SPIRIVA® RESPIMAT®
(tiotropium bromide)

NAME OF THE MEDICINE

Active ingredient: tiotropium (as tiotropium bromide monohydrate)

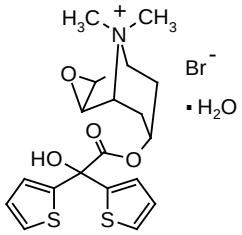
Chemical name: 3-Oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane, 7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-, bromide, monohydrate, (1α, 2β, 4β, 5α, 7β)-

Molecular formula: $C_{19}H_{22}NO_4S_2Br.H_2O$

Molecular weight: 490.4 (monohydrate)

CAS number: 139404-48-1

Structural formula:



DESCRIPTION

Tiotropium bromide is a white to yellowish-white, odourless crystalline powder. It exists as a quaternary ammonium salt, and there are no ionisable functional groups on the molecule. The active substance is not optically active.

Tiotropium bromide is freely soluble in dimethyl sulphoxide, soluble in methanol, sparingly soluble in water and practically insoluble in methylene chloride. The solubility in aqueous solutions at room temperature is approx. 2.5%, independent of pH. At pH 7.4, the apparent partition coefficient (log P_{app}) is -2.25.

A monohydrate form of tiotropium bromide is produced by the synthetic process. The compound melts with decomposition between 225°C and 235°C, when determined by differential scanning calorimetry at a heating rate of 10 K per minute.

Excipients include benzalkonium chloride, disodium edetate, purified water, and hydrochloric acid for pH adjustment.

PHARMACOLOGY

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 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. In non-clinical *in vitro* as well as *in vivo* studies, bronchoprotective effects were dose-dependent. Bronchoprotective effects lasting at least 24 hours were observed in some of the *in vivo* studies. The long duration of effect of tiotropium is likely to be due to its slow dissociation from M_3-receptors. Tiotropium exhibited a significantly longer dissociation half-life from M_3 receptors than ipratropium.

Tiotropium, a N-quaternary anticholinergic agent, is topically (broncho-) selective when administered by inhalation. The high potency (IC_{50} approximately 0.4 nM for M_3) 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.

PHARMACOKINETICS

Tiotropium bromide is a non-chiral quaternary ammonium compound and is sparingly soluble in water. Tiotropium bromide is available as solution for inhalation administered by the RESPIMAT inhaler. Generally with the inhaled route of administration, the majority of the delivered dose is swallowed and deposited in the gastrointestinal tract, and to a lesser extent is delivered to the lungs. 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 tiotropium RESPIMAT pharmacokinetic data described below were obtained with higher doses than recommended for therapy.

Bioequivalence

The primary objective of the Phase II, crossover study 205.458 involving 123 patients with COPD was to compare the pharmacokinetics of 5 µg tiotropium solution for inhalation delivered by the RESPIMAT Inhaler (Tio R 5) with tiotropium powder for inhalation 18 µg delivered by the HandiHaler® (Tio HH 18). The exposure to tiotropium following the use of Tio R 5 was lower compared to Tio HH 18. Using the parameters $AUC_{0\text{-}6,ss}$ and $C_{max,ss}$, bioequivalence was not established between Tio R 5 and Tio HH 18. The ratio of $AUC_{0\text{-}6,ss}$ (Tio R 5/ Tio HH 18) was 75.99% (90% confidence interval of (70.44, 81.98)). The ratio of $C_{max,ss}$ was 80.66% (90% CI: 73.49, 88.52).

Absorption

Following inhalation by young healthy volunteers, urinary excretion data suggests that approximately 33% of the inhaled dose reaches the systemic circulation. It is expected from the chemical structure of the compound that tiotropium is poorly absorbed from the gastro-intestinal tract. This was confirmed in a study in young healthy volunteers, with a low bioavailability of 2-3% for oral solutions. Food is not expected to influence the absorption of tiotropium for the same reason. 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 patients with COPD and decreased rapidly in a multi-compartmental manner. Steady state trough plasma concentrations were 1.60 pg/mL. A steady state tiotropium peak plasma concentration of 5.15 pg/mL was attained 5 minutes after the administration of the same dose to patients with asthma.

Distribution

The drug has a plasma protein binding of 72% and shows a volume of distribution of 32 L/kg.

Local concentrations in the lung are not known, but the mode of administration suggests substantially higher concentrations in the lung. Studies in rats have shown that tiotropium does not penetrate the blood-brain barrier to any relevant extent.

Metabolism

Metabolism does not occur to any great extent in young healthy volunteers, as indicated by 74% renal excretion of unchanged drug after an intravenous dose. The major metabolic pathway is non-enzymatic ester cleavage to the alcohol N-methylscopine and dithienylglycolic acid that are inactive on muscarinic receptors.

In vitro metabolism: In studies in animals and *in vitro* experiments with human liver microsomes and hepatocytes, minor amounts of a variety of glutathione conjugates, after oxidation of the thiophene rings, were observed.

In vitro studies in human liver microsomes revealed that the enzymatic pathway, relevant for only a small amount of tiotropium metabolism, can be inhibited by cytochrome P450 (CYP) 2D6 inhibitor quinidine and CYP 3A4 inhibitors ketoconazole and gestodene.

Tiotropium, even in supra-therapeutic concentrations, does not inhibit CYP 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1 or 3A in human liver microsomes.

Excretion

The effective half-life of tiotropium ranges between 27 to 45 h following inhalation by patients with COPD or asthma.

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. Urinary excretion of unchanged substance in young healthy volunteers is 74% of an intravenous dose. After inhalation of the solution for inhalation by patients with COPD, urinary excretion is 18.6% (0.93 µg) of the dose, the remainder being mainly non-absorbed drug in gut that is eliminated via the faeces.

In patients with asthma, 11.9% (0.595 µg) of the dose is excreted unchanged in the urine over 24 hours post dose at steady state.

The renal clearance of tiotropium exceeds the creatinine clearance, indicating secretion into the urine. After chronic, once daily inhalation, pharmacokinetic steady state was reached by day 7, with no accumulation thereafter.

Tiotropium demonstrates linear pharmacokinetics in the therapeutic range, independent of the formulation.

<u>Special populations</u>

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 patients with COPD <65 years to 275 mL/min in patients with COPD ≥ 65 years. This did not result in a corresponding increase in $AUC_{0-6,ss}$ and $C_{max,ss}$ values.

Exposure to tiotropium was not found to differ with age in patients with asthma.

Paediatric Patients

The peak and total exposure to tiotropium was not found to differ between paediatric patients (aged 6 to 17 years) and adults with asthma. In patients 1 to 5 years old with asthma (n=3), the total exposure as measured by urinary excretion (over 3 hours) was 52 to 60% lower than that observed in patients 6 years and older with asthma; the total exposure data when adjusted for body surface area were found to be comparable in all age groups. SPIRIVA RESPIMAT was administered with a valved holding chamber with facemask in patients 1 to 5 years of age.

Renally impaired patients

Following once daily inhaled administration of tiotropium to steady-state to patients with COPD with mild renal impairment (CL_{CR} 50-80 mL/min) resulted in slightly higher $AUC_{0-6,ss}$ (between 1.8 to 30% higher) and similar $C_{max,ss}$ compared to COPD patients with normal renal function (CL_{CR} >80 mL/min. In patients with COPD with moderate to severe renal impairment (CL_{CR} <50 mL/min), the intravenous administration of tiotropium resulted in a doubling of the total exposure (82% higher AUC_{0-4h} and 52% higher C_{max}) compared to

patients with COPD with normal renal function, which was confirmed by plasma concentrations after dry powder inhalation.

In asthma patients with mild renal impairment (CL_{CR} 50-80 mL/min) inhaled tiotropium did not result in relevant increases in exposure compared to patients with normal renal function.

Hepatically impaired patients

There are no data on the pharmacokinetics of tiotropium in hepatic impairment. Liver insufficiency is not expected to have any relevant influence on tiotropium pharmacokinetics. Tiotropium is predominantly cleared by renal elimination (74% in young healthy volunteers) and by simple non-enzymatic ester cleavage to products that do not bind to muscarinic receptors.

CLINICAL TRIALS

COPD

The clinical Phase III programme for COPD included two 1-year, two 12-week and two 4-week randomised, double-blind studies in 2901 patients with COPD (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, with trough FEV_1 (i.e. FEV_1 measured approximately 10 minutes before the final dose) as the primary endpoint. In addition, the two 1-year studies included health outcome measures of health-related quality of life, dyspnoea, and effect on exacerbations as co-primary endpoints.

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.

Mean trough FEV_1 treatment difference for SPIRIVA RESPIMAT over placebo in the combined 1-year trials at day 337 was 127 mL ($p<0.0001$ vs. placebo). Improvement of lung function was maintained for 24 hours at steady state. Pharmacodynamic steady state was reached within one week. The bronchodilator effects of SPIRIVA RESPIMAT were maintained throughout the 48-week period of administration with no evidence of tolerance.

Mean trough FEV_1 treatment differences for the combined 12-week trials at day 85 was 118 mL for SPIRIVA RESPIMAT over placebo ($p<0.0001$) and 64 mL for SPIRIVA RESPIMAT over ipratropium bromide ($p=0.0060$).

A combined analysis of two randomised, placebo-controlled, crossover, clinical studies demonstrated that the bronchodilator response as measured by mean trough FEV_1 for SPIRIVA RESPIMAT was 29 mL higher than SPIRIVA HandiHaler (18 micrograms) inhalation powder after a 4-week treatment period ($p=0.03$). Since steady state efficacy is reached within 4 weeks, no longer term study comparing the two products has been conducted.

SPIRIVA RESPIMAT significantly improved morning and evening PEFR (peak expiratory flow rate) as measured by patient's daily recordings (morning improvement mean 22 L/min, $p<0.0001$; evening improvement mean 26 L/min, $p<0.0001$). The use of SPIRIVA RESPIMAT resulted in a reduction of rescue bronchodilator use compared to placebo.

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) the magnitude of change being 1.05 units at day 337 ($p<0.0001$ vs. placebo). The mean Baseline Dyspnoea Index was 6.41 units. 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. By day 337 the mean treatment difference improvement in SGRQ total score from placebo (pooled data from the two 1-year studies) was 3.5 for SPIRIVA RESPIMAT ($p<0.0001$ vs. placebo). The mean SGRQ total score at baseline was 44.8.

(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 Ph III studies, pooled analysis[d] (670, 653)	Days to first COPD exacerbation	160[a]	86[a]	29 (16 to 40)[b]	<0.0001[b]
	Mean exacerbation incidence rate per patient year	0.78[c]	1.00[c]	22 (8 to 33)[c]	0.002[c]
	Time to first hospitalised COPD exacerbation	NA[e]	NA[e]	25 (-16 to 51)[b]	0.20[b]
	Mean hospitalised exacerbation incidence rate per patient year	0.09[c]	0.11[c]	20 (-4 to 38)[c]	0.096[c]
1-year Ph IIIb exacerbation study (1939, 1953)	Days to first COPD exacerbation	169[a]	119[a]	31 (23 to 37)[b]	<0.0001[b]
	Mean exacerbation incidence rate per patient year	0.69[c]	0.87[c]	21 (13 to 28)[c]	<0.0001[c]
	Time to first hospitalised COPD exacerbation	NA[e]	NA[e]	27 (10 to 41)[b]	0.003[b]
	Mean hospitalised exacerbation 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 hospitalization.

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 (2 puffs comprise one medicinal dose of 5 micrograms); 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 FEV_1 for SPIRIVA RESPIMAT versus SPIRIVA HandiHaler was -0.010 L (95% CI -0.038 to 0.018 L).

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 48 week, 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, tiotropium 5 microgram, once daily) 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 48-week 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 1).

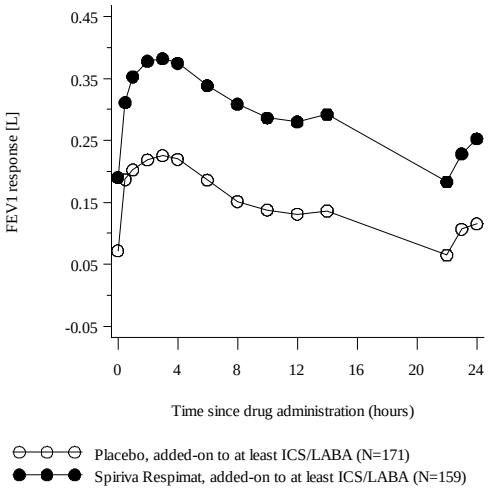


Figure 1: FEV_1 profiles over 24 hours in a subset of patients in the PrimoTinA-asthma studies at week 24

- 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 48-week period of administration with no evidence of tachyphylaxis or tolerance (Figure 2).

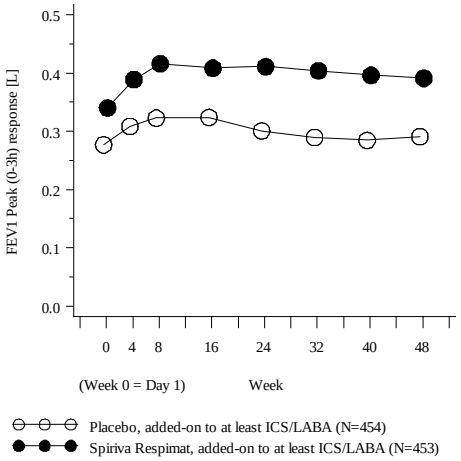


Figure 2: Peak FEV_1 response over 48 weeks in the PrimoTinA-asthma studies

- SPIRIVA RESPIMAT significantly reduced the risk of severe asthma exacerbations (see Table 2 and Figure 3).

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
48-week 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.

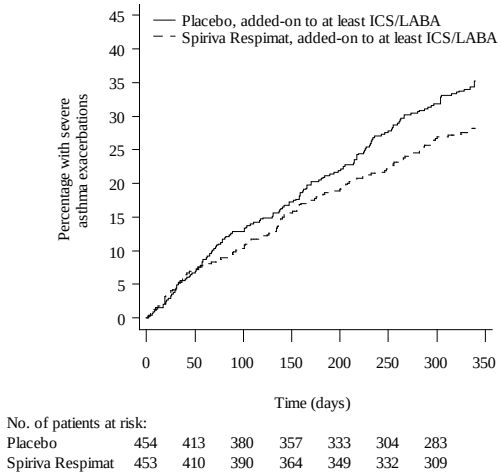


Figure 3: Severe asthma exacerbations over time in PrimoTinA-asthma studies

- 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 (treatment difference: 0.117, 95% CI: 0.011, 0.223, p=0.0312).

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 Patients:

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

- Adolescents (12-17 years): one 1-year and one 12-week randomised, double-blind, placebo-controlled studies in a total of 789 asthma patients (264 receiving SPIRIVA RESPIMAT, tiotropium 5 microgram, once daily)
- 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 tiotropium 5 microgram, once daily)
- Children (1-5 years): one 12-week randomised, double-blind placebo-controlled study in a total of 101 asthma patients (31 receiving SPIRIVA RESPIMAT tiotropium 5 microgram, once daily)

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 with moderate asthma 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 4).

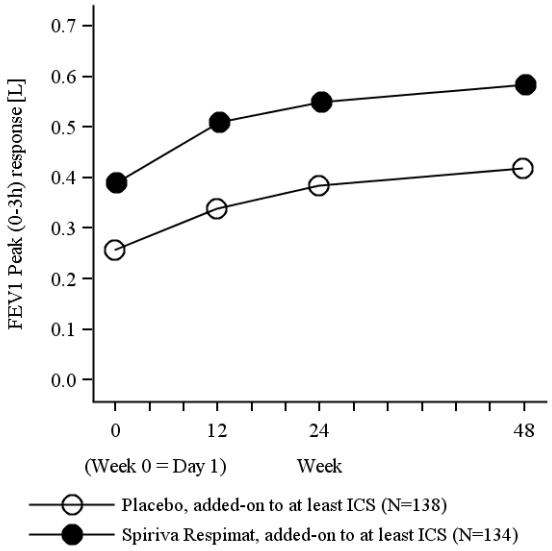


Figure 4: Peak FEV_1 response over 48 weeks in the RubaTinA-asthma study

In the 12-week PensieTinA-asthma study in patients with severe asthma who were symptomatic on maintenance treatment of at least medium dose ICS in combination with 1 or more controller medication (e.g. LABA), SPIRIVA RESPIMAT showed improvements in lung function over placebo when used as add-on to background treatment, however, the differences in peak and trough FEV_1 were not statistically significant.

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

Children (6-11 years)

In the 1-year CanoTinA-asthma study in patients with moderate asthma 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 0.164 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 5).

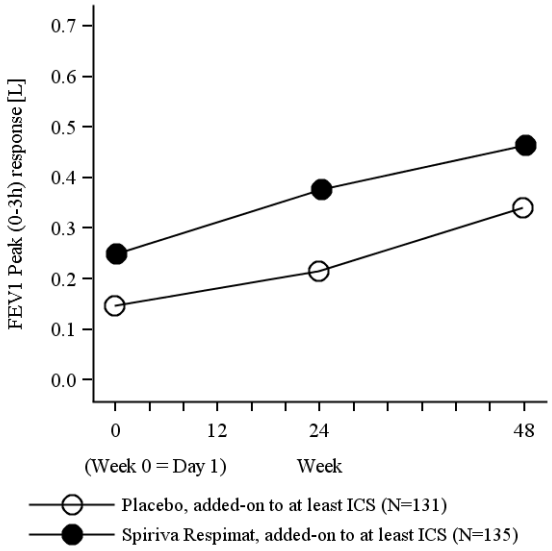


Figure 5: Peak FEV_1 response over 48 weeks in the CanoTinA-asthma study

In the 12-week VivaTinA-asthma study in patients with severe asthma who were symptomatic on maintenance treatment of at least medium dose ICS in combination with 1 or more controller medication (e.g. LABA), 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.

INDICATIONS

COPD

SPIRIVA RESPIMAT is indicated for the long term maintenance treatment of bronchospasm and dyspnoea associated with chronic obstructive pulmonary disease (COPD). SPIRIVA RESPIMAT is indicated for the prevention of COPD exacerbations.

Asthma

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

CONTRAINDICATIONS

SPIRIVA RESPIMAT is contraindicated in patients with a history of hypersensitivity to tiotropium bromide, atropine or its derivatives, e.g. ipratropium or oxitropium or to any other component of this product (see list of excipients in *Description*).

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. Patients with asthma 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 solution for inhalation.

As with other anticholinergic drugs, SPIRIVA RESPIMAT should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction. In a meta-analysis of placebo-controlled trials, SPIRIVA was associated with a non-significant increase in the risk of urinary retention, and a significant increase in the risk of micturition difficulties.

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

Inhaled medicines may cause inhalation-induced bronchospasm.

Tiotropium should be used with caution in patients with recent myocardial infarction < 6 months; any unstable or life-threatening cardiac arrhythmia or cardiac arrhythmia requiring intervention or a change in drug therapy in the past year; hospitalisation of heart failure (NYHA Class III or IV) within the past year. These patients were excluded from the clinical trials and these conditions may be affected by the anticholinergic mechanism of action.

As with all predominantly renally excreted drugs, SPIRIVA use should be monitored closely in patients with moderate to severe renal impairment (creatinine clearance of $\leq$ 50 mL/min) (see *Pharmacokinetics*). There is no long term experience in patients with severe renal impairment.

Patients must be instructed in the correct administration of SPIRIVA. Care must be taken not to allow the solution or mist 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 cartridges are to be used only with RESPIMAT inhaler (see *RESPIMAT inhaler instructions for use*).

Effects on fertility

Clinical data on fertility are not available for tiotropium. Tiotropium (as bromide) did not affect the fertility of male or female rats when administered by inhalation at doses up to 2 mg/kg (750x the maximum recommended human daily dose of the drug, based on body surface area).

Use in Pregnancy: (Category B1)

There is a limited amount of data from the use of tiotropium in pregnant women. Reproductive toxicity studies with tiotropium bromide administered by inhalation to rats and rabbits at doses up to 2.0 and 0.5 mg/kg/day, respectively, produced no evidence of fetal malformations. These doses correspond to 750x and 400x the maximum recommended human daily dose of the drug based on body surface area. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant doses.

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

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.

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.

Paediatric use

COPD does not normally occur in children.

In children aged 1-5 years: One 12-week clinical study was conducted in a total of 101 children 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.

There was no difference in the exploratory symptoms score in those treated with tiotropium versus placebo. The number of asthma adverse events was lower for SPIRIVA RESPIMAT compared to placebo.

Tiotropium has not been studied in children less than 1 year.

Use in the elderly

Elderly patients can use SPIRIVA RESPIMAT at the recommended dose. Renal clearance of tiotropium is likely to be slower in elderly patients (see *Renal Impairment*).

Genotoxicity

Tiotropium (as bromide) did not exhibit any genotoxic effects in assays for gene mutation (bacteria and mammalian cells *in vitro* and *in vivo* mouse micronucleus test) or DNA damage (rat hepatocytes *in vitro*).

Carcinogenicity

Long-term carcinogenicity studies in mice and rats, with tiotropium (as bromide) administered by inhalation, showed no evidence of neoplastic responses. The highest doses studied were approximately 0.8x (male mouse), 38x (female mouse) and 16x (rat) greater than the maximum recommended human daily dose of the drug, based on body surface area.

Hepatic Impairment

There are no data on the use of tiotropium in patients with hepatic impairment. As tiotropium is primarily cleared by renal mechanisms, no dosage adjustment is recommended. However patients should be monitored closely.

Renal Impairment

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 COPD and asthma patients with moderate to severe renal impairment (creatinine clearance ≤ 50 mL/min).

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.

INTERACTIONS WITH OTHER MEDICINES

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.

Limited information about co-administration of other anticholinergic medicines with SPIRIVA is available from a clinical trial. The concomitant use of SPIRIVA RESPIMAT with other anticholinergic agents (e.g. glycopyrronium, aclidinium, umeclidinium, ipratropium) is expected to have additive anticholinergic effects. Acute single dose administration of ipratropium bromide after 19 days of SPIRIVA treatment in healthy volunteers (n=35) was not associated with relevant changes in vital signs or electrocardiographic findings. Adverse events were reported by 3 (9%) of subjects in the study during ipratropium treatment with tiotropium compared to 1 (3%) during placebo treatment with tiotropium. Ipratropium was associated with a 16% decrease in salivary secretions in healthy volunteers. The chronic co-administration of tiotropium bromide with other anticholinergic medicines has not been studied. Therefore, the chronic co-administration of other anticholinergic drugs with SPIRIVA RESPIMAT is not recommended.

ADVERSE EFFECTS

Many of the listed adverse 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.

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, usually mild	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
Skin and subcutaneous tissue disorders, immune system disorders		
Rash	Uncommon	Uncommon
Pruritus	Uncommon	Rare
Angioneurotic oedema	Rare	Rare
Urticaria	Rare	Rare
Skin infection/skin ulcer	Rare	Not known
Dry skin	Rare	Not known
Hypersensitivity (including immediate reactions)	Not known	Rare
Musculoskeletal and connective tissue disorders		
Joint swelling	Not known	Not known
Renal and urinary disorders		
Urinary retention (usually in men with predisposing factors)	Uncommon	Not known
Dysuria	Uncommon	Not known
Urinary tract infection	Rare	Rare

Description of selected adverse effects

In controlled clinical studies of COPD, the commonly observed adverse 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%.

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

An increase in anticholinergic effects may occur with increasing age.

Paedriatic population:

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

DOSAGE AND ADMINISTRATION

The recommended dosage of tiotropium using the SPIRIVA RESPIMAT is 5 micrograms. This is administered as two puffs once daily at the same time each day (see RESPIMAT inhaler Instructions for Use).

The recommended dose should not be exceeded.

In the treatment of asthma, the full benefits will be apparent after several doses of SPIRIVA RESPIMAT.

Paediatric population:

In 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 Instructions for Use).

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.

OVERDOSAGE

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

However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 282 micrograms tiotropium in healthy volunteers. Additionally, no relevant adverse effects, beyond dry mouth, were observed following 7 day dosing of up to 141 micrograms tiotropium in healthy volunteers. In a multiple dose study in patients with COPD, with a maximum daily dose of 36 micrograms tiotropium over four weeks, no significant undesirable effects were observed.

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 patients with COPD when a daily dose of 10 micrograms tiotropium solution for inhalation was given over 4-48 weeks.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

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. The SPIRIVA RESPIMAT inhaler has a green-coloured cap. SPIRIVA RESPIMAT is for oral inhalation only.

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.

In-use shelf life

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

Special precautions for storage

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

NAME AND ADDRESS OF THE SPONSOR

Boehringer Ingelheim Pty Limited

ABN 52 000 452 308

78 Waterloo Road

North Ryde NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG):

30 May 2002

DATE OF MOST RECENT AMENDMENT:

30 April 2018