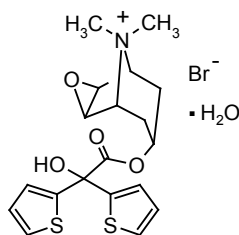


SPIRIVA[®] RESPIMAT[®] (tiotropium bromide)

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, (1 α , 2 β , 4 β , 5 α , 7 β)-
Molecular formula: C₁₉H₂₂NO₄S₂Br.H₂O
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 sulfoxide, 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, water-purified, 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 M₁ to M₅ (K_D 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. 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 M₃-receptors. Tiotropium exhibited a significantly longer dissociation half-life from M₃ receptors than ipratropium.

Tiotropium, a N-quaternary anticholinergic agent, is topically (broncho-) selective when administered by inhalation. The high potency (IC₅₀ approximately 0.4 nM for M₃) 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_{0-6,ss} and C_{max,ss}, bioequivalence was not established between Tio R 5 and Tio HH 18. The ratio of AUC_{0-6,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 gastrointestinal 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 diethyleneglycolic 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.

Special populations

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.

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

Study (N _{Spiriva} , N _{placebo})	Endpoint	SPIRIVA RESPIMAT	Placebo	% Risk Reduction (95% CI) ^a	p-value
	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 FEV₁ (pre-dose).

The time to first COPD exacerbation was similar during the study with SPIRIVA RESPIMAT and SPIRIVA HandiHaler (hazard ratio (SPIRIVA RESPIMAT / SPIRIVA HandiHaler) 0.98 with a 95% CI of 0.93 to 1.03).

The median number of days to the first COPD exacerbation was 756 days for SPIRIVA RESPIMAT and 719 days for SPIRIVA HandiHaler

The bronchodilator effect of SPIRIVA RESPIMAT was sustained over 120 weeks, and was similar to SPIRIVA HandiHaler. The mean difference in trough FEV₁ for SPIRIVA RESPIMAT versus SPIRIVA HandiHaler was -0.010 L (95% CI -0.038 to 0.018 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

The clinical Phase III program for persistent asthma included two 48 week randomised, double-blind, placebo-controlled studies in a total of 907 patients with asthma (453 receiving SPIRIVA RESPIMAT) on a combination of ICS (≥800 µg budesonide/day or equivalent) with a LABA. The studies included lung function measurements and severe exacerbations as primary endpoints.

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 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 1).

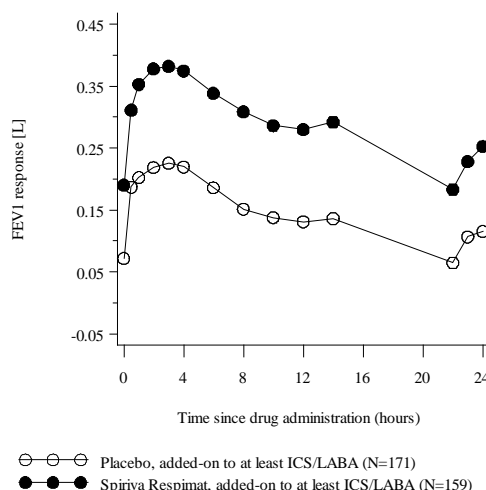


Figure 1: FEV₁ profiles over 24 hours in a subset of patients in the PrimoTinA-asthma studies at week 24

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

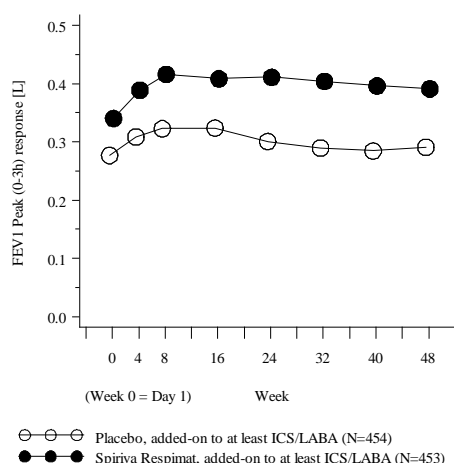


Figure 2: Peak FEV₁ response over 48 weeks in the PrimoTinA-asthma studies

- 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

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 1 st 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 1 st 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

^aHazard 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)

^bTime to first event: days on treatment by when 25% of patients had at least one severe asthma exacerbation/worsening of asthma

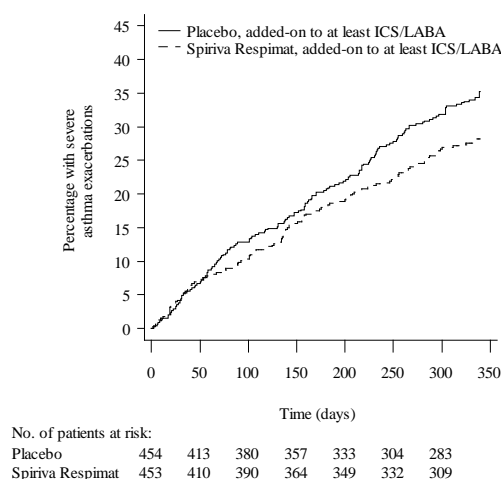


Figure 3: Severe asthma exacerbations over time in PrimoTinA-asthma studies

- 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).

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 adult patients with asthma who are currently treated with the maintenance combination of inhaled corticosteroids (≥ 800 μ g budesonide/day or equivalent) and long-acting β_2 agonists and who experienced one or more severe exacerbations in the previous year.

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 ≤ 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.

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

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

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 1,256 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.

Frequency is defined using the following convention:

Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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
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System Organ Class / MedDRA Preferred Term	Frequency COPD	Frequency Asthma
<u>Metabolism and nutrition disorders</u>		
Dehydration	Not known	Not known
<u>Nervous system disorders</u>		
Dizziness	Uncommon	Uncommon
Insomnia	Rare	Uncommon
<u>Eye disorders</u>		
Glaucoma	Rare	Not known
Intraocular pressure increased	Rare	Not known
Vision blurred	Rare	Not known
<u>Cardiac disorders</u>		
Atrial fibrillation	Rare	Not known
Palpitations	Rare	Uncommon
Supraventricular tachycardia	Rare	Not known
Tachycardia	Rare	Not known
<u>Respiratory, thoracic and mediastinal disorders</u>		
Cough	Uncommon	Uncommon
Epistaxis	Rare	Not known
Pharyngitis	Uncommon	Uncommon
Dysphonia	Uncommon	Uncommon
Bronchospasm	Rare	Uncommon
Laryngitis	Rare	Not known
Sinusitis	Not known	Not known
<u>Gastrointestinal disorders</u>		
Dry mouth, usually mild	Common	Common
Constipation	Uncommon	Rare
Oropharyngeal candidiasis	Uncommon	Uncommon
Dysphagia	Rare	Not known
Gastroesophageal 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
<u>Skin and subcutaneous tissue disorders, immune system disorders</u>		
Rash	Uncommon	Rare
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
<u>Musculoskeletal and connective tissue disorders</u>		
Joint swelling	Not known	Not known
<u>Renal and urinary disorders</u>		
Urinary retention (usually in men with predisposing factors)	Uncommon	Not known
Dysuria	Uncommon	Not known
Urinary tract infection	Rare	Not known

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 1.2%.

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.

DOSAGE AND ADMINISTRATION

The recommended dosage of SPIRIVA RESPIMAT is 5 micrograms of tiotropium given 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.

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.

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 ARTG:

30 May 2002

DATE OF MOST RECENT AMENDMENT:

TBA