Spiriva Respimat
2.5 microgram,
Solution for Inhalation

Boehringer Ingelheim

1. NAME OF THE MEDICINAL PRODUCT

Spiriva Respimat 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. PHARMACEUTICAL FORM

Inhalation solution
Clear, colourless, inhalation solution

3.1 Product description

Spiriva Respimat 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
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.

4.2 Posology and method of administration

The medicinal product is intended for inhalation use only. The cartridge can only be inserted and used in the Respimat inhaler (see Handling Instructions).
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 Spiriva Respimat.

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 cleareance ≤ 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 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
The recommended dosage of tiotropium using the SPIRIVA RESPIMAT 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 Handling Instructions). Tiotropium has not been studied in children less than 1 year

4.3 Contraindications

Spiriva Respimat 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 should not be used as a first-line treatment 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 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.

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).

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 and anti-IgE treatment without clinical evidence of drug interactions.

Common concomitant medications (LABA, ICS and their combinations) used by patients with COPD were 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 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.

Lactation
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 continues/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.

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

Many of the listed undesirable effects can be assigned to the anticholinergic properties of Spiriva Respimat.

Adverse drug reactions were identified from data obtained in clinical trials and spontaneous reporting during post approval use of the drug.

The clinical trial database for COPD includes 3,282 Spiriva Respimat patients from 7 placebo-controlled clinical trials with treatment periods ranging between four weeks and one year, contributing 2,440 person years of exposure.

The clinical trial database for asthma includes 1,930 tiotropium treated patients from 12 placebo controlled trials with treatment period ranging between twelve weeks and one year, contributing 1,128 person years of exposure to tiotropium.

Metabolism and nutrition disorders:
- dehydration

Nervous system disorders:
- dizziness
- insomnia

Eye disorders:

- glaucoma
- intraocular pressure increased
- vision blurred

Cardiac disorders:
- atrial fibrillation
- palpitations
- supraventricular tachycardia
- tachycardia

Respiratory, thoracic and mediastinal disorders:
- cough
- epistaxis
- pharyngitis
- dysphonia
- bronchospasm
- laryngitis
- sinusitis

Gastrointestinal disorders:
- dry mouth, usually mild
- constipation
- oropharyngaeal candidiasis
- dysphagia
- gastrooesophageal reflux disease
- gingivitis
- glossitis
- stomatitis
- intestinal obstruction incl. ileus paralytic

Skin and subcutaneous tissue disorders, Immune system disorders:
- rash
- pruritus
- angioneurotic oedema
- urticaria
- skin infection and skin ulcer
- dry skin
- hypersensitivity (including immediate reactions)

Musculoskeletal and connective tissue disorders:
- joint swelling

Renal and urinary disorders:
- urinary retention (usually in men with predisposing factors)
- dysuria
- urinary tract infection

Paedriatic 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 population are similar as in adults.

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 six long term-studies in COPD patients with a daily dose of 10 microgram tiotropium solution was given 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

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.

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.

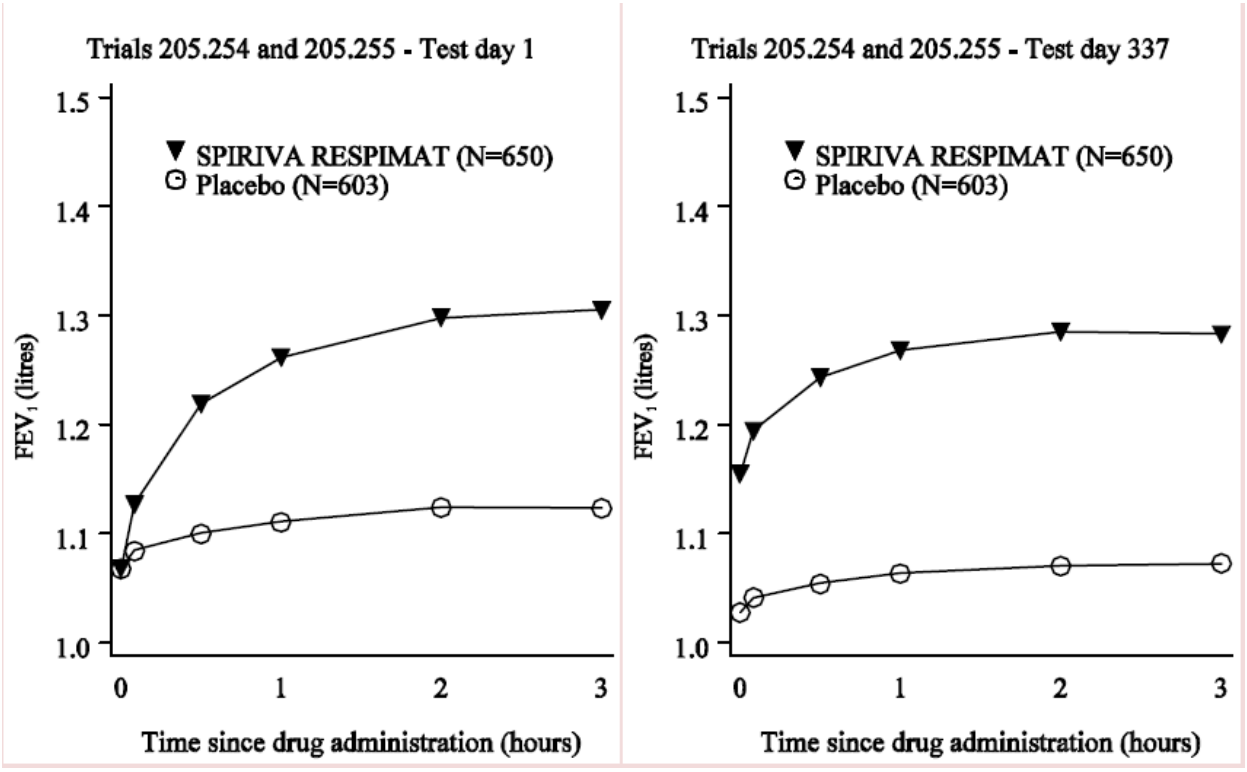
COPD
The clinical Phase III development programme for COPD included two 1-year, two 12-weeks and two 4-weeks randomised, double-blind studies in 2901 COPD patients (1038 receiving the 5 µg tiotropium dose). The 1-year programme consisted of two placebo-controlled trials. The two 12-week trials were both 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
SPIRIVA RESPIMAT, 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, $p<0.0001$).

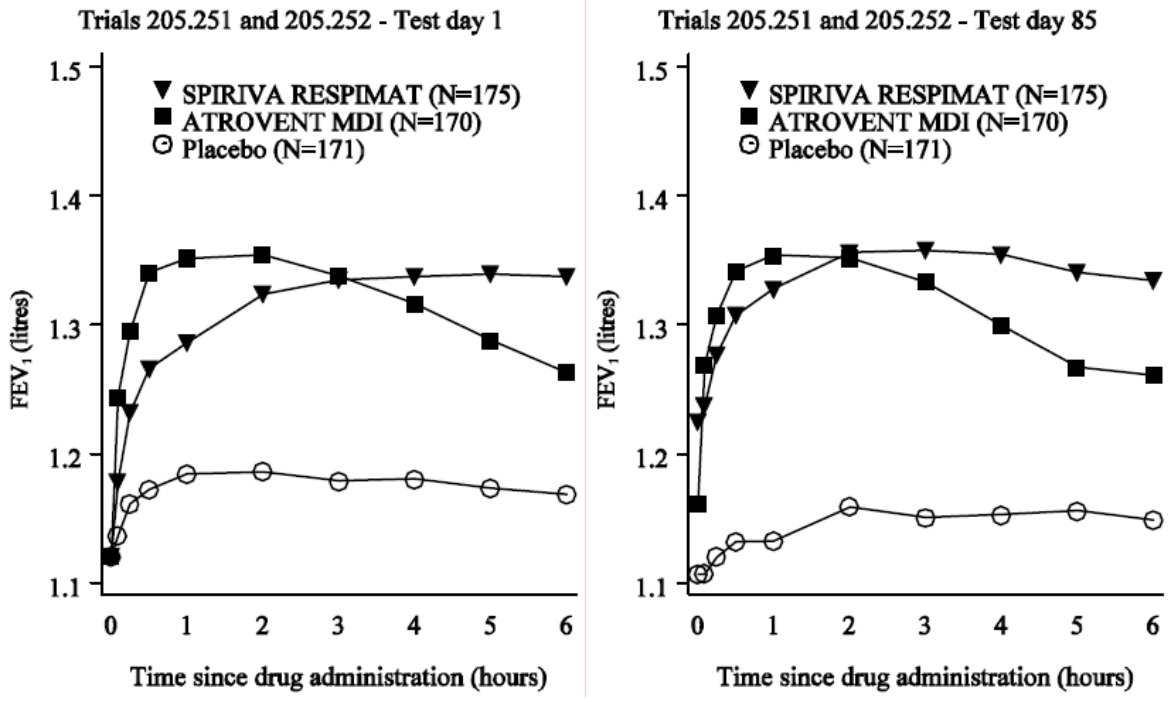
The bronchodilator effects of Spiriva Respimat were maintained throughout the 1-year period of administration with no evidence of tolerance.

Figure 1: Mean FEV1 (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)*



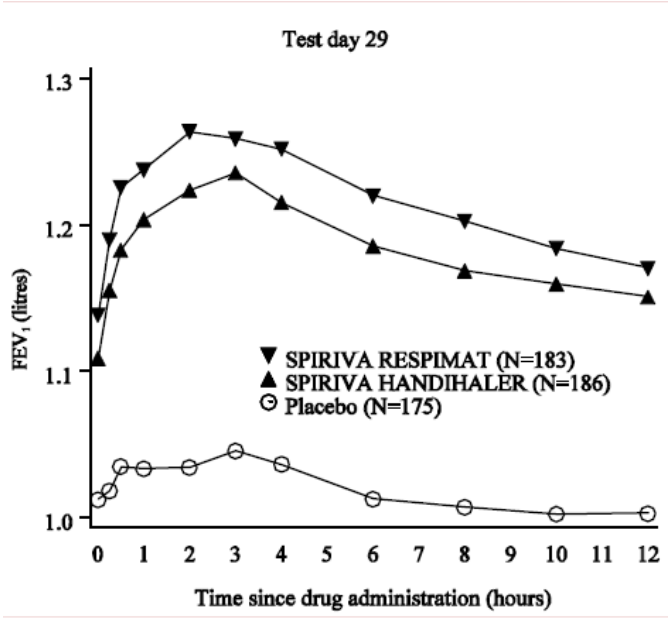
*Means adjusted for center, smoking status and baseline effect. A total of 545 and 434 patients in the SPIRIVA® and placebo groups, respectively completed test day 337. The data for the remaining patients were imputed using last observation or least favourable observation carried forward.

Figure 2: Mean FEV1 (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 FEV1 (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 (5 µg) was numerically higher compared to SPIRIVA HandiHaler (18 µg) inhalation powder after a 4-week treatment period.

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

(a) 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.

(b) 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.

(c) 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 Phase 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)[b]	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 Phase IIIb exacerbation (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 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.

[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 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 FEV1 (pre-dose).

The time to first COPD exacerbation was 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 mL).

All-cause mortality was similar during the study with SPIRIVA RESPIMAT and SPIRIVA HANDIHALER (hazard ratio (SPIRIVA RESPIMAT/ SPIRIVA HANDIHALER) 0.96 with a 95% CI of 0.84 to 1.09).

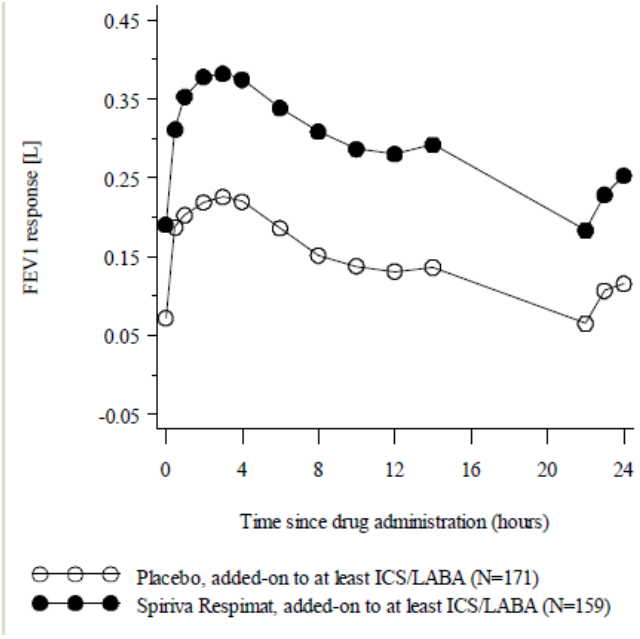
Asthma
Adult patients

The clinical Phase III programme for persistent asthma included two 1-year, two 6-month and one 12-week, randomised, double-blind, placebo-controlled studies in a total of 3,476 asthma patients (1,128 receiving SPIRIVA RESPIMAT) on background treatment of at least ICS or ICS/LABA. The two 6-month studies were also active-controlled (salmeterol). All 5 studies included lung function measurements, assessments of symptoms including exacerbations, and health-related quality of life.

In the two 1-year PrimoTinA-asthma studies in patients who were symptomatic on maintenance treatment of at least high-dose ICS plus LABA, SPIRIVA RESPIMAT showed significant improvements in lung function over placebo when used as add-on to background treatment.

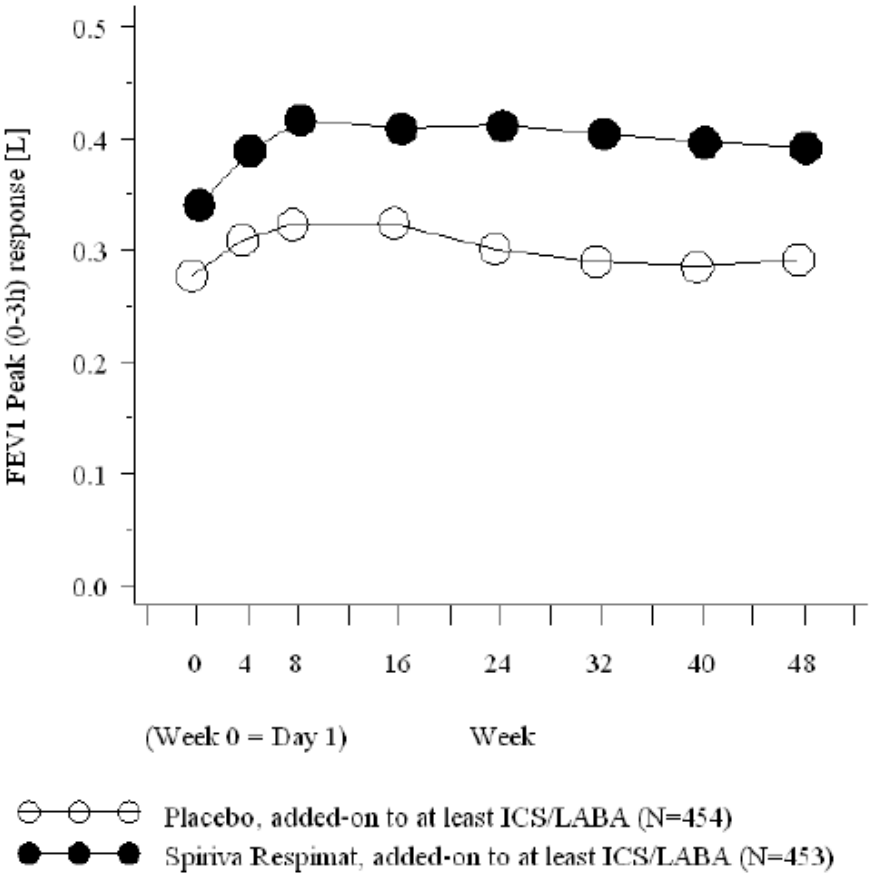
- At week 24, mean improvements in peak and trough FEV_1 were 0.110 litres (95% CI: 0.063 to 0.158 litres, p<0.0001) and 0.093 litres (95% CI: 0.050 to 0.137 litres, p<0.0001), respectively.
- The improvement of lung function compared to placebo was maintained for 24 hours (Figure 4).

Figure 4: FEV_1 profiles over 24 hours in a subset of patients in the PrimoTinA-asthma studies at week 24



- At week 24, SPIRIVA RESPIMAT significantly improved morning and evening peak expiratory flow (PEF; mean improvement in the morning 23 L/min; 95% CI: 16 to 29 L/min, p< 0.0001; evening 26 L/min; 95% CI: 20 to 33 L/min, p<0.0001).
- The bronchodilator effects of SPIRIVA RESPIMAT were maintained throughout the 1 year period of administration with no evidence of tachyphylaxis or tolerance.
  (Figure 5)

Figure 5: Peak FEV_1 response over 48 weeks in the PrimoTinA-asthma studies



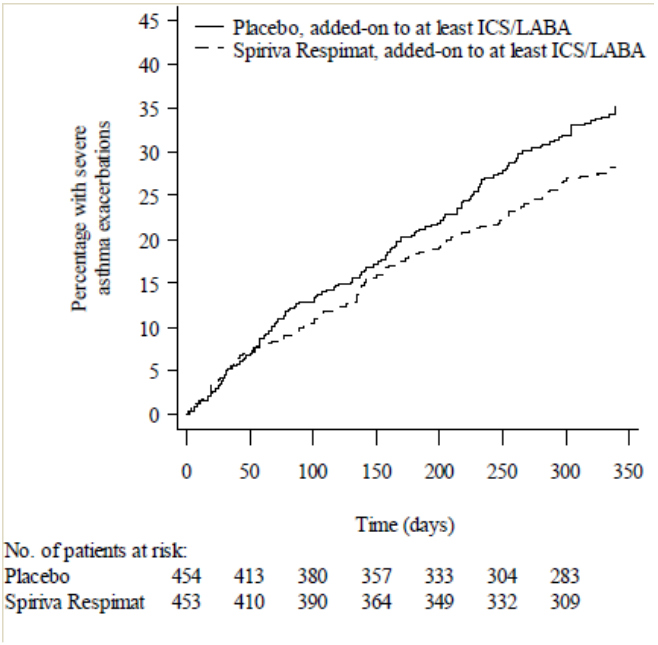
- SPIRIVA RESPIMAT significantly reduced the risk of severe asthma exacerbations (see Table 2 and Figure 6)

Table 2: Exacerbations in Patients symptomatic on ICS plus LABA (Primo TinA-asthma Studies)

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

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

Figure 6: Severe Asthma Exacerbations over time in Primo TinA-asthma studies



- The Asthma Control Questionnaire (ACQ) responder rates defined as percentage of patients improving by at least 0.5 points, were significantly higher with SPIRIVA RESPIMAT (53.9% versus 46.9%; p=0.0427)
- The Asthma Quality of Life Questionnaire (AQLQ(S)) mean scores for SPIRIVA RESPIMAT improved significantly over placebo at week 24.

In the two 6-month MezzoTinA-asthma studies in patients who were symptomatic on maintenance treatment of medium-dose ICS, SPIRIVA RESPIMAT 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 FEV_1 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 FEV_1 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 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 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 Phase III studies, pooled analysis	Placebo, added-on to ICS (N=518)	57.7	
	SPIRIVA RESPIMAT, added-on to ICS (N=513)	64.3	0.0348
	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

In the 12 week GraziaTinA-asthma study in patients who were symptomatic on maintenance treatment with low dose ICS, SPIRIVA RESPIMAT showed significant improvements in lung function over placebo when used as add-on to background treatment. At 12 weeks, the mean improvements in peak and trough FEV1 were 0.128 litres (95% CI: 0.057 to 0.199 litres, p<0.0005) and 0.122 litres (95% CI: 0.049 to 0.194 litres, p<0.0010), respectively.

Paediatric Patients:

The clinical Phase III program for persistent asthma in paediatric patients (1-17 years) included:

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

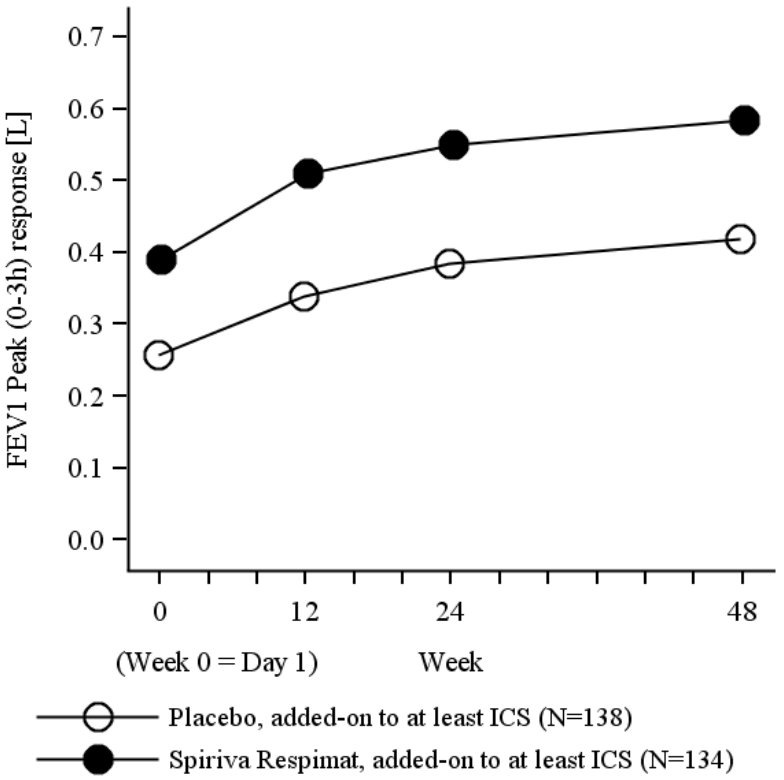
In all these studies, patients were on background treatment of at least ICS.

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® 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® 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® were maintained throughout the 1 year period of administration with no evidence of tachyphylaxis (Figure 7).

Figure 7: 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® 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.

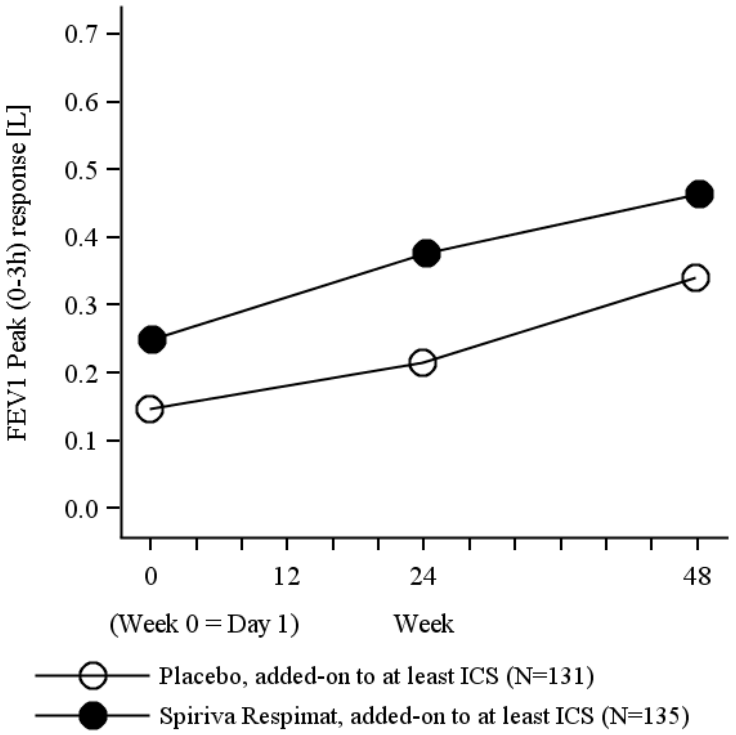
- At week 12, mean improvements in peak and trough FEV1 were 0.090 litres (95% CI: -0.019 to 0.198 litres, p=0.1039) and 0.054 litres (95% CI: -0.061 to 0.168 litres, p=0.3605), respectively.
- At week 12, SPIRIVA® RESPIMAT® significantly improved morning and evening PEF (morning 17.4 L/min; 95% CI: 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® showed 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® were maintained throughout the 1 year period of administration with no evidence of tachyphylaxis (Figure 8).

Figure 8: 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® 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.

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 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.

Maximum tiotropium plasma concentrations were observed 5-7 minutes after inhalation. 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.

At 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 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 45h following inhalation by 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 solution by COPD patients urinary excretion is 18.6 % (0.93µg) 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 from 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.

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).

Renally Impaired Patients

Following once daily inhaled administration of tiotropium to steady-state in COPD patients with mild renal impairment (CLCR 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 (CLCR <50 ml/min) the intravenous administration of tiotropium bromide resulted in doubling of the total exposure (82% higher AUC_{0-4h}) and 52% higher Cmax) 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 (CLCR 50-80mL/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 bromide pharmacokinetics. Tiotropium bromide is predominantly cleared by renal elimination (74% in young healthy volunteers) and simple non-enzymatic ester cleavage to pharmacologically inactive products.

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

Please refer to packaging for information on shelf life.

6.4 Special precautions for storage

Do not freeze.
Do not store above 30°C

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-use Respimat pack: 1 Respimat inhaler (single-use) and 1 cartridge, providing 60 puffs (30 medicinal doses)
Do not reuse single-use Repimat inhaler

Respimat re-usable 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)
Recommended use for Respimat re-usable: 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).

6.6 Special precautions for disposal and other handling

Discard within 3 months of opening

7. MARKETING AUTHORISATION HOLDER/MANUFACTURER

Manufactured by
Boehringer Ingelheim GmbH & Co.KG
Ingelheim am Rhein
Germany
for
Boehringer Ingelheim International GmbH
Ingelheim am Rhein
Germany

8. MARKETING AUTHORISATION NUMBER

MAL20091850AZ
BRU19042574P

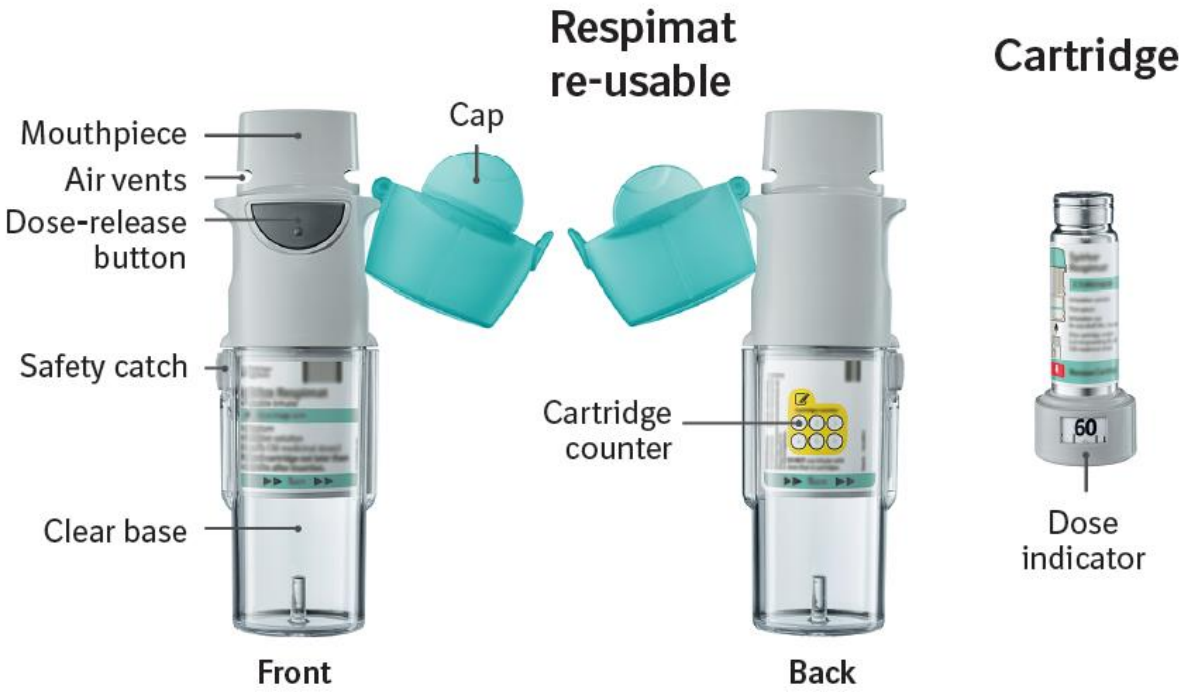
9. DATE OF REVISION OF THE TEXT

24 February 2025

Store in a safe place out of the reach of children!

SPIRIVA RESPIMAT re-usable
Handling Instructions
Read these Handling Instructions before you start using SPIRIVA RESPIMAT re-usable.
You will need to use this inhaler only ONCE A DAY.
Each time you use it take TWO PUFFS.

Children should use SPIRIVA® RESPIMAT® with an adult's assistance.



- 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. Do not use the Respimat re-usable inhaler for more than one year, after having inserted the first cartridge.

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 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.

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.