AUSTRALIAN PRODUCT INFORMATION – BRALTUS® (TIOTROPIUM [AS BROMIDE]) POWDER FOR INHALATION, HARD CAPSULE

1 NAME OF THE MEDICINE

Tiotropium (as tiotropium bromide)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

BRALTUS® tiotropium (as bromide) powder for inhalation, hard capsule. The drug product must be inhaled with the ZONDA® device.

BRALTUS is a generic version of SPIRIVA. Each capsule of BRALTUS and SPIRIVA delivers 10 micrograms of tiotropium and are equivalent.

BRALTUS capsules are colourless and transparent. The capsules contain a white powder.

Excipient(s) with known effect: lactose monohydrate.

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

3 PHARMACEUTICAL FORM

BRALTUS powder for inhalation in capsules.

Each hard BRALTUS capsule contains 13 micrograms tiotropium, equivalent to 15.6 micrograms tiotropium bromide.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended dosage of BRALTUS is inhalation of the contents of one capsule, once daily with the ZONDA device, at the same time each day (see ZONDA instructions for use, in the patient information leaflet provided in each pack of BRALTUS).

The delivered dose (the dose that leaves the mouthpiece of the ZONDA inhaler) is 10 micrograms of tiotropium per capsule.

BRALTUS capsules must not be swallowed.

Do not place a BRALTUS capsule directly into the mouthpiece.

Special populations:

Elderly patients can use BRALTUS at the recommended dose.

Renally impaired patients can use BRALTUS at the recommended dose. However, as with all predominantly renally excreted drugs, tiotropium use should be monitored closely in patients with moderate to severe renal impairment (see Section 5.2 Pharmacokinetic properties).

Hepatically impaired patients can use BRALTUS at the recommended dose.

Paediatric population:

There is no experience with tiotropium in infants, children or adolescents and therefore should not be used in this age group.

Method of administration:

To ensure proper administration of the medicinal product, the patient should be trained in the use of the inhaler by either the prescribing physician or by other healthcare professionals.

The ZONDA inhaler is especially designed for BRALTUS capsules; patients must not use it to take any other medication.

BRALTUS capsules must only be inhaled using the ZONDA inhaler. Patients must not use any other inhalers to take BRALTUS capsules.

The ZONDA inhaler should only be used with the bottle of capsules provided. Do not reuse the inhaler for another bottle of capsules. Discard the ZONDA device after 30 uses.

The capsule shell is not inhaled and remains in the device.

4.3 CONTRAINDICATIONS

BRALTUS 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).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Tiotropium, 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 tiotropium.

As with other anticholinergic drugs, tiotropium 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, tiotropium 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, tiotropium 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). Tiotropium should be used only if the expected benefits outweigh the potential risk. There is no long term experience in patients with severe renal impairment.

Patients must be instructed in the correct administration of tiotropium. 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.

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

An increase in anticholinergic effects may occur with increasing age.

BRALTUS should not be used more frequently than once daily (see Section 4.8 Overdose).

BRALTUS capsules are to be used only with the ZONDA® device (see Section 4.2 Dose and method of administration).

This product contains 18 mg of lactose monohydrate per capsule. The excipient lactose may contain trace amounts of milk proteins. Care should be taken with those with severe hypersensitivity or allergy to milk protein.

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 BRALTUS at the recommended dose. However, as with all predominantly renally excreted drugs, BRALTUS use should be monitored closely in patients with moderate to severe renal impairment. For patients with moderate to severe renal impairment - see Section 5.2 Pharmacokinetic properties.

Use in the elderly

Elderly patients can use tiotropium 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 tiotropium in paediatric patients or adolescents under 18 years of age has not been established. Therefore, BRALTUS should not be used in these 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 tiotropium is available from a clinical trial. The concomitant use of tiotropium with other anticholinergic agents (e.g. glycopyrronium, aclidinium, umeclidinium, ipratropium) is expected to have additive anticholinergic effects. Acute single dose administration of ipratropium bromide monohydrate after 19 days of tiotropium 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 tiotropium 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 – 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 microgram 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 tiotropium 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)

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
Headache	Uncommon
Taste disorder	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
Nausea	Rare
Intestinal obstruction, including ileus paralytic	Rare
Dental caries	Very 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
Anaphylactic reaction	Not known
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

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 www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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.

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

5 PHARMACOLOGICAL PROPERTIES

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

5.1 PHARMACODYNAMIC PROPERTIES

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.

Cardiac electrophysiology

In a dedicated QT study involving 53 healthy volunteers, a dispensed dose of 18 micrograms of tiotropium and a dispensed dose of 54 micrograms of tiotropium over 12 days did not significantly prolong QT intervals of the ECG.

The pharmacokinetic studies conducted using BRALTUS (13 micrograms tiotropium) have demonstrated bioequivalence to the reference product containing a dispensed dose of 18 micrograms tiotropium (see ***BRALTUS pharmacokinetic profile***).

Clinical trials

The reported clinical studies are those of the innovator reference product. Bioequivalence has been demonstrated between BRALTUS (13 micrograms tiotropium) and the innovator reference product (18 micrograms tiotropium). *In vitro* studies have demonstrated that the same delivered dose of tiotropium is obtained from BRALTUS (13 micrograms tiotropium) in combination with the ZONDA device when compared against the innovator inhalation product (18 micrograms tiotropium).

Additionally, an investigation was conducted to assess inspiratory flow rates achieved using the ZONDA device. Two separate studies were performed, the first one in COPD patients and the second one in Healthy Volunteers, using the inhalation device of the innovator product compared to the ZONDA device.

Inhalation profile study in COPD patients

A total of 50 patients with moderate (FEV_1 (forced expiratory volume in 1 second) = 50-79% predicted) (n =26), severe (FEV_1 = 30-49% predicted) (n=18) or very severe ((FEV_1<30% predicted) (n = 6) COPD were randomised and completed the study comparing the ZONDA device and the innovator's dry powder inhaler. Each participant was asked to carry out two inhalations through each dry powder inhaler. The peak inhalation flow, maximum pressure change, inhalation volume, time of inhalation, time to reach the PIF (Tpeak in sec) and the acceleration rate were measured. The study was conducted with empty capsules.

The majority of patients were able to achieve peak flow rates between 30 and 60 L/min for

both devices. The inhalation parameters of the ZONDA device were significantly higher ($p<0.001$) than those of the innovator reference product with respect to peak inhalation flow, pressure change and acceleration rate.

Inhalation profile study in Healthy Volunteers

Fifty healthy volunteers (26 females and 24 males) completed an open label, randomised study using a ZONDA device and the innovator dry powder inhaler. Their ages ranged from 20 to 55 years and their FEV_1 % predicted values ranged from 80.0% to 118.0%. The study was conducted with empty capsules. The results show that the numerical differences in the inhalation parameters of the ZONDA and the innovator's dry powder inhaler are only small and not likely to affect the emitted dose. All peak inhalation flows were above 30L/min and with the inhaled volumes being greater than 1 litre, there would not be any issues for both devices with respect to dose emission, therefore concluding that pharmacokinetic crossover studies would be consistent for both devices.

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 tiotropium. 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 tiotropium, 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 tiotropium.

Lung function

Overall results from the four one-year studies demonstrated that tiotropium, 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. Tiotropium significantly improved morning and evening PEFR as measured by the patient's daily recordings. The bronchodilator effects of tiotropium 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 tiotropium once daily and 371 patients received placebo. Mean differences in FEV_1 between tiotropium 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 tiotropium 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 tiotropium once daily and 179 patients received ipratropium, 2 puffs of 20 micrograms, four times a day. Mean differences in trough FEV_1 between tiotropium 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 tiotropium 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, tiotropium significantly improved dyspnoea in patients, as evaluated using the Mahler Transitional Dyspnoea Index (TDI) and patient daily reported symptoms. Following treatment with tiotropium, 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 tiotropium 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 tiotropium 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 tiotropium 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 tiotropium 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 tiotropium significantly improved ET by 20% to 28% compared with placebo. Increases in ET (seconds) are shown in Table 1.

Additionally in these trials, tiotropium 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. Tiotropium 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 tiotropium 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.

Tiotropium 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 tiotropium 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.

Tiotropium 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 tiotropium 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 tiotropium 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 tiotropium 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 tiotropium and salmeterol were compared, the mean trough FEV_1 in the tiotropium group was significantly higher than that in the salmeterol group

($p<0.05$), beginning on day 57. The difference between tiotropium 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 tiotropium 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 tiotropium 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, tiotropium 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 tiotropium 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 tiotropium compared to placebo ($p=0.045$ and $p=0.019$ respectively). Patients on tiotropium 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 tiotropium group relative to placebo ($p=0.011$). Overall, these data indicate that therapy with tiotropium 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 tiotropium 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 tiotropium 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 tiotropium group relative to the ipratropium group ($p=0.008$ and 0.048, respectively). Overall these data indicate that tiotropium is associated with reduced exacerbations.

Tiotropium 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 tiotropium 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 tiotropium group compared to placebo (relative risk=0.834, $p=0.034$). Fewer tiotropium 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 tiotropium

group, compared to placebo (p=0.013). Similarly, the mean number of hospitalisations days for exacerbations was lower in the tiotropium 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 tiotropium group compared to placebo (relative risk=0.723, p≤0.05). See Figure 1.

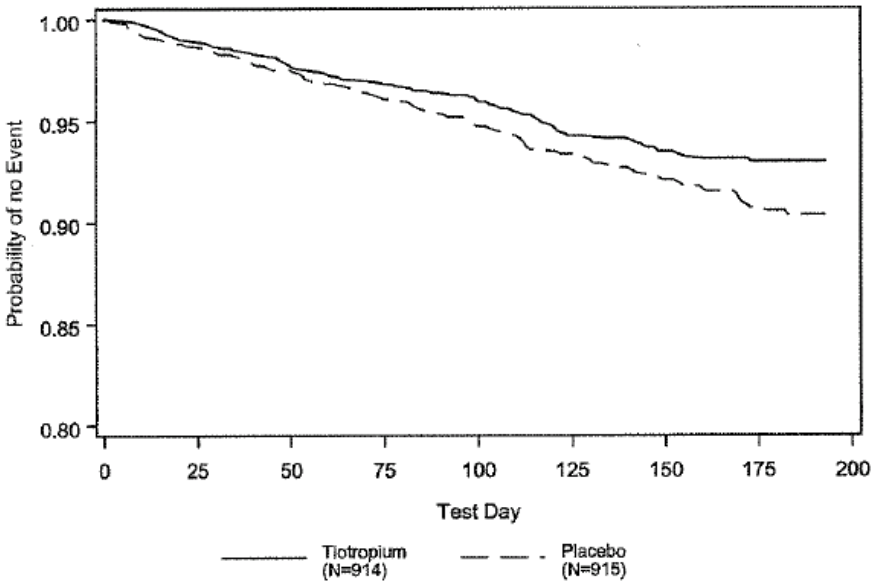


Figure 1: Kaplan-Meier estimates of the probability of no hospitalisation due to COPD exacerbation.

A one-year randomised, double-blind, double-dummy, parallel-group trial compared the effect of treatment with 18 micrograms of tiotropium once daily with that of 50 micrograms 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.

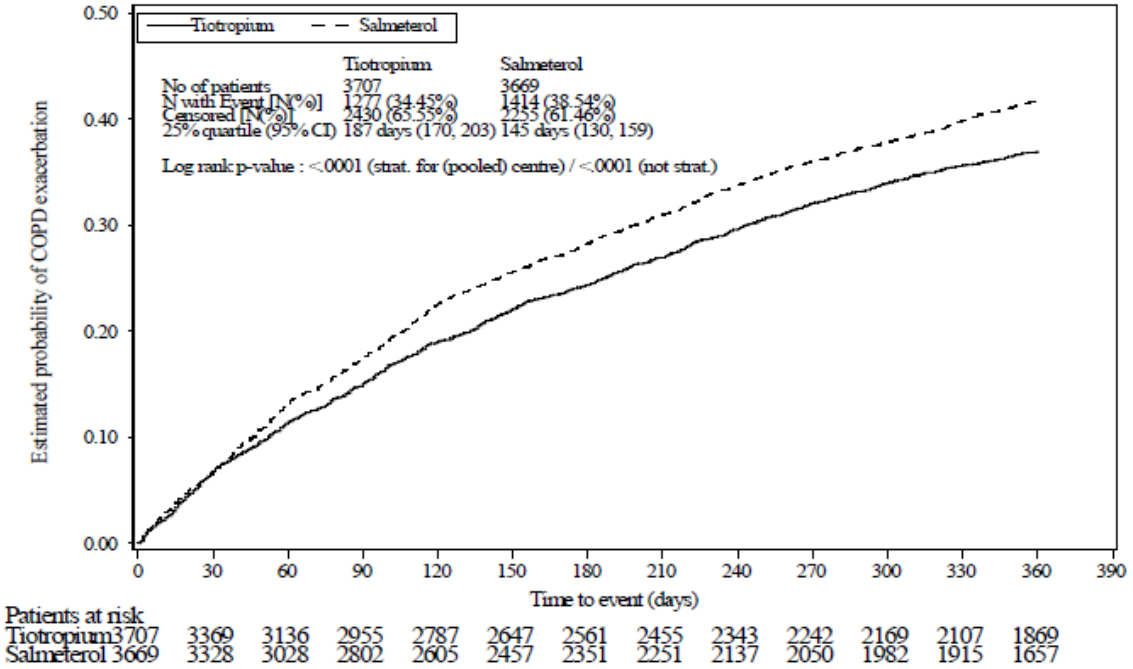


Figure 2: Kaplan-Meier estimates of the time to the first COPD exacerbation / Treated Set

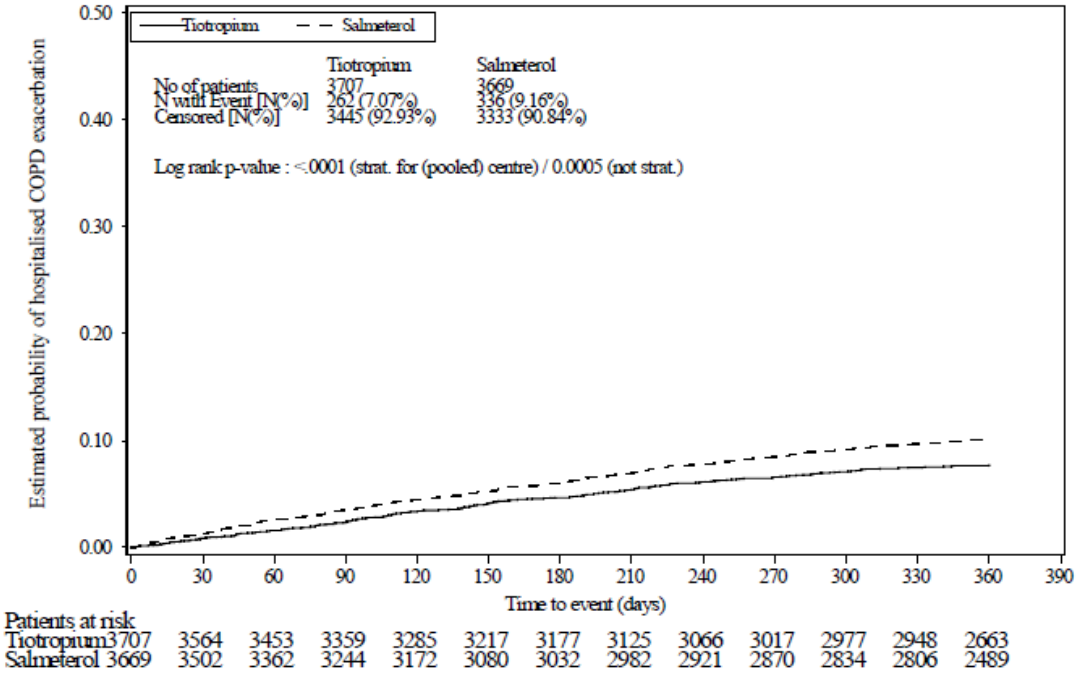


Figure 3: Kaplan-Meier estimates of the time to the first hospitalised COPD exacerbation/Treated Set

Table 2: Summary of exacerbation endpoints

Endpoint	**Tiotropium18 microgram (Dry Powder Inhaler) 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 tiotropium 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, tiotropium 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). Tiotropium 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, tiotropium 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).

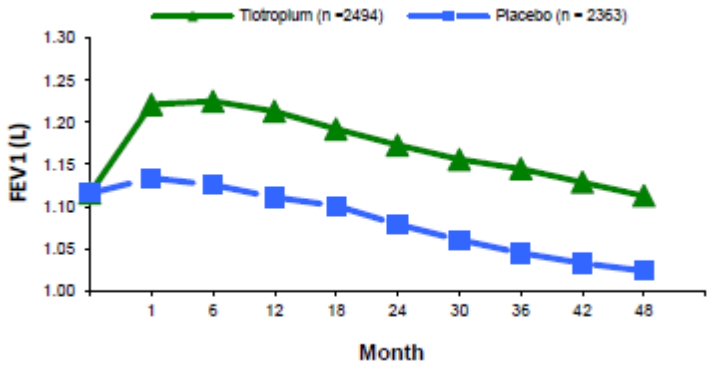


Figure 4: Morning pre-dose FEV_1 (i.e. trough) in the tiotropium and placebo groups over 4 years. P<0.001 for all post-randomisation time points.

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 tiotropium inhalation spray 2.5 micrograms and tiotropium powder for inhalation 18 micrograms (5,711 patients receiving tiotropium 2.5 micrograms (2 puffs comprise one medicinal dose of 5 micrograms); 5,694 patients receiving tiotropium 18 micrograms). 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 tiotropium inhalation spray 2.5 microgram and tiotropium powder for inhalation 18 micrograms (hazard ratio (tiotropium 2.5 micrograms/tiotropium 18 micrograms) 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 tiotropium 2.5 micrograms and 719 days for tiotropium 18 microgram.

The bronchodilator effect of tiotropium 2.5 micrograms was sustained over 120 weeks, and was similar to tiotropium 18 micrograms. The mean difference in trough FEV_1 for tiotropium 2.5 micrograms versus tiotropium18 micrograms was -0.010 L (95% CI -0.038 to 0.018 L).

All-cause mortality was similar during the study with tiotropium 2.5 micrograms and tiotropium 18 micrograms (hazard ratio (tiotropium 2.5 micrograms / tiotropium 18 micrograms) 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 microgram) 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.

<u>Special populations:</u>

<u>Elderly Patients:</u>

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.

BRALTUS pharmacokinetic profile

In a bioequivalence study, BRALTUS (13 micrograms tiotropium) in combination with the ZONDA device was evaluated by comparing it against the innovator inhalation product, SPIRIVA (18 micrograms tiotropium) in combination with the HANDIHALER device, containing the same delivered dose of the active substance. BRALTUS (13 micrograms tiotropium) was shown to be bioequivalent to SPIRIVA (18 micrograms tiotropium) in terms of rate and extent of systemic availability.

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).

Consideration should be given to lower initial loading and maintenance doses in patients >65 years and careful monitoring for the development of hypotension when up titrating the maintenance dose (see Section 4.2 Dose and method of administration).

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 microgram, based on body surface area.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

BRALTUS capsules contain lactose monohydrate. The outer capsule shell is known as a Vcap - The Vegetarian Alternative empty hard capsules size 3 (Natural/Natural) (Ingredient ID

10127).

6.2 INCOMPATIBILITIES

See Section 4.5 Interactions with other medicines and other forms of interactions.

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

Discard the ZONDA device after 30 uses. Do not reuse the inhaler for another bottle of capsules. There is a ZONDA inhalation device provided with each box of BRALTUS capsules.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

BRALTUS capsules for inhalation - Store below 25°C. Keep the bottle tightly closed. Store in the original package to protect from moisture. Do not refrigerate or freeze. Avoid storage in direct sunlight or heat.

6.5 NATURE AND CONTENTS OF CONTAINER

BRALTUS capsules are presented in HDPE bottles with a child resistant HDPE closure containing desiccant. The pack contains a ZONDA inhalation device. The ZONDA inhaler has a green body and a cap with a white push button.

Available in cartons containing a bottle of 30 capsules and the ZONDA device.

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

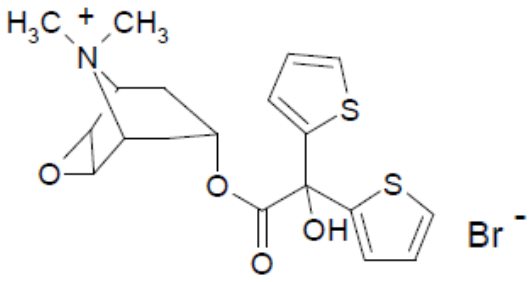
Tiotropium bromide methanol solvate is used in the manufacture of BRALTUS capsules. It is spray dried with lactose where the methanol solvate is evaporated and transformed to tiotropium bromide. Therefore tiotropium bromide is the Active Pharmaceutical Ingredient (API) in the finished product.

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.

Chemical structure

Structural formula:



Chemical name: (1α,2β,4β,5α,7β)-7-[(Hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo [3.3.1.02,4] nonane bromide

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

Molecular weight: 472.412

CAS number

CAS number: 136310-93-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4).

8 SPONSOR

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9 DATE OF FIRST APPROVAL

31 October 2018

10 DATE OF REVISION

31 October 2018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information