AUSTRALIAN PRODUCT INFORMATION – SPIRIVA (tiotropium) powder for inhalation (in capsule)

1 NAME OF THE MEDICINE

tiotropium (as tiotropium bromide monohydrate)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatine SPIRIVA capsule contains 18 micrograms tiotropium, equivalent to 22.5 micrograms tiotropium bromide monohydrate and the excipient lactose monohydrate (which contains milk protein).

Excipients with known effect:

This product contains 5.5 mg of lactose monohydrate per capsule.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

SPIRIVA capsules are light green in colour, with the product code (TI 01) and company logo printed on the capsule. The capsules contain a white powder.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended dosage of SPIRIVA is inhalation of the contents of one capsule, once daily with the HandiHaler device, at the same time each day (*see HandiHaler Instructions for Use*).

SPIRIVA capsules must not be swallowed.

Special populations

Elderly patients can use SPIRIVA at the recommended dose.

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

Hepatically impaired patients can use SPIRIVA at the recommended dose.

Paediatric population

There is no experience with SPIRIVA in infants and children and therefore should not be used in this age group.

4.3 CONTRAINDICATIONS

SPIRIVA 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 Section 6.1 List of excipients and Section 4.4 Special Warnings and Precautions for Use).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

SPIRIVA, as a once daily maintenance bronchodilator, should not be used for the treatment of acute episodes of bronchospasm, i.e. rescue therapy.

Immediate hypersensitivity reactions may occur after administration of SPIRIVA.

As with other anticholinergic drugs, SPIRIVA 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.

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 Section 5.2 Pharmacokinetic Properties).

Patients must be instructed in the correct administration of SPIRIVA. Care must be taken not to allow the powder or 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 should not be used more frequently than once daily (see Section 4.9 Overdose).

SPIRIVA capsules are to be used only with the HandiHaler® device (see *separate HandiHaler Instructions for Use*).

Use in 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.

Use in renal impairment

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

Use in the elderly

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

Paediatric use

The safety and effectiveness of SPIRIVA in paediatric patients has not been established. Therefore, SPIRIVA should not be used in paediatric patients.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Although no formal drug interaction studies have been performed, tiotropium has been used concomitantly with other drugs which are commonly used in the treatment of COPD, including sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids 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 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. Chronic co-administration of other anticholinergic medicines with SPIRIVA has not been studied and is therefore not recommended.

4.6 FERTILITY, PREGNANCY AND LACTATION

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 22.5 μg, 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 22.5 μg based on body surface area. Animal studies do not suggest 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 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, tiotropium should not be used in lactating women unless the expected benefit outweighs any possible risk to the infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

Summary of the safety profile

Many of the listed undesirable 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 includes 9,647 tiotropium patients from 28 placebo-controlled clinical trials with treatment periods ranging between four weeks and four years, contributing 12,469 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
Metabolism and nutrition disorders	
Dehydration	Not known
Nervous system disorders	
Dizziness	Uncommon
Insomnia	Rare
Eye disorders	
Vision blurred	Uncommon
Glaucoma	Rare
Intraocular pressure increased	Rare
Cardiac disorders	
Atrial fibrillation	Uncommon
Palpitations	Rare
Supraventricular tachycardia	Rare
Tachycardia	Rare
Respiratory, thoracic and mediastinal disorders	
Cough	Uncommon
Dysphonia	Uncommon
Pharyngitis	Uncommon
Epistaxis	Rare
Bronchospasm	Rare
Laryngitis	Rare
Sinusitis	Rare
Gastrointestinal disorders	
Dry Mouth, usually mild	Common
Constipation	Uncommon
Oropharyngeal candidiasis	Uncommon
Gastrooesophageal reflux disease	Uncommon
Dysphagia	Rare
Gingivitis	Rare
Glossitis	Rare
Stomatitis	Rare
Intestinal obstruction, including ileus paralytic	Rare
Skin and subcutaneous tissue disorders, immune system disorders	
Rash	Uncommon
Pruritus	Rare
Angioneurotic oedema	Rare
Urticaria	Rare
Hypersensitivity (including immediate reactions)	Rare
Skin infection/skin ulcer	Not known
Dry skin	Not known

System Organ Class / MedDRA Preferred Term	Frequency
Musculoskeletal and connective tissue disorders	
Joint swelling	Not known
Renal and urinary disorders	
Urinary retention (usually in men with predisposing factors)	Uncommon
Dysuria	Uncommon
Urinary tract infection	Rare

4.9 OVERDOSE

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

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 COPD patients, with a maximum daily dose of 36 micrograms tiotropium over four weeks, no significant undesirable effects were observed.

Acute intoxication by inadvertent oral ingestion of tiotropium powder is unlikely, due to low oral bioavailability.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other drugs for obstructive airway diseases, inhalants, anticholinergics; ATC code: R03BB04

Mechanism of action

Tiotropium is a long-acting, specific antimuscarinic (anticholinergic) agent. It has similar affinity to the muscarinic receptor subtypes M_1 to M_5 (K_D 5-41 pM). In the airways, inhibition by tiotropium of M_3-receptors at the smooth muscle results in relaxation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors. 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).

The bronchodilation following inhalation of tiotropium is primarily a local effect on the airways, not a systemic one.

<u>Cardiac electrophysiology</u>

In a dedicated QT study involving 53 healthy volunteers, SPIRIVA 18 mcg and 54 mcg (i.e. three times the therapeutic dose) over 12 days did not significantly prolong QT intervals of the ECG.

Clinical trials

Clinical efficacy

The pivotal clinical development program consisted of four one-year randomised, double-blind studies; two placebo-controlled and two with an active control (ipratropium) in 1456 COPD patients, 906 of which received SPIRIVA. The studies assessed lung function in terms of forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and peak expiratory flow rate (PEFR). Health outcome measures including dyspnoea, exacerbations, hospitalisations and health-related quality of life (as measured by the St George's Respiratory Questionnaire, SGRQ) were also assessed. In addition, the development program included two large trials of six months duration which compared the bronchodilator efficacy and safety of SPIRIVA, with salmeterol inhalation aerosol and placebo in patients with COPD. These two studies randomised a total of 1207 patients, with approximately one-third treated with SPIRIVA.

Lung function

Overall results from the four one-year studies demonstrated that SPIRIVA, administered once daily, provided significant improvement in lung function (FEV_1 and FVC) within 30 minutes following the first dose and that this improvement was maintained for 24 hours. Pharmacodynamic steady state was reached within one week, with near maximal bronchodilation observed by the third day. SPIRIVA significantly improved morning and evening PEFR as measured by the patient's daily recordings. The bronchodilator effects of SPIRIVA were maintained throughout the one-year period of administration with no evidence of tolerance.

In the two one-year, randomised, double blind, placebo-controlled studies, 550 patients received SPIRIVA once daily and 371 patients received placebo. Mean differences in FEV_1 between SPIRIVA and placebo were highly statistically significant at all time points ($p<0.0001$). The mean trough FEV_1 at Day 92 (defined as the primary efficacy endpoint) was 0.14 L greater following SPIRIVA than placebo ($p<0.0001$) and remained significantly different from placebo throughout the one year observation period ($p<0.0001$). The FVC response generally paralleled that of FEV_1.

In the two one-year, randomised, double blind, ipratropium-controlled studies, 356 patients received SPIRIVA once daily and 179 patients received ipratropium, 2 puffs of 20 micrograms, four times a day. Mean differences in trough FEV_1 between SPIRIVA and ipratropium were highly statistically significant at all time points ($p<0.0001$). The mean trough FEV_1 on Day 92 was 0.14 L greater following SPIRIVA than ipratropium ($p<0.0001$). The FVC response generally paralleled that of FEV_1.

Long-term clinical trials (6 months and 1 year)

Dyspnoea, Exercise tolerance

In the one-year trials, SPIRIVA significantly improved dyspnoea in patients, as evaluated using the Mahler Transitional Dyspnoea Index (TDI) and patient daily reported symptoms. Following treatment with SPIRIVA, the dyspnoea score improved significantly when compared to placebo, with changes in each domain, as well as the focal score, being highly statistically significant over one year ($p<0.0002$). The proportion of patients treated with SPIRIVA who achieved a TDI focal score change of at least 1 point over the one-year period, representing a clinically meaningful difference, was statistically greater than the proportion of patients treated with placebo ($p<0.0001$).

When compared to ipratropium, patients treated with SPIRIVA exhibited significantly less dyspnoea at each time point, and the proportion of patients achieving a difference of 1 point in the TDI focal score was significantly greater in the SPIRIVA group.

The impact of improvement in dyspnoea on functional activities was investigated in two randomised, double-blind, placebo-controlled, parallel group studies in 433 COPD patients. The studies investigated whether six weeks treatment with SPIRIVA once daily improves

exercise tolerance in patients with COPD as measured by symptom-limited exercise endurance time (ET) during constant work rate cycle ergometry at 75% of maximal work capacity. Results demonstrated that SPIRIVA significantly improved ET by 20% to 28% compared with placebo. Increases in ET (seconds) are shown in Table 1.

Additionally in these trials, SPIRIVA demonstrated significant reductions in lung hyperinflation at rest and significant reductions in lung hyperinflation and dyspnoea during constant work rate cycle exercise.

Table 1: Endurance time (ET) after 42 days treatment with tiotropium vs placebo in patients with COPD

Study	Pre-treatment Baseline ET (seconds)	Adjusted mean ET (seconds)		Treatment Difference tio – placebo at 42 days (seconds)	p-value
		Tiotropium	Placebo		
Trial A	492	640	535	105	0.0098
Trial B	537	741	577	164	0.0002

Health related quality of life

The SGRQ was the primary instrument used to evaluate disease-specific health related quality of life, with the impact domain stated as the primary endpoint. SPIRIVA was significantly more effective than both placebo and ipratropium in improving health-related quality of life based on the SGRQ. The percentages of patients in the SPIRIVA groups who demonstrated a clinically meaningful improvement (pre-specified criteria of 4 units) over baseline were significantly greater than those in the placebo and ipratropium groups.

SPIRIVA was more effective than placebo in each domain. Generally, the difference between the treatment groups increased between baseline and the last treatment visit. For the primary measure, Impacts score, the difference between the two treatment groups ranged from 1.8 to 4.0 and was statistically significant ($p<0.05$) on all test days.

A significantly greater ($p<0.05$) percentage of patients in the SPIRIVA group showed a clinically meaningful improvement (drop of 4 units) in the Impacts score from six months through to the end of the study and for Total score from three months through to the end of the study.

SPIRIVA was also shown to be more effective than ipratropium in improving health-related quality of life using the SGRQ. For Impacts score, the difference between the two treatment groups in the mean score ranged from 0.6 at 8 days to 4.3 at 364 days and was statistically significant from three months through the end of the study. Statistically significant differences between SPIRIVA and ipratropium were also noted for the Total score on four of six test days.

A significantly greater ($p<0.05$) percentage of patients in the SPIRIVA group showed clinically meaningful improvement (difference greater than 4 units) in both Impacts and Total scores over ipratropium after six months.

Two trials of six months duration compared the bronchodilator efficacy and safety of SPIRIVA once daily with salmeterol inhalation aerosol (50 micrograms twice daily) and placebo in patients with COPD. In one study, designed to evaluate the 12-hour duration of action, when the effects over time for SPIRIVA and salmeterol were compared, the mean trough FEV_1 in the SPIRIVA group was significantly higher than that in the salmeterol group ($p<0.05$), beginning on day 57. The difference between SPIRIVA and salmeterol for trough, average and peak FEV_1 response was statistically significant ($p<0.05$), except for trough response on day 15, and average and peak FEV_1 response on day 1. At the end of the study, trough FVC had improved in the SPIRIVA group significantly above the placebo ($p<0.001$) and the salmeterol ($p<0.01$) groups. At the end of the combined six months trials, the improvement in TDI focal scores for SPIRIVA above placebo was 1.1 units ($p<0.001$), which was both statistically and clinically significant, and for salmeterol above placebo was 0.7 units ($p<0.05$), which was not clinically significant.

COPD exacerbations

In the analysis of the pooled data from the four one-year studies, SPIRIVA significantly reduced both the number of COPD exacerbations and the number of hospitalisations associated with COPD exacerbations. In addition, time to first COPD exacerbation and to first hospitalisation associated with a COPD exacerbation was significantly prolonged.

In the placebo-controlled trials, the percentage of patients with at least one exacerbation during the treatment period was 36% in the SPIRIVA group and 42% in the placebo group (p=0.03); at least one hospitalisation for exacerbation occurred in 5.5% and 9.4% of patients respectively (p=0.019). The number of exacerbations and hospitalisations associated with exacerbations (expressed as events per 100 patient years) were significantly fewer for patients treated with SPIRIVA compared to placebo (p=0.045 and p=0.019 respectively). Patients on SPIRIVA also spent significantly fewer days in hospital for exacerbations compared to placebo (p=0.023). The time to first exacerbation was significantly delayed in the SPIRIVA group relative to placebo (p=0.011). Overall, these data indicate that therapy with SPIRIVA is associated with a delayed onset and a lower incidence of COPD exacerbations.

In the ipratropium-controlled trials, the percentage of patients with an exacerbation during the treatment period was 35% in the SPIRIVA group and 46% in the ipratropium group, a difference that was statistically significant. A similar trend was seen for hospitalisations for exacerbation (7.3% vs. 11.7%; p=0.108). The number of exacerbations and exacerbation days impacted by these events was also less in the SPIRIVA group compared to ipratropium (p=0.006 and p=0.002, respectively). A similar trend was observed for hospitalisations (p=0.0803) and hospitalisation days for exacerbations (p=0.86). The time to first exacerbation, as well as for hospitalisation for exacerbation, was significantly delayed in the SPIRIVA group relative to the ipratropium group (p=0.008 and 0.048, respectively). Overall these data indicate that SPIRIVA is associated with reduced exacerbations.

SPIRIVA significantly reduced the percentage of patients experiencing one or more COPD exacerbations compared with placebo in a six-month randomised, double-blind, placebo-controlled trial of 1,829 patients with COPD (27.9% vs. 32.3%, respectively, p=0.0368). The mean number of exacerbations per patient-year was significantly lower in the SPIRIVA group compared to placebo (0.85 vs. 1.05, respectively, p=0.003), as was the number of exacerbation days (p<0.0001). Time to first exacerbation was significantly increased in the SPIRIVA group compared to placebo (relative risk=0.834, p=0.034). Fewer SPIRIVA patients were hospitalised because of COPD exacerbation (7.0% vs. 9.5%, respectively; p=0.056), although this difference was not statistically significant. The number of hospitalisations for exacerbations per patient-year was significantly lower in the SPIRIVA group, compared to placebo (p=0.013). Similarly, the mean number of hospitalisations days for exacerbations was lower in the SPIRIVA group compared to placebo (1.43 vs 1.70 days per patient-year, p=0.0013). The time to first hospitalisation for an exacerbation was significantly increased in the SPIRIVA group compared to placebo (relative risk=0.723, p≤0.05). See Figure 1.

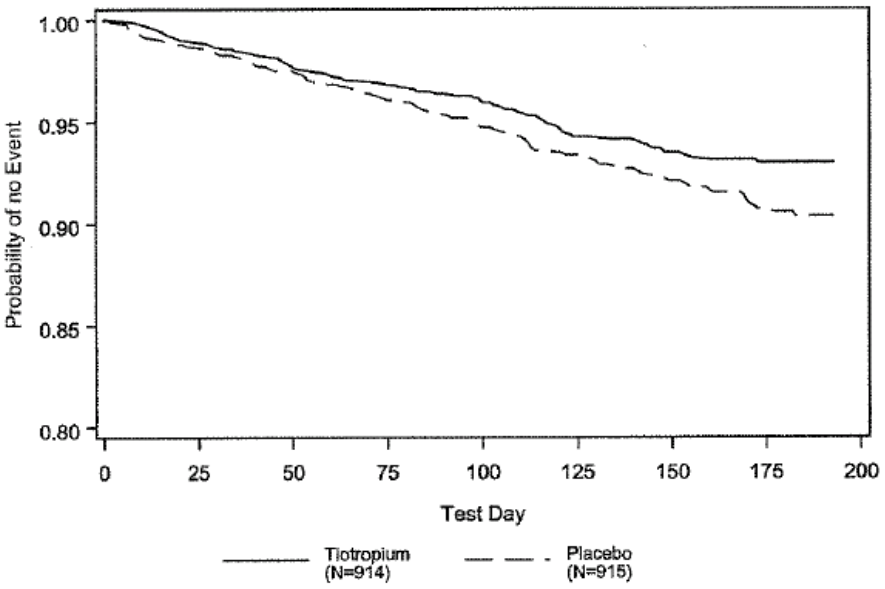


Figure 1: Kaplan-Meier estimates of the probability of no hospitalisation due to COPD exacerbation.

A one-year randomised, double-blind, double-dummy, parallel-group trial compared the effect of treatment with 18 mcg of SPIRIVA once daily with that of 50 mcg of salmeterol HFA pMDI twice daily with the primary endpoint time to first moderate or severe exacerbation in 7,376 patients with COPD and a history of exacerbations in the preceding year (74.6% of treated patients were men, 99.6% white, and 48.1% current smokers; the mean age was 62.9 years and the mean FEV_1 was 49.3% predicted). The treatment groups were balanced with respect to demographics, COPD characteristics, pulmonary medication use at baseline, and concomitant diagnoses. Patients were allowed to continue their usual medications for COPD, except for anticholinergic drugs and long-acting β2-agonists, during the double-blind treatment phase. Short-acting β2-agonists were also permitted, as necessary, as rescue medications for acute relief of COPD symptoms.

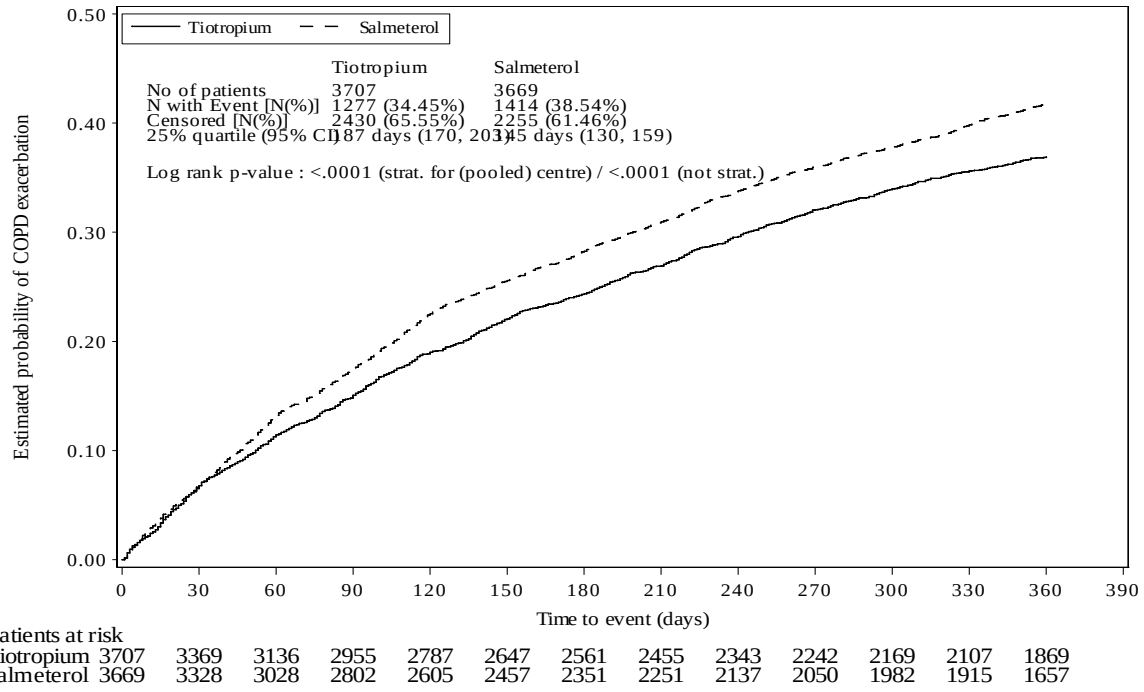


Figure 2: Kaplan-Meier estimates of the time to the first COPD exacerbation / Treated Set

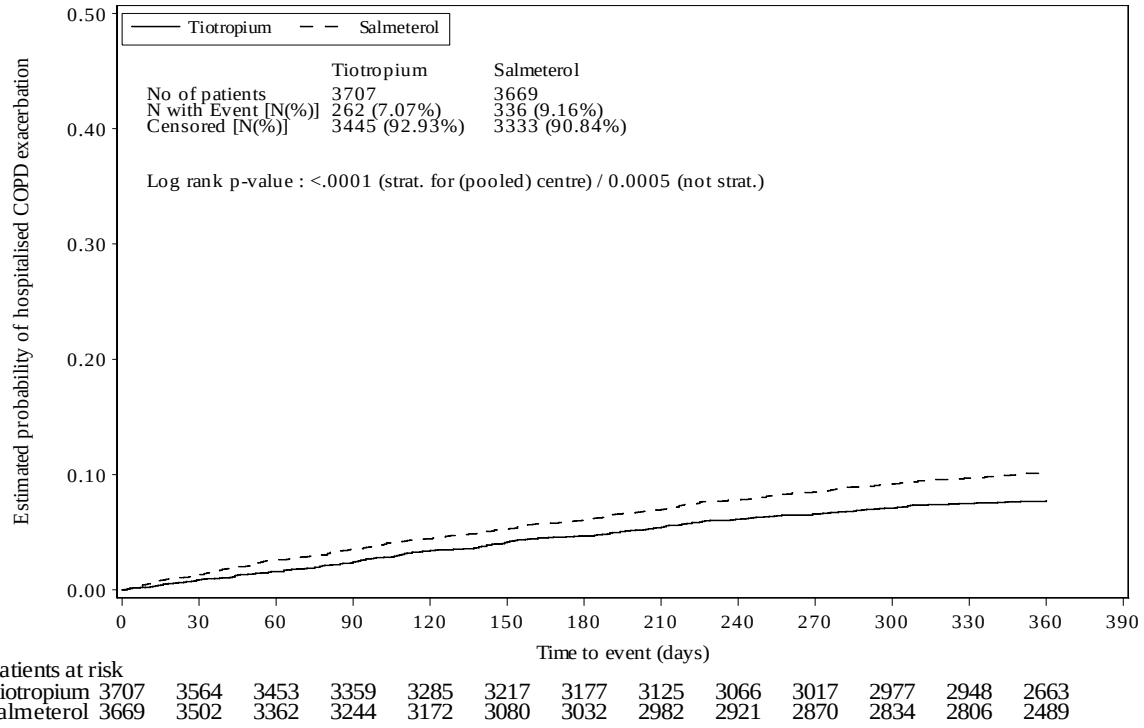


Figure 3: Kaplan-Meier estimates of the time to the first hospitalised COPD exacerbation / Treated Set

Table 2: Summary of exacerbation endpoints

Endpoint	SPIRIVA 18 microgram (HandiHaler) N = 3,707	Salmeterol 50 microgram (HFA pMDI) N = 3,669	Ratio (95% CI)	p-value
Time [days] to first exacerbation†	187	145	0.83 (0.77 - 0.90)	<0.001
Time to first severe (hospitalised) exacerbation§	-	-	0.72 (0.61 - 0.85)	<0.001
Patients with ≥1 exacerbation, n (%)*	1,277 (34.4)	1,414 (38.5)	0.90 (0.85 - 0.95)	<0.001
Patients with ≥1 severe (hospitalised) exacerbation, n (%)*	262 (7.1)	336 (9.2)	0.77 (0.66 - 0.89)	<0.001
Mean exacerbation incidence rate per patient year#	0.64	0.72	0.89 (0.83 - 0.96)	=0.002
Mean severe (hospitalised) exacerbation incidence rate per patient year#	0.09	0.13	0.73 (0.66 - 0.82)	<0.001

† Time to event analysis was done using Cox's proportional hazards regression model with (pooled) centre and treatment as covariate; ratio refers to hazard ratio. Number in column 2 and 3 denote the time in days to first exacerbation for the 1st quartile of patients on SPIRIVA experiencing an exacerbation and the 1st quartile of patients on Salmeterol experiencing an exacerbation, respectively.

§ Time to event analysis was done using Cox's proportional hazards regression model with (pooled) centre and treatment as covariate; ratio refers to hazard ratio. Time [days] for the 1st quartile of patients cannot be calculated, because proportion of patients with severe exacerbation is too low.

* Number of patients with event were analysed using Cochran-Mantel-Haenszel test stratified by pooled centre; ratio refers to risk ratio.
# Number of event analysis was done using Poisson regression correcting for overdispersion and adjusting for treatment exposure; ratio refers to rate ratio.

Compared with salmeterol, SPIRIVA increased the time to the first exacerbation (187 days vs. 145 days), with a 17% reduction in risk (hazard ratio, 0.83; 95% CI, 0.77 to 0.90; P<0.001). SPIRIVA also increased the time to the first severe (hospitalised) exacerbation (hazard ratio, 0.72; 95% CI, 0.61 to 0.85; P<0.001), reduced the annual number of moderate or severe (hospitalised) exacerbations (0.64 vs. 0.72; rate ratio, 0.89; 95% CI, 0.83 to 0.96; P=0.002), and reduced the annual number of severe (hospitalised) exacerbations (0.09 vs. 0.13; rate ratio, 0.73; 95% CI, 0.66 to 0.82; P<0.001).

Long-term clinical trials (<1 up to 4 years)

In a 4-year trial of 5,993 patients, SPIRIVA did not alter the annualised rate of decline of FEV_1 (primary endpoint), but maintained improvements in the secondary endpoint of the difference in FEV_1 at clinic visits throughout 4 years (Figure 4).

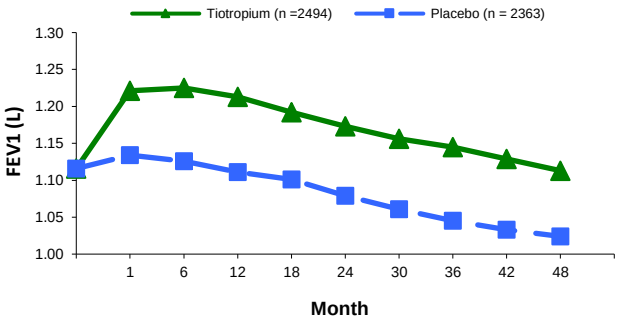


Figure 4: Morning pre-dose FEV_1 (i.e. trough) in the tiotropium and placebo groups over 4 years. P<0.001 for all post-randomisation time points.

A significantly higher proportion of patients in the tiotropium group than in the placebo group had an improvement of ≥4 units in the secondary endpoint of SGRQ total scores (i.e. exceeded the minimal clinically important difference) from baseline at 1 year (49% vs. 41%), 2 years (48% vs. 39%), 3 years (46% vs. 37%), and 4 years (45% vs. 36%) (p<0.001 for all comparisons).

In the following secondary endpoints, tiotropium significantly delayed the time to the first exacerbation and significantly delayed the time to the first hospitalisation for an exacerbation. The Hazard Ratios (95% confidence interval [CI]) for an exacerbation or exacerbation leading to hospitalisation were 0.86 (0.81, 0.91) and 0.86 (0.78, 0.95), respectively. Tiotropium was also associated with a reduction in the mean number of exacerbations of 14% (p<0.001). The mean numbers of exacerbations leading to hospitalisations were infrequent and did not differ significantly between the tiotropium and placebo groups.

During treatment, there was a 16% reduction in the risk of death. The incidence rate of death was 4.79 per 100 patient years in the placebo group vs. 4.10 per 100 patient years in the tiotropium group (hazard ratio (tiotropium/placebo) = 0.84, 95% CI = 0.73, 0.97).

For the 4-year, protocol-defined study period up to day 1440, the effect of tiotropium extended to end of treatment period. Among patients for whom vital-status information was available (95% of patients), 921 patients died: 14.4% in the tiotropium group and 16.3% in the placebo group (hazard ratio, 0.87; 95% CI, 0.76 to 0.99). During a period of 4 years plus 30 days (1470 days) included in the intention-to-treat analysis, 941 patients died: 14.9% in the tiotropium group and 16.5% in the placebo group (hazard ratio, 0.89; 95% CI, 0.79 to 1.02). Fewer vital status data were available for the day 1470 analyses (75% of patients). The effect became non-significant within the 30-day follow-up period, when according to protocol, patients were discontinued from their study medication.

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).

5.2 PHARMACOKINETIC PROPERTIES

Tiotropium is a non-chiral quaternary ammonium compound and is sparingly soluble in water. Tiotropium is administered by dry powder inhalation. 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.

Absorption

Following inhalation in young healthy volunteers, the absolute bioavailability of 19.5% suggests that the proportion reaching the lung is highly bioavailable. The bioavailability is the apparent bioavailability, which is dependent upon the amount of tiotropium that is effectively inhaled. 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 in patients with COPD were 12.9 pg/mL and decreased rapidly in a multi-compartmental manner. Steady state trough plasma concentrations were 1.71 pg/mL.

Distribution

Studies in rats have shown that tiotropium does not penetrate the blood-brain barrier to any relevant extent. Tiotropium has a plasma protein binding of 72% and shows a volume of distribution of 32 L/kg.

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. 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. Following inhalation of tiotropium by patients with COPD to steady state, urinary excretion is 7% (1.3 μg) of the unchanged dose over 24 hours, the remainder being mainly non-absorbed drug in the gut that is eliminated via the faeces. The renal clearance of tiotropium exceeds the creatinine clearance, indicating secretion into the urine. After chronic, once daily inhalation by patients with COPD, 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 (365 mL/min in patients with COPD < 65 years to 271 mL/min in patients with COPD > 65 years). This did not result in a corresponding increase in $AUC_{0-6,ss}$ or $C_{max,ss}$ values.

Renally Impaired Patients

Following once daily inhaled administrations of tiotropium to steady-state in patients with COPD with mild renal impairment (CL_{CR} 50-80 mL/min) resulted in slightly higher $AUC_{0-6,ss}$ (between 1.8 – 30% higher) and similar $C_{max,ss}$ values compared to patients with COPD 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 plasma concentrations (82% increase in 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.

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.

5.3 PRECLINICAL SAFETY DATA

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 22.5 μg, based on body surface area.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

SPIRIVA includes the excipient lactose monohydrate.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

In-use shelf life

SPIRIVA capsules for inhalation - Use within 5 days of opening each blister strip of 5 capsules.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25°C. Do not freeze. Avoid storage in direct sunlight or heat.

6.5 NATURE AND CONTENTS OF CONTAINER

SPIRIVA capsules are presented in Aluminium / PVC / Aluminium blister packs.

Available in cartons containing 10, 30 or 60 capsules and hospital packs containing 150 or 300 capsules.

Combination packs of 10s, 30s and 150s with the HandiHaler device are also available.

Not all pack sizes are being distributed in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

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.

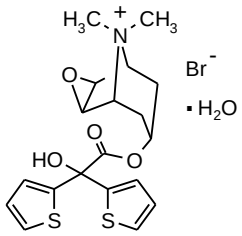
Tiotropium bromide is freely soluble in dimethyl sulphoxide, soluble in methanol, sparingly soluble in water and practically insoluble in methylene chloride. The solubility in aqueous solutions at room temperature is approx. 2.5%, independent of pH. At pH 7.4, the apparent partition coefficient (log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

Chemical structure

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)

Structural formula:



CAS number
139404-48-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

Boehringer Ingelheim Pty Limited

ABN 52 000 452 308

78 Waterloo Road

North Ryde NSW 2113

www.boehringer-ingelheim.com.au

9 DATE OF FIRST APPROVAL

30 MAY 2002

10 DATE OF REVISION

12 MAY 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Reformatting based on the new Form for PI.
4.4	‘Directions for Use’ revised to ‘Instructions for Use’