5.15 TIOTROPIUM

Capsule containing powder for oral inhalation 13 mcg (as bromide) (for use in Zonda® device), Braltus®, TEVA Australia Pty Ltd

1 Purpose of Application

1.1 The minor submission requested listing of a new form of tiotropium (as bromide), as 13 microgram powder for inhalation capsule (Braltus®) with a different delivery device to the currently listed tiotropium (as bromide monohydrate) 18 microgram power for inhalation capsule (Spiriva®). Both products provide the same delivered dose of 10 micrograms.

2 Requested listing

2.1 The minor submission requested the following new listing based on the listing for the alternative brand Spiriva®.

2.2 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty (packs)	Max Qty (units)	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
TIOTROPIUM Capsule containing powder for oral inhalation 13 mcg tiotropium (as bromide), 30 capsules	1	30	5	TBC	Braltus® TEVA Australia Pty Ltd

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	N/A
Severity:	N/A
Condition:	~~N/A~~ *Chronic obstructive pulmonary disease (COPD)*
PBS Indication:	Chronic obstructive pulmonary disease (COPD)
Treatment phase:	~~Initial & Continuing~~
Restriction Level / Method:	☒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
Administrative Advice	*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.*

2.3 The minor submission proposed an AEMP of $[redacted]. The Secretariat noted that the DPMQ is to be confirmed with the minor submission stating that, as the first generic entrant Braltus® would be priced in accordance with the requirements of division 3A of Part VII of the National Health Act 1953.

2.4 The PBAC noted that the requested listing is consistent with the existing Spiriva® PBS listing, item number 8626B.

2.5 The minor submission sought substitution at the pharmacy level ("a" flag) with tiotropium (as bromide monohydrate) 18 microgram power for inhalation capsule (Spiriva®).

For more detail on PBAC's view, see section 5 PBAC outcome.

3 Background

3.1 Braltus® containing tiotropium (as bromide) was registered by the TGA on 31 October 2018 for the long-term maintenance treatment of bronchospasm and dyspnoea associated with COPD and for the prevention of COPD exacerbations. 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. The Braltus® Product Information (PI) noted that additional investigations were conducted in patients with

COPD and in healthy volunteers to assess inspiratory flow rates achieved using the Zonda® device compared with the inhalation device of the innovator product.

3.2 Two main differences are evident between the Braltus® and Spiriva® products. Firstly, the active ingredient content are presented differently on the Braltus® label and PI compared to that of Spiriva® capsules. Both Braltus® and 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). The recommended dose stated in the PI of both Braltus® and Spiriva® is the inhalation of one capsule, once daily. Secondly, Braltus® is delivered via a Zonda® device whereas Spiriva® is delivered via a HandiHaler device®.

3.3 The Secretariat noted that differences in labelled metered dose between the Braltus® and Spiriva® products may lead to potential prescriber, pharmacist or patient confusion. The minor submission stated that to avoid potential confusion the PI, Consumer Medicine Information (CMI) and Package Leaflet emphasise the use of one "capsule" once daily rather than focusing on the micrograms of tiotropium in the metered or delivered device.

3.4 The minor submission also outlined a number of Quality Use of Medicine (QUM) initiatives to ensure that prescribers, pharmacists and patients are informed of the equivalence of the delivered dose of tiotropium in both products. The minor submission stated that an agreement is in place with the TGA to provide a "Dear Healthcare provider" facsimile, to coincide with PBS listing of Braltus®. The agreed distribution list includes Respiratory Specialists, General Practitioners, Pharmacists, The Lung Foundation, Pharmaceutical Society of Australia and the Pharmacy Guild. The minor submission also stated that that additional detail are included on the carton and bottle label to disclose both the metered and the delivered dose of tiotropium for the Braltus® product. The pre-PBAC response stated that the latest Australian labelling order (TGO 91) applicable to all registered prescription medicines in Australia requires that the delivered dose be disclosed on the label of all dry power inhalers with all sponsors obliged to have compliant labels in place ready for stock released by September 2020. The pre-PBAC response argued that this will ensure a consistency in the disclosure of delivered dose across dry powder inhaler products in Australia and address concerns raised about different metered doses.

3.5 The minor submission stated that the operational steps of the Zonda® and HandiHaler® devices are similar. The Secretariat noted that the Braltus® capsules for use in the Zonda® device are transparent and are available in a bottle. A Zonda® device is supplied in a carton with every bottle of 30 capsules. The Braltus® PI states that the drug product must be used with the Zonda® device and that the device should be replaced after 30 capsules. The minor submission indicated that a green colour thread is evident on the Zonda® device, the bottle label and carton to reinforce the association. The Secretariat noted that the Spiriva® capsules are light green and are, according to the Spiriva® PI, presented in blister packs in cartons without the HandiHaler® or in combination with the HandiHaler®. The Spiriva® PI states that

Spiriva® capsules are only to be used with the HandiHaler® device and the minor submission noted that the HandiHaler® is washed and reused. The pre-PBAC response argued that there is a distinct difference between the colours associated with the Braltus® and Spiriva® brands.

3.6 The Secretariat noted that education of both healthcare professionals and patients would be required to ensure correct use of the delivery device dispensed and that the capsule appropriate for the device is used. The Secretariat noted that a May 2018 Medicines and Healthcare products Regulatory Agency Braltus® capsule safety alert highlighted the importance of training patients to ensure appropriate use.[1] The pre-PBAC response noted that a graphic demonstrating the correct placement of the capsule in the Zonda® device appears on the top flap of the Braltus® carton and will be visible to the patient upon opening.

3.7 The minor submission argued that QUM measures are in place to support the sponsors request for an "a" flag marking the suitability of substitution at the pharmacy level with tiotropium (as bromide monohydrate) 18 microgram power for inhalation capsule (Spiriva®). This includes: the "Dear Healthcare provider" facsimile; the PI, CMI and Package Inserts including statements confirming that Braltus® and Spiriva® both deliver 10 micrograms of tiotropium and are equivalent; additional detail on the carton and bottle label to disclose both the metered and the delivered dose of tiotropium; colouring of the Zonda® device and Braltus® logo; and the provision of placebo capsule/inhaler packs to train healthcare professionals on the correct use of the product. The minor submission also stated that the sponsor undertakes to provide a healthcare provider training program focused on ensuring a clear understanding of the bioequivalence of Braltus® and Spiriva® capsules and on mastery of the Zonda® device.

3.8 Braltus® has not been considered by the PBAC previously.

3.9 The PBAC considered a submission for the listing of a new brand of budesonide with formoterol (DuoResp® Spiromax®) with a different delivery device to the already listed Symbicort® Turbuhaler® at the July and then November 2017 meeting. The PBAC did not recommend the listing in July 2017 due to the inability to back titrate the dose with a similar device and concerns regarding potential confusion the new device may have for the patients (Paragraphs 6.1 and 6.4, budesonide with eformoterol Public Summary Document (PSD), July 2017). However, the PBAC made a positive recommendation at the November 2017 meeting and in addition recommended that the DuoResp® 200/6 and 400/12 Spiromax® and the Symbicort® 200/6 and 400/12 Turbuhaler® could be marked as equivalent (i.e. "a" flagging) in the Schedule of Pharmaceutical Benefits. The PBAC considered that any differences in the devices could be managed in the course of the regular patient education and counselling on

[1] https://www.gov.uk/drug-safety-update/braltus-tiotropium-risk-of-inhalation-of-capsule-if-placed-in-the-mouthpiece-of-the-inhaler

the use of the devices that is provided to patients by prescribers and pharmacists (Paragraphs 6.1, 6.9 and 6.10, budesonide with eformoterol PSD, November 2017). In March 2018 the PBAC reaffirmed its recommendations from the November 2017 meeting (budesonide with eformoterol, March 2018 PBAC Outcomes – Other Matters).

4 Consideration of the evidence

Sponsor hearing

4.1 There was no hearing for this item as it was a minor submission.

Consumer comments

4.2 The PBAC noted and welcomed the input from organisations (1) via the Consumer Comments facility on the PBS website. The comments from the Lung Foundation Australia described a range of issues in regards to the treatment of COPD with Braltus® including the potential for confusion at pharmacy and patient level about appropriate dosing and the need to educate patients on the correct use of new inhaler devices. The comments emphasised the need to restrict pharmacy level substitution ("a" flagging) for new delivery devices of existing medications.

Clinical trials

4.3 As a minor resubmission, no clinical trials were presented in the submission. The clinical trials used to support TGA registration were summarised in the TGA approved PI that were the same clinical trials as in the Spiriva® TGA PI.

Estimated PBS usage & financial implications

4.4 The submission requested a cost minimisation to the currently listed Spiriva®. The Secretariat noted that, while not a matter for the PBAC, a recommendation to list Braltus® would result in a 25% statutory price reduction under division 3A of Part VII of the National Health Act 1953.

4.5 The minor submission estimated there to be no financial implications to the PBS beyond those resulting from the above noted statutory price reduction.

For more detail on PBAC's view, see section 5 PBAC outcome.

5 PBAC Outcome

5.1 The PBAC recommended the Section 85 Restricted Benefit listing of a new brand of tiotropium, Braltus® as an alternative brand to the currently listed Spiriva® brand.

5.2 The PBAC noted the two main differences between the Braltus® and Spiriva® products: both Braltus® and 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); Braltus® is delivered via a Zonda® device whereas Spiriva® is delivered via a HandiHaler device®.

5.3 The PBAC noted that the TGA has accepted that bioequivalence has been established between the Braltus® and Spiriva® products.

5.4 The PBAC noted concerns that the differences in labelled metered dose between the Braltus® and Spiriva® products may lead to potential prescriber, pharmacist or patient confusion. The PBAC noted the QUM initiatives outlined in the minor submission aimed at informing prescribers, pharmacists, patients and peak bodies on the equivalence of the delivered dose of tiotropium in both products. The PBAC also noted that Australian labelling requirements now specify that the delivered dose be disclosed on the label of all dry powder inhalers.

5.5 The PBAC noted that the delivery device for Braltus® Zonda® was different to the delivery device for Spiriva® HandiHaler®. The PBAC considered that the operational steps for the two devices are similar. However, the PBAC considered that education would be required for healthcare professionals and consumers to ensure correct use of the delivery device and that the capsule appropriate for the device is used. The PBAC noted the QUM measures proposed to support the sponsors request for an "a" flag marking the suitability of substitution with Spiriva® HandiHaler® at the pharmacy level. The PBAC noted that the QUM measures included, among other strategies, a healthcare provider education program and the provision of placebo capsule/inhaler packs.

5.6 The PBAC considered that the information and education measures proposed by the sponsor had addressed key QUM concerns regarding the differences in the labelled metered dose and devices between the Braltus® and Spiriva® products.

5.7 The PBAC considered that the differences in the labelled metered dose and devices could be managed in the course of the regular patient education and counselling on the use of the devices that is provided to patients by prescribers and pharmacists, and that these differences were not sufficient to preclude marking the two brands as equivalent. The PBAC expected and was confident that the dispensing pharmacist would ensure that any change in delivery device would be communicated to the patient and that appropriate education on the use of the device would be provided.

5.8 The PBAC advised that tiotropium (as bromide) 13 microgram powder for inhalation capsule (Braltus®) and tiotropium (as bromide monohydrate) 18 microgram powder for inhalation capsule (Spiriva®) could be marked as equivalent in the Schedule of Pharmaceutical Benefits for the purposes of substitution by the pharmacist at the point of dispensing.

5.9 The PBAC considered the following administrative advice is appropriate for inclusion in both the Braltus® and Spiriva® listings "Pharmaceutical benefits that have the form tiotropium 18 microgram powder for inhalation and pharmaceutical benefits that have the form tiotropium 13 microgram powder for inhalation are equivalent for the purposes of substitution".

5.10 The PBAC noted that there would be no financial implications to the PBS/RPBS from

listing beyond savings resulting from the statutory price reduction.

5.11 The PBAC recommended that the Early Supply Rule should apply, as is the case for currently listed products.

5.12 The PBAC advised that tiotropium is suitable for prescribing by nurse practitioners, as is the case for currently listed products.

5.13 The PBAC noted that this minor submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

6 Recommended listing

6.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty (packs)	Max Qty (units)	№.of Rpts	Proprietary Name and Manufacturer
TIOTROPIUM Capsule containing powder for oral inhalation 13 mcg tiotropium (as bromide), 30 capsules	1	30	5	Braltus® TEVA Australia Pty Ltd

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	N/A
Severity:	N/A
Condition:	Chronic obstructive pulmonary disease (COPD)
PBS Indication:	Chronic obstructive pulmonary disease (COPD)
Treatment phase:	-
Restriction Level / Method:	☒Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☐Streamlined
Population criteria:	N/A

Administrative Advice	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. Pharmaceutical benefits that have the form tiotropium 18 microgram powder for inhalation and pharmaceutical benefits that have the form tiotropium 13 microgram powder for inhalation are equivalent for the purposes of substitution.

7 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

8 Sponsor's Comment

The sponsor had no comment.