Request for PBS listing of Braltus® tiotropium (as bromide)

13 mcg tiotropium (as bromide) powder for inhalation in hard capsule
Delivered dose tiotropium 10 micrograms

Bioequivalent to Spiriva® tiotropium 18 micrograms (as bromide monohydrate) powder for inhalation in hard capsule
Delivered dose tiotropium 10 microgram

Minor Submission for December 2018 PBAC Meeting

Contents

1 SUMMARY

Braltus® tiotropium (as bromide) 13 mcg powder for inhalation in hard capsule was approved by the TGA on the 31st Oct 2018. *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.*

Product approval is based on the TGA's acceptance of demonstrated bioequivalence of Braltus tiotropium 13 microgram (as bromide) powder for inhalation in hard capsule (hereafter referred to as Braltus) and the innovator, SPIRIVA® tiotropium 18 micrograms (as bromide monohydrate) powder for inhalation in hard capsule (hereafter referred to as Spiriva). The delivered dose for both products is 10 mcg of tiotropium. Braltus is supplied with an inhalation device (the Zonda device) in every pack.

This application seeks PBS listing of Braltus as a generic brand of tiotropium powder for inhalation with an "a" flag marking its suitability for substitution for Spiriva tiotropium 18 mcg (as bromide monohydrate) powder for inhalation. As detailed further within this document, this request is justified, not only on the basis of demonstrated bioequivalence but also on the:

- attributes of the associated Zonda inhalation device
- the QUM measures in place to support launch
- the additional treatment choice it offers patients
- the government savings to be realised through inclusion of a bioequivalent lower cost high quality alternative to Spiriva capsules for inhalation.

2 INTRODUCTION

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline recommends tiotropium, a long-acting muscarinic antagonist (LAMA), for the treatment of COPD,[1] and in practice tiotropium bromide is considered gold standard and widely prescribed due to its strong clinical and safety profile.[1,2] This is attributed to its long duration of action (at least 24 hours per dose)[3] and its capacity to improve symptoms, reduce exacerbations and amplify the effectiveness of pulmonary rehabilitation.[4,5] Tiotropium is currently available as Spiriva® in two forms: HandiHaler® (a dry powder inhaler [DPI]) and Respimat® (a soft mist inhaler [SMI]). Spiriva® HandiHaler® is the leading LAMA therapy.

Despite the availability of effective medications, suboptimal medication adherence is common among COPD patients, which may be attributed to a number of factors including

the medication, delivery device, the patient and the healthcare professional caring for the patient.[17] Suboptimal medication adherence adversely affects disease management, potentially resulting in poor clinical outcomes for the patient (including significantly increased risk of exacerbations and hospitalisations)[7,8] and increased healthcare expenditure.[7-10]
Given that ease of use and presence of a feedback mechanism are important features for COPD patients,[7,11,12] an inhaler with these features is anticipated to improve inhaler-related patient satisfaction and be a well-received choice for patients and HCPs.

Braltus® is a novel once-daily single capsule DPI delivering tiotropium (10 µg delivered dose) for the management of COPD. Braltus®, when administered with the Zonda® inhaler, (supplied in every Braltus pack), has demonstrated bioequivalence to Spiriva® administered with the HandiHaler® in terms of efficacy and safety,[13] and has inhaler attributes that are aligned with patient preferences.[7,11]
The Zonda® inhaler has been ergonomically designed with a compact size and shape, a comfortable mouthpiece with a protective cover and an easy-to-press piercing button to facilitate ease of use; features that have been shown to promote inhaler-related satisfaction among COPD patients.[7,11,12]
In addition, Braltus® uses transparent capsules which serve as a visual feedback mechanism to confirm drug delivery. Presence of a feedback mechanism is important for respiratory patients and is associated with improved treatment adherence. Braltus® capsules are packaged in a protective plastic bottle. Compared to other existing presentation the plastic bottle may be preferred by some patients (e.g. for patients with poor vision).

In addition to supporting the improvement of clinical outcomes and patient choice, as the first generic entrant Braltus® will be priced in accordance with the requirements of division 3A of Part VII of the *National Health Act 1953*, namely at 25% less than the current Spiriva ex-manufacturer price.
The health budget savings, combined with demonstrated bioequivalence to Spiriva and the possession of features that are important to COPD patients,[7,11] ultimately supports the suitability of the proposed Braltus brand for Australian patients and PBS listing.

3 REQUESTED PBS INDICATION

Category / Program	Section 85 Braltus tiotropium (as bromide) 13 mcg powder for inhalation,30 capsules
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	N/A
Severity:	N/A

Condition:	N/A
PBS Indication:	Chronic obstructive pulmonary disease (COPD)
Treatment phase:	Initial & Continuation
Restriction: *Restricted Benefit*	☒Restricted Benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required – Electronic ☐Streamlined
Treatment criteria:	• The treatment must not be used in combination with a LAMA/LABA or SAMA • A LAMA/LABA includes aclidinium/formoterol, glycopyrronium/indacaterol, tiotropium/olodaterol, or umeclidinium/vilanterol. • A SAMA includes ipratropium • Diagnosis of COPD should include measurement of airflow obstruction using spirometry, with confirmation of post-bronchodilator airflow obstruction. • Adherence to current treatment and device (inhaler) technique should be reviewed at each clinical visit and before "stepping up" a patient's medication regimen.
Clinical criteria:	Aligned with current criteria for PBS item number: 8626B Chronic obstructive pulmonary disease (COPD)
Population criteria:	N/A

4 PBS SUBSTITUTION

TEVA Australia seeks PBS substitution ("a" flag) status with Spiriva tiotropium 18 mcg (as bromide monohydrate) powder for inhalation (in hard capsules). The basis for this request is two fold:

1. The TGA's acceptance of established bioequivalence. The TGA product approval letter provides confirmation through inclusion of the following statement (see ATTACHMENT 1, page 1) "*The application for registration of the generic tiotropium 13 microgram (as bromide) powder for inhalation in hard capsule delivering tiotropium 10 microgram included data that established to the TGA's satisfaction that the product can be considered bioequivalent to SPIRIVA tiotropium 18 micrograms (as bromide monohydrate) powder for inhalation (in hard capsule) delivering tiotropium 10 microgram sponsored by Boehringer Ingelheim Pty Ltd.*

2. TEVA Australia undertakes to provide a Health Care Provider (HCP) training program, focused on ensuring a clear understanding of the bioequivalence of Braltus and Spiriva hard capsules and on mastery of the Zonda inhalation device, which accompanies every pack of Braltus. Training on the delivery device will be supported by the availability of placebo capsule/inhaler demonstration packs.

The requested PBS listing for DuoResp Spiromax is as follows:

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
Capsule containing powder for oral inhalation 13 micrograms (as bromide) (for use in Zonda inhaler, supplied with each pack)	1	30	5	TBC	Braltus, Teva

5 COMPARABILITY OF BRALTUS AND SPIRIVA

Detailed comparability of Braltus and Spiriva is outlined in Table 1 (see below)

One difference of note is the metered dose of Braltus hard capsules compared to Spiriva. Braltus and the reference product Spiriva® deliver the same dose of active substance to the patient (10 microgram per capsule) but have a different labelled metered dose (13 and 18 microgram per capsule respectively). To avoid potential confusion the product information texts (Product Information, Consumer Medicine Information and Package Leaflet) emphasise the use of one "capsule" once daily as opposed to dwelling on the micrograms of tiotropium in the metered or delivered dose. This posology approach is in line with the reference product and so there is immediately a common dosing schedule between the two products. In addition, instruction is included on the packaging (carton and leaflet), to "inhale the contents of one capsule once daily".

Based on exchanges with the TGA throughout the registration process a comprehensive QUM initiative is agreed to support correct use of Braltus in the community and ensure that prescribers, pharmacists and patients are well informed on the equivalence of the delivered dose of tiotropium in both products. This initiative is multifaceted and may be summarised as follows;

- An agreement is in place with the TGA to provide a 'Dear Healthcare provider' facsimile, (see ATTACHEMENT 2) to coincide with PBS listing of Braltus. The agreed distribution list include;
    - • Respiratory Specialists
    - • General Practitioners
    - • Pharmacists
    - The Lung Foundation
    - Pharmaceutical Society of Australia

- Pharmacy Guild.

The intent of the Dear HCP communication is to explain that the difference in metered dose between Braltus and the originator product (Spiriva®) does not impact the bioequivalence of the two products nor does it impact the dosing schedule. The nominal dosing schedule of one capsule once daily is the same for Braltus and originator product (Spiriva® – tiotropium bromide).

- The Product Information, Consumer Medicine Information and Package Insert include statements confirming that Braltus and Spiriva both deliver 10 micrograms of tiotropium and are equivalent. (see ATTACHMENT 3)

- Product packaging - additional detail is included on the carton and bottle label to disclose both the metered and the delivered dose of tiotropium.
- Colouring of the Zonda inhaler and Braltus logo is in place (see ATTACHMENT 4) to reinforce the association between the two and support the messages in all labelling documents that Braltus capsules must be inhaled with the Zonda inhaler.
- Placebo capsule/inhaler packs will be widely available to train HCPs on the correct use of the product and in turn, train their patients correctly.

Table 1: TGA and PBS criteria for use of Braltus and Spiriva in COPD

Disease	TGA & PBS Criteria	Braltus	Spirivar	Key product differences
Chronic obstructive pulmonary disease (COPD)	TGA Indication	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.	Spiriva 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.	None
	PBS indication*	Chronic obstructive pulmonary disease (COPD)	Chronic obstructive pulmonary disease (COPD)	None
	Recommended age in PI	>18 years	>18 years	None
	Daily dose	Inhalation of the contents of one capsule, once daily	Inhalation of the contents of one capsule, once daily	None
	PBS strengths	Each hard BRALTUS capsule contains 13 micrograms tiotropium, equivalent to 15.6 micrograms tiotropium bromide. Delivered dose is 10 micrograms per capsule	Each hard SPIRIVA capsule contains 18 micrograms tiotropium, equivalent to 22.5 micrograms tiotropium bromide (monohydrate). Delivered dose is 10 micrograms per capsule	The delivered dose in Braltus and Spiriva capsules is the same The metered dose in Braltus and Spiriva capsules differs.
	Packaging	Available in cartons containing a bottle of 30 capsules and the ZONDA device.	SPIRIVA capsules are presented in Aluminium / PVC / Aluminium blister packs of 30 capsules. Available in packs with and without the Handihaler delivery device	The Zonda delivery device is supplied with every pack of Braltus. No additional device costs for patients are associated with Braltus use.
	Device	For inhalation with the Zonda inhaler, supplied with every pack.	For inhalation with the HandiHaler device, may or may not be supplied with the Spiriva capsule pack	The inhalation device is unique to each product. The operational steps of each are similar. However the Zonda inhaler only must be used for inhalation of Braltus capsules. The Zonda device is replaced after 30 capsules (a device is supplied with every pack). The Handihaler device is washed and reused.
	ATC Code	R03BB04	R03BB04	None

6 COPD AND THE USE OF TIOTROPIUM DPI IN AUSTRALIA

In the 2014–15 ABS National Health Survey (NHS), the prevalence of COPD (captured here as self-reported emphysema and/or bronchitis) in Australians aged 45 and over was 5.1%, an estimated 460,400 people. The prevalence did not differ significantly between males and females (5.2% and 4.9% respectively).

A large international study (Burden of Obstructive Lung Disease (BOLD)) tested the lung function of nearly 10,000 people. BOLD estimated the overall prevalence of COPD in 12 countries to be 10% for people aged 40 and over. In Australia, the prevalence of COPD was estimated to be 7.5% for people aged 40 years and over and 30% for people aged 75 and over.

Source: https://www.aihw.gov.au/reports/chronic-respiratory-conditions/copd/contents/copd

6.1 GOLD RECOMMENDATIONS FOR PHARMACOLOGIC TREATMENT

A proposed model for initial pharmacological management of COPD (based on GOLD guidelines, and according to the individualised assessment of symptoms and exacerbation risk, is shown in Table 2.

Table 2. Initial pharmacologic management of COPD[4]

Patient group	Recommended first choice*	Alternative choice*
A	SAMA or SABA	SABA/SAMA combination or LABA or LAMA
B	LAMA or LABA	LABA/LAMA combination
C	ICS/LABA combination or LAMA	LABA/LAMA combination or PDE4i/LABA combination or PDE4i/LAMA combination
D	ICS/LABA combination or LAMA	ICS /LABA/LAMA combination or ICS/LABA/PDE4i combination or LABA/LAMA combination or LAMA/PDE4i combination

*Medications in each box are mentioned in alphabetical order, and therefore not in the order they are prescribed or recommended.
ICS, inhaled corticosteroids, LABA, long-acting beta$_2$-agonist; LAMA, long-acting muscarinic antagonist; PDE4i, phosphodiesterase-4 inhibitor; SABA, short-acting beta$_2$-agonist; SAMA, short-acting muscarinic antagonist

Clinical guidelines recommend a LAMA therapy delivered by an inhaler for the treatment of moderate to severe COPD (patient groups B, C and D).

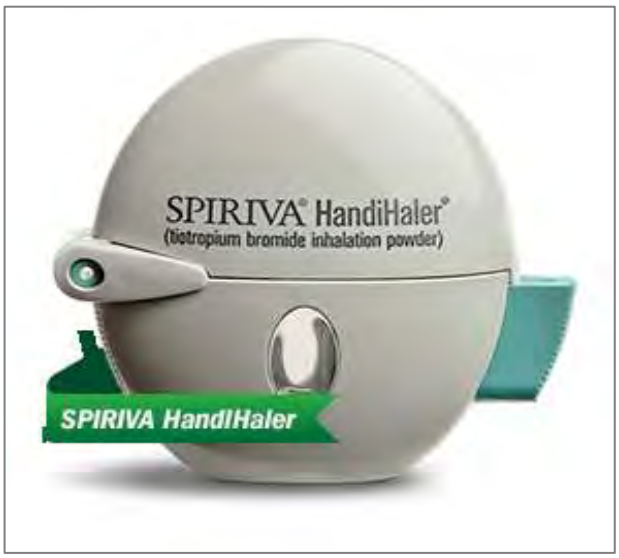
6.2 TIOTROPIUM

Tiotropium is the gold standard LAMA for the treatment of COPD and is most commonly available in the form of Spiriva® HandiHaler®.[1,2]

With a duration of action of more than 24 hours,[14,15] tiotropium reduces exacerbations and related hospitalisations, improves symptoms and health status,[16,17] and improves the effectiveness of pulmonary rehabilitation.[5] Tiotropium is available as Spiriva® in two forms: HandiHaler® (DPI; Figure 1) and Respimat® (Figure 1). Spiriva® HandiHaler® is the leading form of tiotropium and the leading LAMA maintenance therapy for COPD in Australia.

Figure 1. Spiriva® HandiHaler® (a) and Spiriva® Respimat® (b)

A



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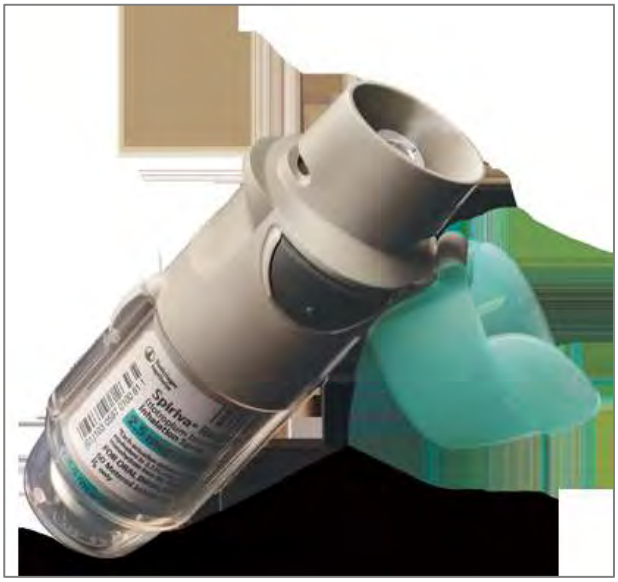

6.3 EFFICACY AND TOLERABILITY OF SPIRIVA® HANDIHALER®

The Spiriva® HandiHaler® (tiotropium bromide) clinical development program has been previously reviewed and accepted by the PBAC to support its PBS listing. The data are not represented but may be summarised, as follows; six Phase 3 studies in 2,663 patients with COPD (1,308 receiving Spiriva® HandiHaler®): two 1-year, placebo-controlled studies; two 6-month, placebo- and salmeterol-controlled studies and two 1-year, ipratropium-controlled studies.[4] These studies enrolled patients who had a clinical diagnosis of COPD, were 40 years of age or older, had a history of smoking greater than 10 pack-years, had an $FEV_1 \leq 60\%$ or 65% of predicted, and a ratio of $FEV_1/FVC \leq 0.7$. An overview of the key results of six Phase 3 clinical trials is presented in Table 3

Table 3. Overview of tiotropium (Spiriva®) clinical trials results

COPD study	Duration	Comparators	N	Trough FEV_1 change from baseline (mL)[a]	Peak FEV_1 response from baseline (mL)	Morning ΔPEFR (L/min)	Exacerbations per patient per year	Proportion of patients with ≥1 exacerbation	SGRQ[b]
Casaburi *et al*. 2002[87]*	1 year	Placebo	921	110±10–130±10	190±10–220±10	11±4-25±6	PLA = 0.95 TIO = 0.76	PLA = 42% TIO = 36%	49%
Vincken *et al*. 2002[15]**	1 year	Ipratropium	535	120	NR	10-18	IPA = 0.96 TIO = 0.73	IPA = 46% TIO = 35%	52%
Brusasco *et al*. 2003[86]***	6 months	Salmeterol Placebo	1,207	120±10[c]	NR Values statistically superior to SAL	NR	PLA = 1.49 SAL = 1.23 TIO = 1.07	PLA = 39% SAL = 35% TIO = 32%	48.9%
Niewoehner *et al*. 2005[88]	6 months	Placebo	1,829	NR	NR	NR	NR	PLA = 32.3% TIO = 27.9%	NR
Tashkin *et al*. 2008[89]	4-year	Placebo	5,993	NR	NR	NR	PLA = 0.85 TIO = 0.73	PLA = 68.2% TIO = 67%	45%

Note: * reported the combined results of the two 1-year placebo-controlled trials; ** reported the combined results of the two 1-year ipratropium-controlled trials; *** reported the combined results of the two 6-months placebo-controlled trials.

[a] expressed as mean ± standard error of the mean.

[b] expressed as percentage of patients in the tiotropium group that showed at least a four-unit improvement in total score at the end of the study.

COPD, chronic obstructive pulmonary disease; N, total number of patients enrolled in the study/studies; FEV_1, forced expiratory volume in one second; IPA = ipratropium; MCS, mental component summary; NR, not reported; PCS, physical component summary; ΔPEFR, difference in peak expiratory flow rate between tiotropium and comparator groups; PLA = placebo; SAL = salmeterol; SF-36, short form 36 health survey; SGRQ, St. George's Respiratory Questionnaire; SEM, standard error of the mean; TIO = tiotropium.

[c] expressed as the increase in trough FEV_1 compared to placebo.

7 CLINICAL DATA - BRALTUS

Braltus® Zonda® is bioequivalent to Spiriva® HandiHaler® in terms of efficacy and safety.[24]

The clinical programme of Braltus® Zonda® includes three PK studies, one pilot study and two pivotal studies, to demonstrate bioequivalence to Spiriva® HandiHaler® (Table 4).[13] The primary objective of the pilot study was to evaluate the bioavailability of the two test formulations of tiotropium bromide (12 µg and 18 µg inhalation powder) compared with Spiriva®. However, given that the DPI inhalation device was not the final version of Braltus® Zonda® used in the pivotal studies, the results of this study have not been included.

Table 4. Overview of PK/PD studies comparing Braltus® Zonda® with Spiriva® HandiHaler®[13]

Study	Primary objective	Endpoints
Pilot study	Evaluate the bioavailability of the following, post oral inhalation of a single dose: Test 1: Tiotropium 12 µg inhalation powder Test 2: Tiotropium 18 µg inhalation powder Reference: Spiriva HandiHaler 18 µg inhalation powder	Extent and rate of absorption, in terms of drug plasma concentration ($AUC_{(0-t)}$) and peak plasma concentration (C_{max}) Tolerability
Study CLL12003	Post oral inhalation of a single dose, assess the PK profile of Braltus® Zonda® and Spiriva® HandiHaler®	Primary: Drug plasma concentration ($AUC_{(0-t)}$) Peak plasma concentration (C_{max}) Secondary: Adverse events Clinical (including vital signs) and laboratory safety examinations
Study CLL13002	Post oral inhalation of a single dose, assess the PK profile of Braltus® Zonda® and Spiriva® HandiHaler®	Primary: Drug plasma concentration ($AUC_{(0-t)}$) Peak plasma concentration (C_{max}) Secondary: Adverse events Clinical (including vital signs) and laboratory safety examinations

The two pivotal studies were similarly designed in accordance with EMA guidelines on the investigation of bioequivalence[23] and both of them were randomised, three-way, semi-replicate, crossover PK studies in a two stage design.[13] In the first study (CLL12003), the primary objective was to assess the systemic exposure of a 10 µg delivered dose of tiotropium via the Braltus® Zonda® device compared with 10 µg of tiotropium delivered by Spiriva® HandiHaler®. The data generated in this study could not be adequately evaluated

and thus progression to the second stage was terminated. Consequently, the results of this study have not been.[13]

In the second pivotal study (CLL13002; EudraCT number: 2013-002277-21), Braltus® Zonda® demonstrated bioequivalence to Spiriva® HandiHaler® in terms of efficacy (i.e. peak plasma concentration (C_{max}) and plasma concentration from time zero to the last time point with measurable concentration ($AUC_{(0-t)}$)) and comparable tolerability.[13,23] The full details of this study are presented in the following sections.

Study objectives and methodology

The primary study objective was to assess the efficacy (in terms of systemic exposure) of Braltus® Zonda® compared to Spiriva® HandiHaler®.

The secondary objective was to investigate the safety of the two products.

The study had a two-stage design with one interim analysis and sample-size re-assessment in healthy male and female subjects, with duration of hospitalisation of 12 h to 13 h and with a real wash-out period of 14 days in all subjects.[13] There were seven inclusion criteria for subjects Table 5:

- Caucasian subjects;
- 18–55 years of age;
- Physically and mentally healthy as judged by means of a medical and standard laboratory examination;
- Non-smokers or ex-smokers (stopped at least 6 months ago), confirmed by urine cotinine test;
- Weight within the normal range according to accepted normal values for the body mass index (18.5–30.0 kg/m^2);
- Informed consent provided in writing;
- FEV_1 ≥80% of the predicted value regarding age, height, gender and ethnicity.[24]

Table 5. Subjects for study 2013-002277-21[13]

Study subjects	First stage	Second stage
Enrolled (study population)	27	44
Screened only	9	14
Randomised (safety analysis population)	18	30
Dropouts	0	0
Completed	18	30
Dataset for pharmacokinetic analysis	18	30
Dataset for statistical analysis (per protocol population)	18	30

In the morning of day 1 of each study period, each subject received (under fasting conditions) a single inhalation of either Braltus® Zonda® or Spiriva® HandiHaler® (i.e. four inhalations of either product). Intervals between inhalations lasted for 20 seconds, including a 10 second breath-hold. In each study period, blood was sampled at pre-dose, 0:01, 0:02, 0:04, 0:06, 0:08, 0:15, 0:30, 0:45, 1:00, 2:00, 4:00, 8:00, 12:00, 24:00, 36:00; and 48:00 hours after the end of the last fourth inhalation.[13]

A pooled analysis of all subjects from both stages was conducted using the parametric ANOVA-log method. For the interim analysis of the first stage, a confidence level (α) of 0.001 was used (i.e. $\alpha_1 = 0.001$). For the pooled analysis of both stages, an α of 0.049 was used (i.e. $\alpha_2 = 0.049$). Thus, a 90.20% CI of log-transformed values was calculated for Braltus® Zonda® versus Spiriva® HandiHaler® for $AUC_{(0\text{-}t)}$ and C_{max} of tiotropium and then compared to pre-defined acceptance limits (80.00–125.00% for both endpoints). For evaluation of safety, a descriptive statistical evaluation was undertaken.[13]

Results

Comparative bioavailability

The interim evaluation (involving 18 subjects) indicated that a sample size of 30 subjects (including the interim group) was required to achieve a 90% power for demonstration of bioequivalence. As such, 12 additional subjects were randomised in the second stage of the study.[24]

Evaluation of comparative bioavailability of the primary endpoints is presented in Table 6. The 90.20% CIs for $AUC_{(0\text{-}t)}$ and C_{max} were within their ranges (between 101.33–111.64% and 87.26–106.60%, respectively), and thus within the pre-specified acceptance limits of 80.00–125.00% for log-transformed values.[13]

Table 6. 90.20% CIs of tiotropium (pooled analysis of both stages)[13]

Endpoint	Point estimator	CIs
$AUC_{(0\text{-}t)}$	106.36%	101.33–111.64%
C_{max}	96.45%	87.26–106.60%

$AUC_{(0\text{-}t)}$ is the area under the plasma concentration-time curve from time zero to the last time point with measurable concentration; C_{max} is the peak drug concentration in the plasma
CIs, confidence intervals

7.1 SAFETY

Braltus® Zonda® and Spiriva® HandiHaler® were both well tolerated by patients. The safety profiles of both products were similar. Four non-serious adverse events (AEs) were registered in four subjects over the course of the trial:

- One pre-treatment AE (pyrexia) was observed on day 0 in study period 1. The subject was withdrawn from the study and remained only as a screened subject;
- Two AEs (asthenia and dizziness) registered after Braltus® Zonda® administration were judged as 'unlikely related';
- One AE (asthenia) observed after Spiriva® HandiHaler® administration was judged as 'unlikely related'.[13]
- All AEs resolved completely. The results of laboratory screening gave no indications for AEs or adverse drug reactions.[24]

7.2 FLOW RATE STUDIES

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 (FEV1 (forced expiratory volume in 1 second) = 50-79% predicted) (n =26), severe (FEV1 = 30-49% predicted) (n=18) or very severe ((FEV1<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 FEV1 % 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.

The data support the bioequivalence of Braltus (when used with the Zonda inhaler) and Spiriva (when used with the HandiHaler®) in terms of efficacy and safety and the suitability of the Zonda device to deliver Braltus in the target patient group.[13]

8 INHALER CHOICE AND DEVICE FEATURES

Inhaler choice is critical for ensuring optimal management of COPD and is influenced by a wide range of factors.[1,18,19] Internationally renowned healthcare organisations recognise that the choice of inhaler and the ability of patients to use inhalers correctly are critical for achieving successful COPD management:

- The ERS/International Society for Aerosols in Medicine (ISAM) Task Force report concludes that "The use of an inhaler by a patient has a strong scientific basis that is related to the dose of drug that is deposited into the lungs. Because the dose delivered to the lungs is so dependent on the correct use of the delivery system, those who prescribe inhaler devices should ensure that patients can and will use them correctly[18]
- The GOLD – According to internationally recognised GOLD guidelines, "attention to effective drug delivery and training in inhaler technique is essential" when treatment is given by the inhaled route.[1,20]

8.1 FACTORS INFLUENCING INHALER CHOICE

Inhaler choice will depend on a range of factors, including availability, cost, the prescribing physician and the skills and ability of the patient to use an inhaler device.[1] Notably, COPD patients may have problems with coordination and may therefore find it hard to use a metered-dose inhaler (MDI). Alternative breath-activated or spacer devices are available.[1] In general, particle deposition from DPIs will tend to be more central with the fixed airflow limitation and lower inspiratory flow rates in COPD. This is beneficial for patients, particularly the elderly who may struggle obtaining maximum respiratory flow.[20,21]

Thus greater patient choice will allow the patient to be better matched to the inhaler.

Inhaler device mishandling is common among COPD patients and may be attributed to insufficient inhaler-related patient satisfaction (stemming from inhaler features). Improved inhaler satisfaction has been demonstrated to improve adherence to COPD treatment,[7,12] improve clinical and humanistic outcomes,[7,8] and reduce the economic burden attributed to COPD.[7-10].

8.2 DEVICE FEATURES – ZONDA INHALER

Braltus® when used in conjunction with the Zonda® inhaler delivers the same dose of tiotropium (10 µg) to the lungs as Spiriva® when used in conjunction with

HandiHaler®.[24]

A key concern from PBAC deliberations on previous DPI generics is assurance that patients will be adequately trained on the delivery device that is relevant to the specific brand of dry powder inhaler dispensed to the patient.

Further to the targeted HCP education detailed earlier, including the availability of placebo capsule/device pack for training purposes, the detail provided below illustrates the simplicity of the Zonda device and the instructions provided with every pack to allow users to feel confident in its use.

8.3 ZONDA® HAS A NUMBER OF ATTRIBUTES THAT ARE VALUED BY COPD PATIENTS

Braltus® Zonda® is ergonomically designed to promote ease of use, treatment preference and satisfaction in COPD patients.[18,22,23]

Features of DPIs that are important to COPD patients are primarily those that relate to ease of use[7] and confirmation of drug delivery[11]. Braltus when used with the Zonda inhaler combines tiotropium with an enhanced ergonomic design compared to Handihaler® that facilitates ease of use - demonstrated by a well-fitting mouthpiece, an easy-to-press piercing button - and additionally demonstrates a feedback mechanism via the use of transparent capsules to provide confirmation of drug delivery[24] - features which are aligned with the preferences of COPD patients and are anticipated to improve treatment satisfaction.[7-11]

8.4 BRALTUS® ZONDA® HAS BEEN ERGONOMICALLY DESIGNED TO FACILITATE EASE OF USE

Braltus® Zonda® is discrete and lightweight with an ergonomic shape, and is also easy to carry, manipulate and inhale from.[24]

The ergonomic features of Braltus® Zonda® enable ease of use[24] - a property of DPIs that is associated with inhaler satisfaction and treatment adherence, according to findings from a large, multinational, cross-sectional, real-world survey of 1,443 COPD patients.[7] The study objective was to examine the relationships between inhaler satisfaction, treatment adherence and health status in patients with COPD. During the survey, respiratory specialists and primary care physicians provided information on six consecutive patients with COPD, who were then asked to complete a questionnaire. Physician-assessed adherence was scored (5-point Likert scale) and patients rated overall satisfaction with their maintenance inhaler (7-point Likert scale). Health status assessments included frequency of exacerbations and hospitalisations due to exacerbations in the past 12 months.[7]

Key inhaler attributes that were most important in determining overall patient satisfaction related to durability, ergonomics and ease of use.[7]

[redacted]

[redacted][25]

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[redacted]

8.6 BRALTUS® HAS A FEEDBACK MECHANISM ALLOWING PATIENTS TO CONFIRM DRUG DELIVERY

Braltus® Zonda® uses transparent capsules which are available in an easy-to-open bottle, to confirm drug delivery.[111]

Braltus® for inhalation with the Zonda device uses transparent powder capsules which enable users of the device to confirm that drug delivery has occurred. COPD patients consider the presence of a feedback mechanism to be an important feature of their DPI,[11] attributed to the fact that feedback mechanisms provide patients with reassurance that intake of the full dose of the drug has occurred.

Braltus® Zonda® capsules are packaged in a bottle instead of conventional blister packaging. This feature is anticipated to be a welcome choice to elderly COPD patients who may prefer a bottle option to blister packs due to, for example poor vision.

The product packaging (see ATTACHEMENT 4) and the Zonda inhaler are colour matched to reinforce the pairing of the two. This further reinforces the carton and leaflet instructions that Braltus must be taken only with the Zonda inhaler, provided with each pack.

8.7 BRALTUS® ZONDA® INSTRUCTIONS FOR USE

The Zonda® device incorporates five features that aid the handling of the device.

Figure 3. Braltus® Zonda® components

1. Dust cap
2. Mouthpiece
3. Base
4. Piercing button
5. Centre chamber

Inhaler instruction for use:

1. Pull the cap upwards.
2. Hold the base of the inhaler firmly and open the mouthpiece by pulling it upwards to open it.
3. Remove a Braltus® Zonda® capsule from the bottle immediately before use and close the bottle tightly. Place one capsule in the capsule-shaped compartment in the base of the inhaler.
4. Never place a capsule directly into the mouthpiece.
5. Close the mouthpiece until a click is heard, leaving the cap open.
6. Hold the inhaler with the mouthpiece upwards, and press the piercing button completely in only once. Release the button.
7. Breathe out fully. It is important to do this away from the mouthpiece. Avoid breathing into the mouthpiece at any time. This will pierce the capsule and allows the medication to be released when the patient breathes in.

8. Place the mouthpiece in your mouth and keep your head in an upright position. Close your lips around the mouthpiece and breathe in slowly and deeply enough to hear or feel the capsule vibrating inside the compartment.
9. Hold your breath for as long as you comfortably can whilst taking the inhaler out of your mouth. Then breathe normally. Repeat steps 7 and 8 to empty the capsule completely.
10. After use, open the mouthpiece again, and tip out the empty capsule. Close the mouthpiece and cap, and store the Zonda inhaler.

9 QUALITY USE OF MEDICINES

One difference of note between Spiriva and Braltus is the metered dose. Braltus and the reference product Spiriva® provide the same delivered dose of active substance to the patient (10 microgram per capsule) but have a different labelled metered dose (13 and 18 microgram per capsule respectively). To avoid potential confusion the product information texts (Product Information, Consumer Medicine Information and Package Leaflet) emphasise the use of one “capsule” once daily as opposed to dwelling on the micrograms of tiotropium in the metered or delivered dose. This posology approach is in line with the reference product and so there is immediately a common dosing schedule between the two products. In addition, instruction is included on both the outer packaging (carton) and the container label, to “inhale the contents of one capsule once daily”.

Based on discussion with the TGA throughout the registration process a QUM initiative is agreed to support correct use of Braltus in the community and ensure that prescribers, pharmacists and patients are well informed on the equivalence of the delivered dose of tiotropium in both products. This initiative is multifaceted and may be summarised as follows;

- An agreement is in place with the TGA to provide a ‘Dear Healthcare provider’ facsimile, (see ATTACHEMENT 2) to coincide with PBS listing of Braltus. The agreed distribution list includes;

    - • Respiratory Specialists
    - • General Practitioners
    - • Pharmacists
    - The Lung Foundation
    - Pharmaceutical Society of Australia
    - Pharmacy Guild.

    The intent of the Dear HCP communication is to explain that the difference in metered dose between Braltus and the originator product (Spiriva®HandiHaler®) does not impact

the bioequivalence of the two products nor does it impact the dosing schedule. The nominal dosing schedule of one capsule once daily is the same for Braltus and originator product (Spiriva®HandiHaler® – tiotropium bromide).

- The Product Information, Consumer Medicine Information and Package Insert include statements confirming that Braltus and Spiriva both deliver 10 micrograms of tiotropium and are equivalent.

- Product packaging - additional detail is included on the carton and bottle label to disclose both the metered and the delivered dose of tiotropium.
- Colour coding of the of the Zonda inhaler and Braltus product packaging is in place (see ATTACHMENT 4) to reinforce the association between the two and support the messages in all labelling documents that Braltus capsules must be inhaled with the Zonda inhaler.
- Placebo capsule/inhaler packs will be widely available to train HCPs on the correct use of the product, and in turn train their patients correctly.

10 FINANCIAL ESTIMATES

The financial impact of the proposed listing is not presented in this minor submission as it is a request to list a generic brand of a currently listed pharmaceutical item and there is no expectation that patient numbers will change as a consequence of this listing.

As such, in accordance with division 3A of Part VII of the *National Health Act 1953* a statutory price reduction of 25% is expected to be applied. Accordingly, the proposed inclusion of Braltus tiotropium DPI, second brand to Spiriva DPI) on the Pharmaceutical Benefit Schedule will be at a lower cost. The enclosed PB11a is completed accordingly.

It follows that the proposed listing on the PBS will deliver significant savings to government as a consequence of legislated price reductions.

[redacted]

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12 ATTACHMENTS

ATTACHEMENT 1	TGA Approval letter
[redacted]	
ATTACHMENT 3	Product Information/Consumer Medicine Information/Pack Insert/Pack Components
ATTACHMENT 4	Product packaging
ATTACHMENT 5	PBS Spend Worksheet