NEW ZEALAND DATASHEET

1. PRODUCT NAME

SPIRIVA® RESPIMAT® 2.5 microgram, solution for inhalation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect:
This medicine contains 0.0011 mg benzalkonium chloride in each actuation.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Clear, colourless, solution for inhalation.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

COPD
SPIRIVA RESPIMAT is indicated for the long term once daily maintenance treatment of bronchospasm and dyspnoea associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. SPIRIVA reduces the frequency of exacerbations and improves exercise tolerance and health-related quality of life.

Asthma
SPIRIVA RESPIMAT is indicated as add-on maintenance treatment for the improvement of asthma symptoms and reduction of exacerbations, in adult patients with asthma who remain symptomatic on at least inhaled corticosteroids.

SPIRIVA RESPIMAT is indicated as add-on maintenance treatment for the improvement of respiratory function in patients aged 6 to 17 years old with moderate asthma who remain symptomatic on at least inhaled corticosteroids.

4.2 Dose and method of administration

Dose
SPIRIVA RESPIMAT is intended for oral inhalation use only. The cartridge can only be inserted and used in the Respimat inhaler (see Patient's instructions for use and handling).

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 benefits will be apparent after several doses of SPIRIVA RESPIMAT.

Special populations
Elderly patients can use SPIRIVA RESPIMAT at the recommended dose.

Renally impaired patients can use SPIRIVA RESPIMAT at the recommended dose. However, as with all predominantly renally excreted drugs, SPIRIVA RESPIMAT use should be monitored closely in patients with moderate to severe renal impairment.

Hepatically impaired patients can use SPIRIVA RESPIMAT at the recommended dose.

Paediatric population
COPD does not normally occur in children.

In asthma, the recommended dosage of SPIRIVA RESPIMAT in patients 6 to 17 years of age is inhalation of the spray of two puffs once daily from the RESPIMAT inhaler, at the same time of day (see Patient's instructions for use and handling).

The efficacy and safety of SPIRIVA RESPIMAT in paediatric patients below 6 years of age with asthma has not been established.

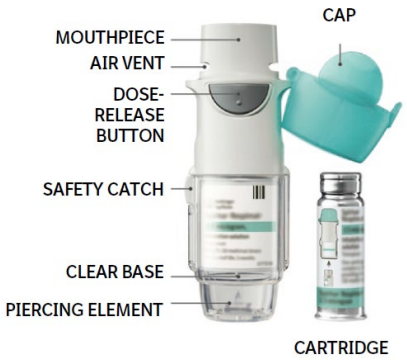
Method of administration
To ensure proper administration of the medicinal product, the patient should be shown how to use the inhaler by a physician or other health professionals.

Instructions for use and handling

Read these Instructions for Use before you start using Spiriva Respimat.

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

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

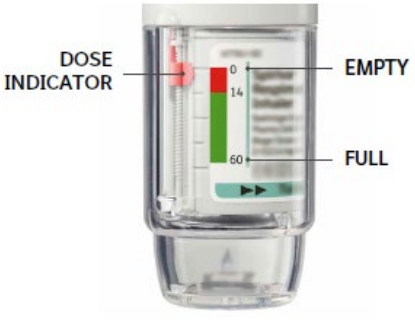


- If not been used for more than 7 days release one puff towards the ground.
- If not been used for more than 21 days repeat steps 4 to 6 until a cloud is visible. Then repeat steps 4 to 6 three more times.

How to care for your SPIRIVA RESPIMAT
Clean the mouthpiece including the metal part inside the mouthpiece with a damp cloth or tissue only, at least once a week.

Any minor discoloration in the mouthpiece does not affect your SPIRIVA RESPIMAT inhaler performance.

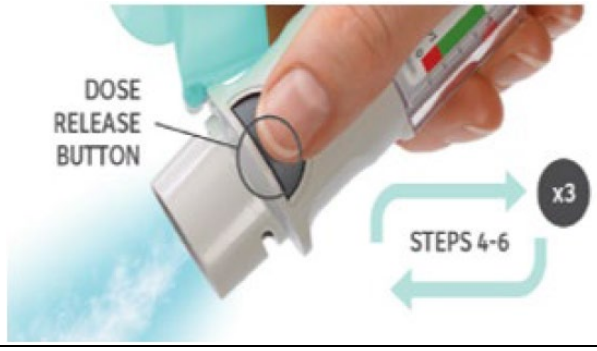
When to get a new SPIRIVA RESPIMAT



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

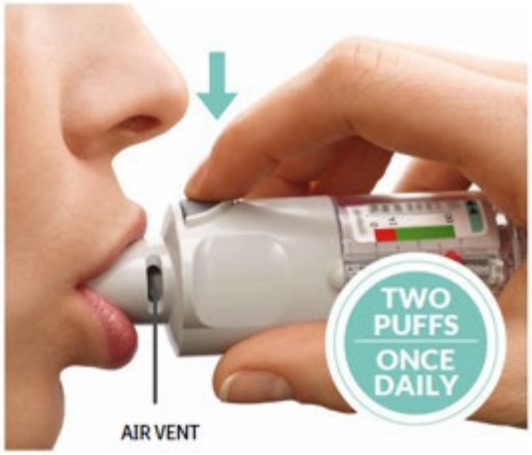
Prepare for first use

1. <u>Remove clear base</u> • Keep the cap closed. • Press the safety catch while firmly pulling off the clear base with your other hand.	
2. <u>Insert cartridge</u> • Insert the narrow end of the cartridge into the inhaler. • Place the inhaler on a firm surface and push down firmly until it snaps into place.	
3. <u>Replace clear base</u> • Put the clear base back into place until it clicks.	

4. <u>Turn</u> • Keep the cap closed. • Turn the clear base in the direction of the arrows on the label until it clicks (half a turn).	
5. <u>Open</u> • Open the cap until it snaps fully open.	
6. <u>Press</u> • 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.	

Daily use

TURN • Keep the cap closed. • <u>TURN</u> the clear base in the direction of the arrows on the label until it clicks (half a turn).	
OPEN • <u>OPEN</u> the cap until it snaps fully open.	

PRESS • Breathe out slowly and fully. • Close your lips around the mouthpiece without covering the air vents. • While taking a slow, deep breath through your mouth, PRESS the dose-release button and continue to breathe in. • Hold your breath for 10 seconds or for as long as comfortable. • Repeat Turn, Open, Press for a total of 2 puffs. • Close the cap until you use your inhaler again.	

4.3 Contraindications

SPIRIVA RESPIMAT is contraindicated in patients with a history of hypersensitivity to atropine or its derivatives, e.g. ipratropium or oxitropium or to any component of this product (see section 6.1).

4.4 Special warnings and precautions for use

Benzalkonium chloride may cause wheezing and breathing difficulties. Patients with asthma are at an increased risk for these adverse events.

SPIRIVA RESPIMAT, as a once daily maintenance bronchodilator, should not be used for the 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 SPIRIVA RESPIMAT inhalation solution.

As with other anticholinergic drugs, SPIRIVA RESPIMAT 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 ≤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.

SPIRIVA RESPIMAT should be used with caution in patients with known cardiac rhythm disorders.

Patients must be instructed in the correct administration of SPIRIVA RESPIMAT. Care must be taken not to allow the spray to enter into the eyes. Eye pain or discomfort, blurred vision, visual halos or coloured images in association with red eyes from conjunctival congestion and corneal oedema may be signs of acute narrow-angle glaucoma. Should any combination of these symptoms develop specialist advice should be sought immediately. Miotic eye drops are not considered to be effective treatment.

SPIRIVA RESPIMAT should not be used more frequently than once daily (see section 4.9).

SPIRIVA solution for inhalation cartridges are to be used only with the RESPIMAT inhaler (see section 4.2).

4.5 Interactions with other medicines and other forms of interactions

Although no formal drug interaction studies have been performed, tiotropium bromide has been used concomitantly with other drugs which are commonly used in the treatment of COPD and asthma, including sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids, antihistamines, mucolytics, leucotriene 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 chronic co-administration of tiotropium bromide with other anticholinergic drugs has not been studied. Therefore, the chronic co-administration of other anticholinergic drugs with SPIRIVA RESPIMAT is not recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy
Category B1
There is a 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 section 5.3).

As a precautionary measure, it is preferable to avoid the use of SPIRIVA RESPIMAT during pregnancy.

Breastfeeding
Clinical data from lactating women exposed to tiotropium are not available. Based on studies in lactating rats, a small amount of tiotropium is excreted in breast milk.

Therefore, SPIRIVA RESPIMAT should not be used in lactating women unless the expected benefit outweighs any possible risk to the infant.

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 section 5.3).

4.7 Effects on ability to drive or operate machinery

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

4.8 Undesirable effects

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

Tabulated summary of adverse reactions

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 to tiotropium.

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.

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

System Organ Class/ MedDRA preferred term	**Frequency COPD**	**Frequency Asthma**
Metabolism and nutrition disorders		
Dehydration	Not known	Not known
Nervous system disorders		
Dizziness	Uncommon	Uncommon
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	Rare	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
Gingivitis	Rare	Rare
Glossitis	Rare	Not known
Stomatitis	Not known	Rare
Intestinal obstruction, including ileus paralytic	Not known	Not known

System Organ Class/ MedDRA preferred term	**Frequency COPD**	**Frequency Asthma**
Skin and subcutaneous tissue disorders, immune system disorders		
Rash	Uncommon	Uncommon
Pruritus	Uncommon	Rare
Angioneurotic oedema	Rare	Rare
Urticaria	Rare	Rare
Skin infection and skin ulcer	Rare	Not known
Dry skin	Rare	Not known
Hypersensitivity (including immediate reactions)	Not known	Rare
Musculoskeletal and connective tissue disorders		
Joint swelling	Not known	Not known
Renal and urinary disorders		
Urinary retention	Uncommon	Not known
Dysuria	Uncommon	Not known
Urinary tract infection	Rare	Rare

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

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

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

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

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

For advice on the management of overdose, please contact the National Poisons Centre on 0800 POISON (0800 764766).

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

No relevant adverse events, beyond dry mouth/throat and dry nasal mucosa, were observed following 14-day dosing of up to 40 micrograms tiotropium solution for inhalation in healthy subjects 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 when a daily dose of 10 micrograms tiotropium solution for inhalation 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

Mechanism of action
Tiotropium is a long-acting, specific antimuscarinic (anticholinergic) agent. It has similar affinity to the muscarinic receptor subtypes M_1 to M_5 (K_D 5-41 pM). In the airways, inhibition by tiotropium of M_3-receptors at the smooth muscle results in relaxation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In non-clinical *in vitro* as well as *in vivo* studies, bronchoprotective effects were dose-dependent lasting at least 24 hours. The long duration of effect of tiotropium is likely to be due to its very slow dissociation from M_3-receptors, exhibiting a significantly longer dissociation half-life than that seen with ipratropium.

Pharmacodynamic effects
Tiotropium, a N-quaternary anticholinergic agent, is topically (broncho-) selective when administered by inhalation, demonstrating an acceptable therapeutic range before giving rise to systemic anti-cholinergic effects. 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.

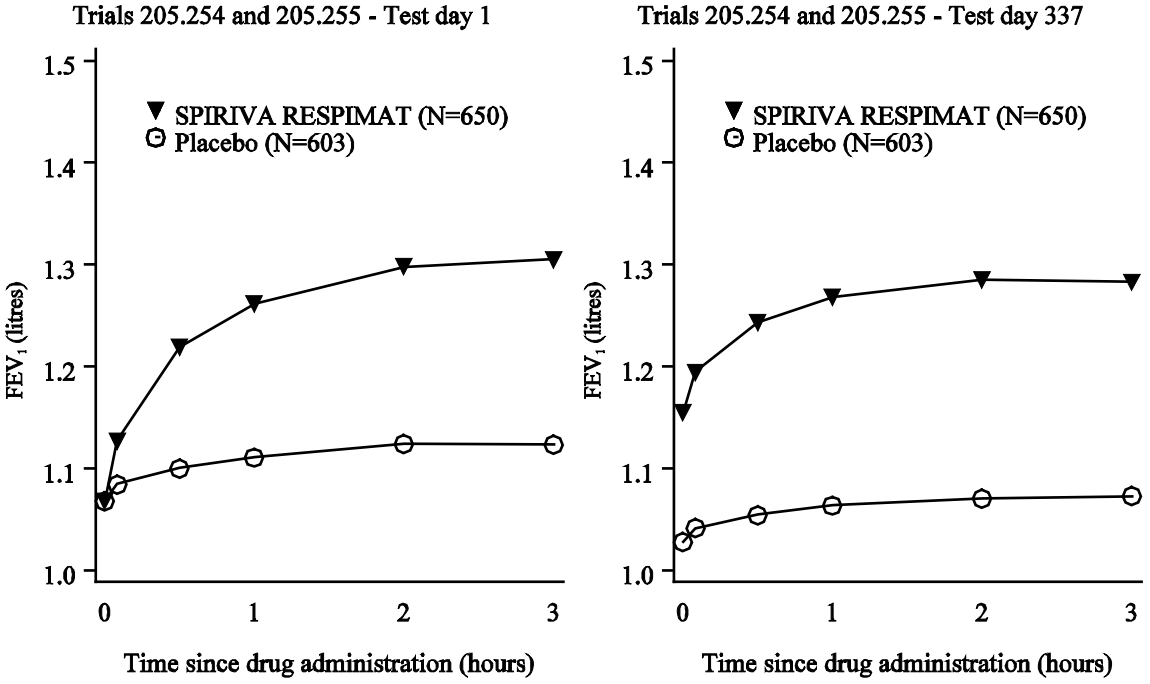
The high potency and slow receptor dissociation is associated with a significant and long-acting bronchodilation in patients with chronic obstructive pulmonary disease (COPD) and asthma. The bronchodilation following inhalation of tiotropium is primarily a local effect on the airways, not a systemic one.

Clinical efficacy and safety in COPD
The clinical Phase III programme included two 1-year, two 12-week and two 4-week randomised, double-blind studies in 2901 COPD patients (1038 receiving the 5 microgram 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 health-related quality of life, dypsnoea, 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. Improvement of lung function was maintained for 24 hours at steady state. 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. The use of SPIRIVA RESPIMAT resulted in a reduction of rescue bronchodilator use compared to placebo.

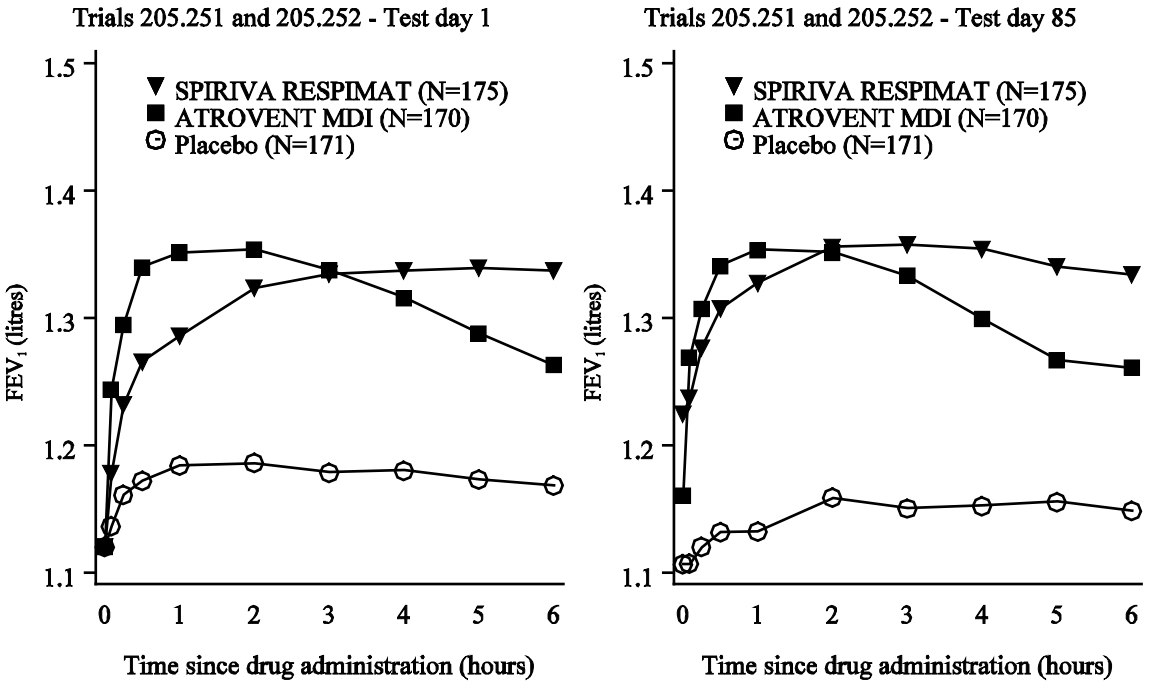
The bronchodilator effects of SPIRIVA RESPIMAT were maintained throughout the 48-week period of administration with no evidence of tolerance.

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)*



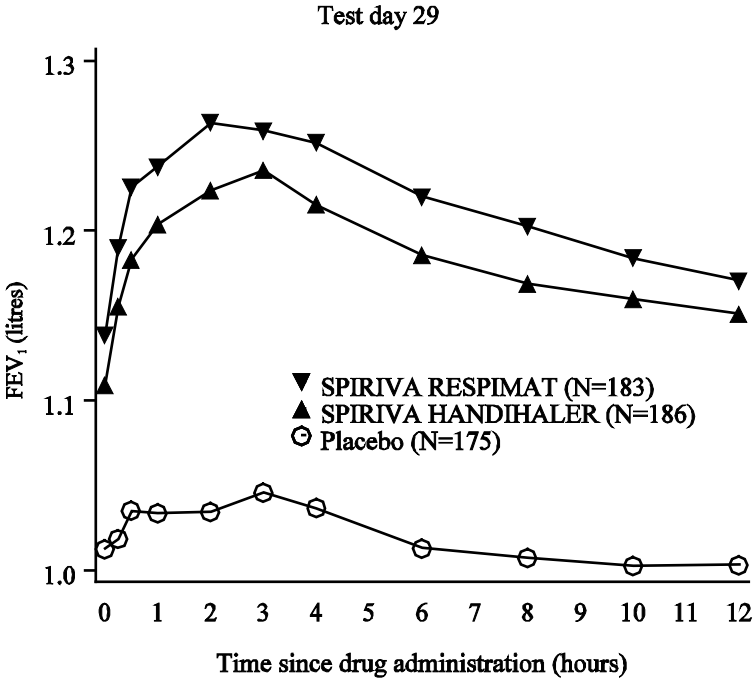
*Means adjusted for centre, smoking status and baseline effect. A total of 545 and 434 patients in the SPIRIVA and placebo groups, respectively completed test day 337. The data for the remaining patients were imputed using last observation or least favourable observation carried forward.

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 centre, patient (within centre), 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). An improvement was maintained throughout the treatment period.

(b) Patients' evaluation of their Quality of Life (as measured using the St. George's Respiratory Questionnaire) showed that SPIRIVA RESPIMAT had positive effects on the psychosocial impacts of COPD, activities affected by COPD and distress due to COPD symptoms.

The improvement in mean total score between SPIRIVA RESPIMAT versus placebo at the end of the two 1-year studies was statistically significant and maintained throughout the treatment period.

(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 Hospitalised 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 analysisd (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.[20b]
	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 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 / hospitalised 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 an observation period up to 3 years has been performed to compare the efficacy and safety of SPIRIVA RESPIMAT and SPIRIVA HANDIHALER (5,711 patients receiving SPIRIVA RESPIMAT 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 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).

Clinical efficacy and safety in asthma

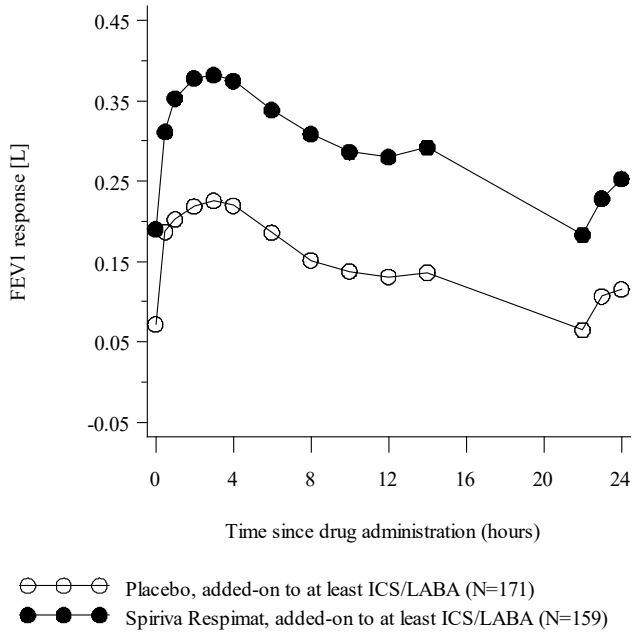
The clinical Phase III programme for persistent asthma included two 1-year, two 6-month and one 12-week, randomised, double-blind, placebo-controlled studies in a total of 3,476 asthma patients (1,128 receiving SPIRIVA RESPIMAT) on background treatment of at least ICS or ICS/LABA. The two 6-month studies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

Primo TinA-asthma studies

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.

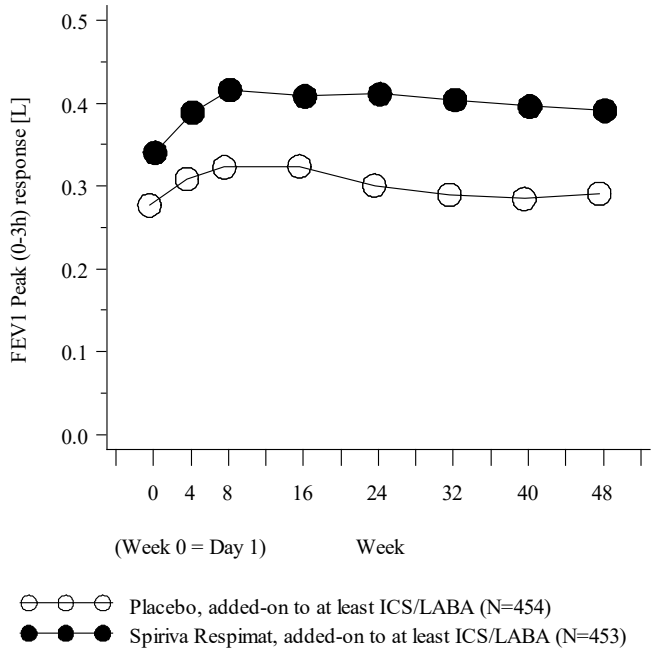
- At week 24, mean improvements in peak and trough FEV_1 were 0.110 litres (95% CI: 0.063 to 0.158 litres, p<0.0001) and 0.093 litres (95% CI: 0.050 to 0.137 litres, p<0.0001), respectively.
- The improvement of lung function compared to placebo was maintained for 24 hours (Figure 4).

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



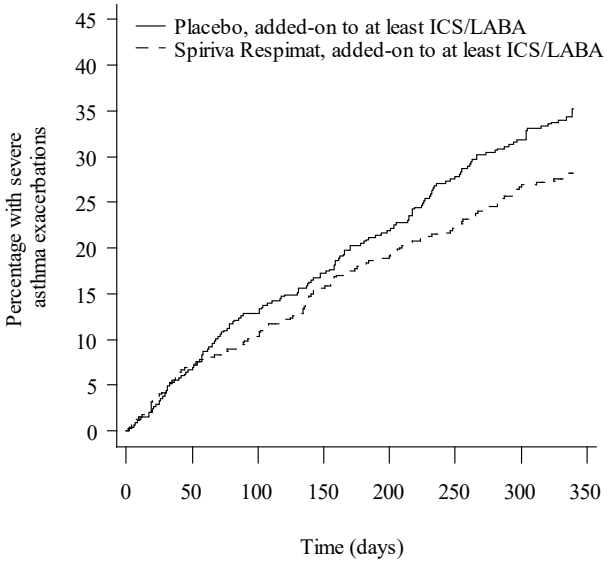
- SPIRIVA RESPIMAT significantly reduced the risk of severe asthma exacerbations (see Table 2 and Figure 6).

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 Ph 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 PrimoTinA-asthma studies



No. of patients at risk:

Placebo	454	413	380	357	333	304	283
Spiriva Respimat	453	410	390	364	349	332	309

- 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.

MezzoTinA-asthma studies

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 Ph 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 FEV_1 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 population

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).

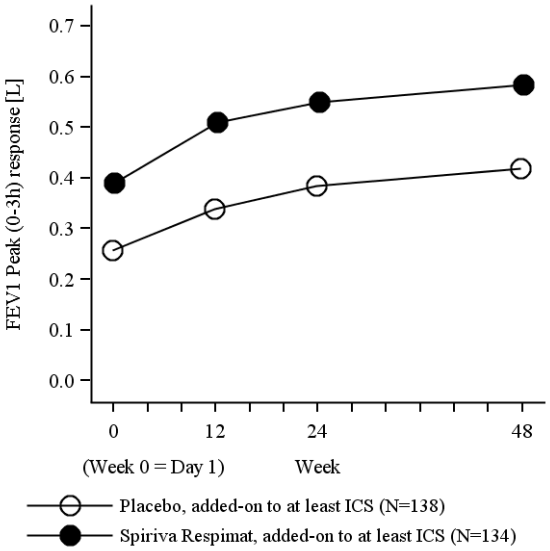
In all these studies, patients were on background treatment of at least ICS.

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 FEV_1 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 FEV_1 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 FEV_1 were not statistically significant.

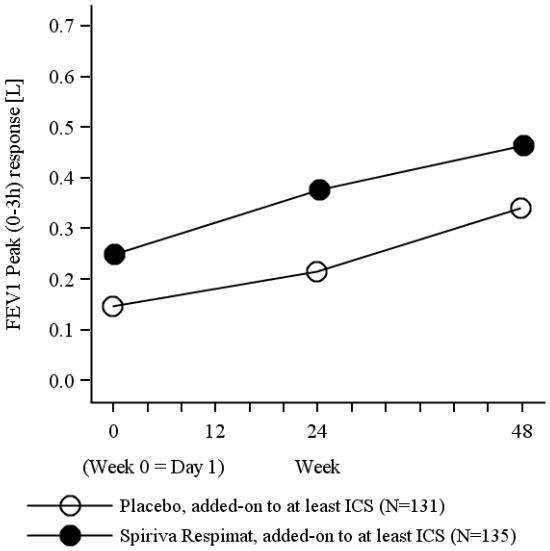
- At week 12, mean improvements in peak and trough FEV_1 were 0.090 litres (95% CI: -0.019 to 0.198 litres, p=0.1039) and 0.054 litres (95% CI: -0.061 to 0.168 litres, p=0.3605), respectively.
- At week 12, SPIRIVA RESPIMAT significantly improved morning and evening PEF (morning 17.4 L/min; 95% CI: 5.1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

Efficacy has not been confirmed for severe asthma in patients aged 12 years to 17 years.

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 FEV_1 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 FEV_1 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 FEV_1 were 0.139 litres (95% CI: 0.075 to 0.203 litres, p<0.0001) and 0.087 litres (95% CI: 0.019 to 0.154 litres, p=0.0117), respectively.

Children (1-5 years)
One 12-week randomised, double-blind, placebo-controlled, phase II/III clinical study (NinoTinA-asthma) was conducted in a total of 101 children (31 received SPIRIVA RESPIMAT) with asthma on background treatment of at least ICS.

An Aerochamber® Plus Flow-Vu® valved holding chamber with facemask was used to administer trial medication 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 compared to placebo. Exploratory efficacy evaluations did not show differences for SPIRIVA RESPIMAT from placebo.

5.2 Pharmacokinetics 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 of tiotropium RESPIMAT is deposited in the lungs, the target organ, the remaining amount being deposited in the gastrointestinal tract. Some of the pharmacokinetic data described below were obtained with higher doses than recommended for therapy.

(b) General Characteristics of the Active Substance after Administration of the Medicinal Product
Absorption: Following inhalation by young healthy volunteers, urinary excretion data suggests that approximately 33% of the inhaled dose reach the systemic circulation. Oral solutions of tiotropium have an absolute bioavailability of 2-3%. Food is not expected to influence the

absorption of tiotropium for the same reason. Maximum tiotropium bromide 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.

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% to plasma proteins 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. Tiotropium bromide, an ester, is nonenzymatically cleaved to the alcohol N-methylscopine and dithienylglycolic acid, both not binding to 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 dependent oxidation and subsequent glutathione conjugation to a variety of Phase II-metabolites. This enzymatic pathway can be inhibited by the CYP450 2D6 (and 3A4) inhibitors, quinidine, ketoconazole and gestodene. Thus CYP450 2D6 and 3A4 are involved in the metabolic pathway that is responsible for the elimination of a smaller part of the dose. Tiotropium bromide even in supra-therapeutic concentrations does not inhibit cytochrome P450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1 or 3A in human liver microsomes.

Elimination: The effective half-life of tiotropium ranges between 27 to 45 hrs 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 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 bromide 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.

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 C_{max} compared to COPD patients with normal renal function, which was confirmed by plasma concentrations after dry powder inhalation).

In asthma patients with mild renal impairment (CLCR 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 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.

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.

(d) Pharmacokinetic/Pharmacodynamic Relationship(s)

There is no direct relationship between pharmacokinetics and pharmacodynamics.

5.3 Preclinical Safety Data

The acute inhalation and oral toxicity in mice, rats, and dogs was low; therefore, toxic effects from acute human drug over-dosage are unlikely. The single dose safety pharmacology studies showed the expected effects of an anticholinergic drug including mydriasis, increased heart rate and prolonged gastro-intestinal transit time.

The side effects of the repeat-dose studies in rats, mice and dogs were related to anticholinergic properties of tiotropium bromide including mydriasis, increased heart rate, constipation, decreased body weight gain, reduced salivary and lacrimal gland secretion. Other relevant changes noted were: mild irritancy of the upper respiratory tract in rats evinced by rhinitis and epithelial changes of the nasal cavity and larynx, and prostatitis along with proteinaceous deposits and lithiasis in the bladder of male rats, increased lung weights in rats and decreased heart weights in dogs.

In the reproduction studies in rabbits and rats harmful effects with respect to pregnancy, embryo/foetal development, parturition or postnatal development could only be demonstrated at maternally toxic dose levels. 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.

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.

In a series of *in vivo* and *in vitro* mutagenicity assays, tiotropium bromide did not cause gene mutations in prokaryotes and in eucaryotes, chromosomal damage *in vitro* and *in vivo* conditions or primary DNA damage.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride
Disodium edetate
Purified water
Hydrochloric acid for pH adjustment

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

In-use shelf-life: 3 months

6.4 Special precautions for storage

Store below 25°C.

Do not freeze.

6.5 Nature and contents of container

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

Each pack consists of one RESPIMAT inhaler and one cartridge, delivering 60 puffs (30 medicinal doses).

6.6 Special precautions for disposal and other handling

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Boehringer Ingelheim (N.Z.) Limited
P O Box 76216
Manukau City
Auckland 2241
NEW ZEALAND

Telephone: 0800 802 461

9. DATE OF FIRST APPROVAL

18 December 2008

10. DATE OF REVISION OF THE TEXT

25 July 2021

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
2	Minor editorial change – correction of typographical error.
4.2	Update to instructions for use to include additional instructional text. Minor editorial changes.
5.2	Minor editorial change.