New Zealand Datasheet

Name of Medicine
SPIRIVA® RESPIMAT®
Tiotropium 2.5 mcg

Presentation
SPIRIVA RESPIMAT 2.5 micrograms/puff, solution for inhalation. Each puff contains tiotropium 2.5 micrograms, equivalent to tiotropium bromide monohydrate 3.124 micrograms. The cartridge containing the solution for inhalation is used with the RESPIMAT inhaler.

SPIRIVA RESPIMAT cartridges contain a clear, colourless, solution for inhalation filled into a plastic container which is inside an aluminium cylinder (cartridge) for use with the RESPIMAT inhaler. SPIRIVA RESPIMAT is for oral inhalation only.

Uses

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

Tiotropium is a long-acting, specific antimuscarinic (anticholinergic) agent. It has similar affinity to the muscarinic receptor subtypes M₁ to M₅ (Kᵢ 5-41 pM). In the airways, inhibition by tiotropium of M₃-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 M₃-receptors, exhibiting a significantly longer dissociation half-life than that seen with ipratropium.

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 M₂-receptors is faster than from M₃, which in functional in vitro studies, elicited (kinetically controlled) receptor subtype selectivity of M₃ over M₂.

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

Pharmacokinetics
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.

Absorption
Following inhalation by young healthy volunteers, urinary excretion data suggest 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

**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.

**Metabolism**
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 [30]. Tiotropium bromide, an ester, is nonenzymatically [34] 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. 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.

**Elderly 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 $\text{AUC}_{0-6,ss}$ (between 1.8 to 30% higher) and similar $C_{\text{max,ss}}$ 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 $\text{AUC}_{0-4h}$ and 52% higher $C_{\text{max}}$ 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.

Indications
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.

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.

Dosage and Administration
The recommended dosage of SPIRIVA RESPIMAT is two puffs once daily at the same time each day (see RESPIMAT inhaler instructions for use under Further Information).

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. The safety and effectiveness of SPIRIVA RESPIMAT in paediatric patients have not been established.

The efficacy and safety of SPIRIVA RESPIMAT in paediatric patients with asthma has not yet been established.

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.
Warnings and Precautions

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-inflammmatory 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 Overdose).

SPIRIVA solution for inhalation cartridges are to be used only with the RESPIMAT® inhaler (see RESPIMAT inhaler instructions for use).

Use in Pregnancy

Category B1

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 (please refer to section Toxicology).

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

Use in Lactation

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 non-clinical study performed with tiotropium showed no indication of any adverse effect on fertility (please refer to section Toxicology).

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.

Adverse Effects
Many of the listed adverse effects can be assigned to the anticholinergic properties of tiotropium.

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 twelve weeks and one year, contributing 2,440 person years of exposure to tiotropium.

The clinical trial database for asthma includes 1,256 tiotropium treated patients from 6 placebo controlled trials with treatment period ranging between twelve weeks and one year, contributing 705 person years of exposure to tiotropium.

Metabolism and nutrition disorders:
dehydration

Nervous system disorders:
dizziness
insomnia

Eye disorders:
vision blurred
intraocular pressure increased
glaucoma

Cardiac disorders:
supraventricular tachycardia
atrial fibrillation
palpitations
tachycardia

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

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

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

**Musculoskeletal and connective tissue disorders:**
- joint swelling

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

**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.

**Overdosage**
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.

**Pharmaceutical Precautions**
Store below 25°C in a safe place out of the reach of children. Do not freeze.

The SPIRIVA RESPIMAT cartridge has an in-use shelf-life of 3 months after insertion in the RESPIMAT inhaler.

**Medicine Classification**
Prescription Medicine
Package Quantities
Each pack consists of one RESPIMAT inhaler and one cartridge, delivering 60 metered puffs. Each puff contains tiotropium 2.5 micrograms, equivalent to tiotropium bromide monohydrate 3.1 micrograms.

Further Information
SPIRIVA® and RESPIMAT® are registered trademarks.

Clinical Trials
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 micrograms 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, dyspnoea, 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 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 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 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 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 Hospitalized COPD Exacerbations in Patients with Moderate to Very Severe COPD

<table>
<thead>
<tr>
<th>Study (N&lt;sub&gt;Spiriva&lt;/sub&gt;, N&lt;sub&gt;Placebo&lt;/sub&gt;)</th>
<th>Endpoint</th>
<th>Spiriva Respimat</th>
<th>Placebo</th>
<th>% Risk Reduction (95% CI)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>p-value</th>
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<tbody>
<tr>
<td>1-year Ph III studies, pooled analysis&lt;sup&gt;d&lt;/sup&gt; (670, 653)</td>
<td>Days to first COPD exacerbation</td>
<td>160&lt;sup&gt;a&lt;/sup&gt;</td>
<td>86&lt;sup&gt;a&lt;/sup&gt;</td>
<td>29 (16 to 40)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.0001&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Mean exacerbation incidence rate per patient year</td>
<td>0.78&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.00&lt;sup&gt;c&lt;/sup&gt;</td>
<td>22 (8 to 33)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.002&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>Time to first hospitalised COPD exacerbation</td>
<td>NA&lt;sup&gt;e&lt;/sup&gt;</td>
<td>NA&lt;sup&gt;e&lt;/sup&gt;</td>
<td>25 (-16 to 51)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.20&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Mean hospitalised exacerbation incidence rate per patient year</td>
<td>0.09&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.11&lt;sup&gt;c&lt;/sup&gt;</td>
<td>20 (-4 to 38)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.096&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Study (N&lt;sub&gt;Spiriva&lt;/sub&gt;, N&lt;sub&gt;Placebo&lt;/sub&gt;)</td>
<td>Endpoint</td>
<td>Spiriva Respimat</td>
<td>Placebo</td>
<td>% Risk Reduction (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>p-value</td>
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<tr>
<td>1-year Ph IIIb exacerbation study (1939, 1953)</td>
<td>Days to first COPD exacerbation</td>
<td>169&lt;sup&gt;a&lt;/sup&gt;</td>
<td>119&lt;sup&gt;a&lt;/sup&gt;</td>
<td>31 (23 to 37)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.0001&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Mean exacerbation incidence rate per patient year</td>
<td>0.69&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.87&lt;sup&gt;c&lt;/sup&gt;</td>
<td>21 (13 to 28)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&lt;0.0001&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>Time to first hospitalised COPD exacerbation</td>
<td>NA&lt;sup&gt;e&lt;/sup&gt;</td>
<td>NA&lt;sup&gt;e&lt;/sup&gt;</td>
<td>27 (10 to 41)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.003&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Mean hospitalised exacerbation incidence rate per patient year</td>
<td>0.12&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.15&lt;sup&gt;c&lt;/sup&gt;</td>
<td>19 (7 to 30)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.004&lt;sup&gt;c&lt;/sup&gt;</td>
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<sup>a</sup> 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).

<sup>b</sup> Hazard ratios were estimated from a Cox proportional hazard model. The percentage risk reduction is 100(1 - hazard ratio).

<sup>c</sup> Poisson regression. Risk reduction is 100(1 - rate ratio).

<sup>d</sup> Pooling was specified when the studies were designed. The exacerbation endpoints were significantly improved in individual analyses of the two one year studies.

<sup>e</sup> 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<sub>1</sub> (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 FEV<sub>1</sub> 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
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 FEV1 were 0.110 litres (95% CI: 0.063 to 0.158 litres, p<0.0001) and 0.093 litres (95% CI: 0.050 to 0.137 litres, p<0.0001), respectively.
• The improvement of lung function compared to placebo was maintained for 24 hours (Figure 4).

**Figure 4:** FEV1 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)
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).

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

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

- 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)

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>ACQ responder (%)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 week Ph III studies, pooled analysis</td>
<td>Placebo, added-on to ICS (N=518)</td>
<td>57.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SPIRIVA RESPIMAT, added-on to ICS (N=513)</td>
<td>64.3</td>
<td>0.0348</td>
</tr>
<tr>
<td></td>
<td>Salmeterol, added-on to ICS (N=535)</td>
<td>66.5</td>
<td>0.0039</td>
</tr>
</tbody>
</table>
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.

**Toxicology**

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 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.

**Excipients**

Benzalkonium chloride, disodium edetate, purified water and hydrochloric acid for pH adjustment.

**Name and Address**

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