT re-usable has been used up too early.

Did you use Respimat re-usable as indicated (two puffs/once daily)? Respimat will last 30 days if used at two puffs once daily.

Did you spray in the air often to check whether the Respimat re-usable is working? Once you have prepared Respimat re-usable, no test-spraying is required if used daily.

Did you take off and put the clear base multiple times back? Do not remove the clear base before the cartridge is used up. Each time you take off the clear base without cartridge exchange, the dose counter records one puff and the remaining doses are reduced.

My Respimat re-usable doesn’t spray.

Did you insert a cartridge? If not, insert a cartridge. If not, insert a cartridge. Once your RESPIMAT re-usable is assembled, do not remove the clear base or the cartridge until the cartridge is used up.

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 use”.

Does the dose indicator on your cartridge display a white arrow on a red background? Your cartridge is used up. Insert a new cartridge.

My RESPIMAT re-usable 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). The dose counter will count each incomplete turn and the number of remaining doses is reduced.

Was the cap open when you replaced the cartridge? Close the cap, then replace the cartridge.