

6.18 TIOTROPIUM

Capsule containing powder for oral inhalation 18 micrograms (as bromide monohydrate) (for use in HandiHaler®), 30 capsules, Spiriva®, Boehringer Ingelheim Pty Ltd

1 Purpose of Application

- 1.1 A new product containing tiotropium (as bromide) 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®) was considered by the PBAC at its March 2019 meeting. Both products provide the same delivered dose of 10 micrograms.
- 1.2 The minor submission requested that the PBAC not recommend that the Braltus® and Spiriva® brands of tiotropium be marked as equivalent ('a' flagged) in the Schedule of Pharmaceutical Benefits.

2 Requested listing

- 2.1 The minor submission proposed no changes to the existing Spiriva® listing.

3 Background

- 3.1 Spiriva® was registered by the Therapeutic Goods Administration (TGA) on 30 May 2002 for the long term maintenance treatment of bronchospasm and dyspnoea associated with chronic obstructive pulmonary disease (COPD) and for the prevention of COPD exacerbations.
- 3.2 Spiriva® is available on the PBS as a capsule formulation (powder for inhalation, PBS item 8626B) to be used in the HandiHaler® device and as a solution for inhalation formulation (inhalation solution, PBS items 11043F and 10509D) which is used in the Respimat® device. The minor submission noted that these two formulations are not bioequivalent.
- 3.3 The minor submission noted that a new product containing tiotropium, Braltus®, had been listed on the Australian Register of Therapeutic Goods (ARTG) by Teva Pharma Australia Pty Ltd. The minor submission noted that Braltus® capsules are to be used in the Zonda® inhaler device.

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

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 that no consumer comments were received for this item.

Current Situation

4.3 The minor submission argued that an ‘a’ flag applying to the two tiotropium capsule brands is not appropriate and should not be recommended by the PBAC on the basis of:

- Uncertainty in bioequivalence;
- Differences in labelled strengths and likely differences in pharmaceutical items, which could lead to prescriber, pharmacist and patient confusion;
- Adverse events (AEs) observed for Braltus[®], including due to incorrect inhaler use; and
- Quality use of medicines (QUM) concerns potentially leading to worsening of lung function.

4.4 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 Braltus[®] 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 stated 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.¹

4.5 The minor submission noted the active ingredient content is presented differently on the Braltus[®] label 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 minor submission argued that differences in the capsule labelled strengths may lead to patient confusion, stating that some patients may confuse the labelled dosage instructions and use two Braltus[®] capsules with the aim of reaching their previous daily dose with Spiriva[®] capsules. The minor submission also stated that health care professional confusion may also occur and noted that the release of Braltus[®] in Denmark was accompanied by a Direct Healthcare Professional Communication letter about the differences in capsule strengths.²

4.6 The minor submission noted that AEs due to incorrect inhaler use have been reported with Braltus[®]. The Medicines and Healthcare products Regulatory Agency (MHRA)

¹ <https://www.tga.gov.au/sites/default/files/foi-946-1819-01.pdf>

² <https://laegemiddelstyrelsen.dk/en/sideeffects/direct-healthcare-professional-communication/delivered-dhpcs/~media/EA186BA3684843888ECC623834FFBA2F.ashx>

published a safety alert in May 2018 highlighting the need to train patients to place the Braltus[®] capsule in the correct chamber of the Zonda[®] device.³ The safety alert noted MHRA had received reports of patients who have inhaled a Braltus[®] capsule from the mouthpiece into the back of the throat, resulting in coughing and risking aspiration or airway obstruction. The minor submission also noted that as of 7 January 2018, the Netherlands Pharmacovigilance Centre Lareb had received 10 reports from consumers suggesting decreased efficacy associated with substitution from Spiriva[®] capsules to the Braltus[®] brand.⁴

- 4.7 The minor submission argued that there are additional potential QUM issues for PBAC consideration of substitutability of Spiriva[®] capsules and Braltus[®] capsules. The minor submission noted that Braltus[®] is delivered via a Zonda[®] device whereas Spiriva[®] is delivered via a HandiHaler[®] device. The Secretariat noted that the operational steps of each device are similar. The minor submission highlighted that the HandiHaler[®] device can be reused whereas the Zonda[®] device should be discarded after 30 uses. The minor submission stated that ‘a concerning issue is that patients with COPD may attempt to use Spiriva[®] capsules in the Zonda[®] device or Braltus[®] capsules in the HandiHaler[®] device’. The minor submission argued that switching patients from one inhaled drug to another delivered by a different inhaler may have a negative impact on patient adherence and ultimately disease control.^{5,6} The minor submission proposed that differences in each of the inhaler designs may lead to potential handling errors or differences in taste and sensation. The minor submission stated that patients need to be trained on any new devices received as a result of switching especially when a prescriber is not consulted, i.e. where products are ‘a’ flagged.⁷
- 4.8 The minor submission noted that the two capsules are presented differently i.e. Braltus[®] capsules are presented in high density polyethylene bottles whereas Spiriva[®] capsules are presented in blister packs. The minor submission reported on a Spiriva[®] sponsor funded study that investigated the impact of air exposure resulting from potential storage errors (e.g. capsules stored in a pill box or not closing the bottle correctly) for the two different types of packaging.⁸ The impact was evaluated in vitro using fine particle dose (FPD). The minor submission argued that the potential impact

³ <https://www.gov.uk/drug-safety-update/braltus-tiotropium-risk-of-inhalation-of-capsule-if-placed-in-the-mouthpiece-of-the-inhaler>

⁴ http://databankws.lareb.nl/Downloads/Signals_2018_Tiotropium%20and%20decreased%20therapeutic%20response.pdf

⁵ Lavorini F, et al. Asthma and COPD: interchangeable use of inhalers. A document of Italian Society of Respiratory Medicine (SIMeR) and Italian Society of Allergy, Asthma and Clinical Immunology (SIAACI). *Pulm Pharmacol Ther* 2015;32:25-30

⁶ <https://www.sunderlandccg.nhs.uk/wp-content/uploads/2017/02/Braltus-info.pdf>

⁷ Rigby D. Switching inhaler devices. *Aust J Pharm* 2018; 99:9-10

⁸ Wolkenhauer M, et al. Effect of Unintentional Storage and Handling Errors of Inhaled Medications: What Does This Mean for Therapeutic Equivalence Considerations? *J Aerosol Med Pulm Drug Deliv* 2018. DOI: 10.1089/jamp.2018.1480

on FPD was larger for the bottles if a storage error occurred and suggested that a loss of FPD could impact the amount of medicine reaching a patient's lungs.

- 4.9 The minor submission noted that the PBAC considered a submission for the listing of follitropin alfa (Bemfola[®]) as a biosimilar of follitropin alfa (Gonal-f[®]) at its March 2016 meeting. The minor submission noted that the PBAC recommended the listing but advised that the Gonal-f[®] and Bemfola[®] brands of follitropin alfa could not be marked as equivalent in the Schedule of Pharmaceutical Benefits ('a' flagged), for the purposes of substitution by the pharmacist at the point of dispensing. The PBAC advised that this is primarily due to differences in the strengths, number of pens per pack and maximum quantities between the brands, which make substitution at the pharmacy level difficult from a practical perspective (Paragraphs 7.1 and 7.3, follitropin alfa Public Summary Document, March 2016). The PBAC considered that differences in the setting, device or indication for use influenced considerations associated with a recommendation as to whether brands of a medicine should be marked as equivalent in the Schedule of Pharmaceutical Benefits ('a' flagged), for the purposes of substitution by the pharmacist at the point of dispensing.

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

5 PBAC Outcome

- 5.1 Contrary to what was requested in the minor submission, the PBAC advised that the Minister should determine that, for the purposes of section 103(2A)(b) of the Act, tiotropium (as bromide) 13 microgram powder for inhalation capsule (Braltus[®]) and tiotropium (as bromide monohydrate) 18 microgram powder for inhalation capsule (Spiriva[®]) are to be treated as equivalent, and accordingly 'a'-flagged in the Schedule of Pharmaceutical Benefits.
- 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 minor submission raised concerns regarding uncertainty in bioequivalence. However, the PBAC noted that the TGA has accepted that bioequivalence has been established between the Braltus[®] and Spiriva[®] products.
- 5.4 The PBAC acknowledged the concerns raised in the submission that the differences in labelled metered dose between the Braltus[®] and Spiriva[®] products may lead to potential prescriber, pharmacist or patient confusion. However, the PBAC considered that this could be adequately addressed through provision of information and educational measures for prescribers, pharmacists, patients and peak bodies on the equivalence of the delivered dose of tiotropium in both products. The PBAC considered that in addition to any measures being undertaken by the sponsor of Braltus[®] to address QUM concerns, it would also be appropriate for the Department

to refer the matter to the NPS MedicineWise to deliver additional educational materials.

- 5.5 The PBAC noted that the delivery device for Braltus® Zonda® was different to the delivery device for Spiriva® HandiHaler®, and noted the sponsor’s concerns around potential QUM and AE outcomes. 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.
- 5.6 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 both 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.
- 5.7 The PBAC noted the ability for prescribers and pharmacists to substitute generic brands for originator brands is an important part of encouraging appropriate use of generics on the PBS.
- 5.8 The PBAC noted for any individual prescription, a prescriber may choose to not permit brand substitution by indicating ‘substitution not permitted’ on the prescription. Likewise, when substitution is permitted, a patient may nominate which ‘a’ flagged brand they wish to receive from the pharmacist. The substitution process allows for patient and prescriber choice and is not automatic.
- 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 this submission is not eligible for an Independent Review, as the request was not seeking listing for an entirely different disease or condition, an objectively different subtype of disease, or targeting a different population.

Outcome:

Rejected

6 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.

7 Sponsor's Comment

The sponsor had no comment.