Australian Government
Department of Health
Therapeutic Goods Administration

Risk Minimisation Material Review Report

Tiotropium (BRALTUS)

Sponsor: Teva Pharma Australia

Report date: 15 September 2018

TGA Health Safety Regulation

RISK MINIMISATION MATERIAL EVALUATION REPORT

Submission type: New generic product
Sponsor: Teva Pharma Australia
Generic name: **Tiotropium**
Trade name: **BRALTUS**
Dose form and strength: Powder for inhalation in capsule; 13micrograms (metered dose)

RMP file No: E18-343944
TRIM reference: D18-10969662

EU-RMP/ASA Version: n/a

Documents reviewed: Direct healthcare professional communication
Information for the patient (package insert)

Evaluator: [redacted]
Authorised by: [redacted]
Date authorised: 15 September 2018

Reason(s) for review: Request by delegate

[1]Priority for RMP compliance monitoring: Not required

[1] EI2 advice: due to the nature of the DHPC, no ongoing compliance monitoring is required. However, sponsor should still provide a plan to demonstrate the viability and effectiveness of the action.

1. RECOMMENDATIONS

Recommendation 1. The sponsor has advised in the PI that BRALTUS and SPIRIVA are bioequivalent. This bioequivalence is established between the use of BRALTUS with ZONDA device and the use of SPIRIVA with HANDIHALER device. Although the suggested inhalation techniques are similar for both products, there are significant differences between ZONDA device and HANDIHALER device:

1) HANDIHALER device is expected to be reused with different bottles of capsule for inhalation. The device is dispensed separately from SPIRIVA capsules. In contrast, each BRALTUS capsule bottle contains a new ZONDA device which is not expected for use more than 30 times.

2) The colour and shape of the two devices are different.

3) HANDIHALER device is expected to be cleaned with water once a month. ZONDA device is expected to be cleaned with dry cloth or tissue if necessary.

To ensure adequate counselling for patients, it is recommended that the following advice is added to the DHPC:

Each box of BRALTUS contains a new ZONDA inhaler and inhalation capsules. Patients being switched from SPIRIVA must use the ZONDA inhaler with BRALTUS to deliver the intended dose. The ZONDA inhaler should be discarded after 30 uses.

Recommendation 2. The proposed electronic distribution of the Direct Healthcare Professional Communication (DHPC) is acceptable. The sponsor should include relevant nurse practitioners on the distribution list.

Recommendation 3. The sponsor should provide its implementation plan for the DHPC. The following aspects should be included:

a. Planned delivery time frame;
b. How will the list of individual recipients be obtained to ensure the intended recipients are included;
c. How will the DHPC be delivered electronically? If the DHPC is to be delivered by email, delivery and read receipts should be requested.

Recommendation 4. It is noted that unlike the instructions for use provided in the CMI for SPIRIVA, no instructions on cleaning with water have been provided for BRALTUS. It is unclear whether this is because the ZONDA device is not expected to be reused for more than 30 times and therefore, does not require water cleaning. The sponsor should provide clarification as to whether the ZONDA device can be cleaned and rinsed with water. Advice on/against water cleaning should be provided in both 'Information for the patient' and the CMI to ensure adequate maintenance of the device.

Recommendation 5. The delegate has made a specific request for advice[2] from the RMP evaluator on the following matter:

We (PCS) would prefer that the delivered dose was displayed in a more prominent location in addition to the metered dose. See below for an example:

'Braltus

Tiotropium (as bromide) 13 microgram metered dose

Tiotropium (as bromide) 10 microgram delivered dose'

The RMP evaluator supports the proposed label change to show the delivered dose in addition to the metered dose to avoid confusion. However, it has been noted that the DHPC states '13 microgram' as 'pre-metered dose' whilst the label states '13 microgram' as 'metered dose'. It is recommended that the term is used consistently to avoid confusion.

1.1. WORDING FOR CONDITIONS OF REGISTRATION

No RMP has been provided for this submission. Therefore, no RMP versions are provided for inclusion in conditions of registration.

[2] TGA delegate request, TRIM reference: D18-10959934

2. BACKGROUND

- Teva Pharma Australia has applied to register a new generic product, tiotropium (BRALTUS). BRALTUS is proposed to be used for the long-term maintenance treatment of bronchospasm and dyspnoea associated with chronic obstructive pulmonary disease (COPD).
- The reference product is SPIRIVA which was first registered in the ARTG in May 2002. No RMP was evaluated for the reference product as the submission predated the requirement for RMP evaluation in Australia.
- BRALTUS has been approved in the EU through a decentralised procedure in 2016.
- The RMPE section provided advice that an RMP evaluation was not required for this generic submission. Consequently, no RMP has been submitted for evaluation.
- In its S31 response, the sponsor provided a copy of the draft direct healthcare professional communication (DHPC). The DHPC is proposed by the sponsor to mitigate the risk of medication errors between SPIRIVA (reference product) and BRALTUS (generic product). The TGA delegate has requested that the draft DHPC is reviewed with the draft PI and labels by the RMPE section.
- As requested, the focus of this review is on the adequacy of the proposed DHPC and package insert, with the assumption that these materials are for a generic product that is bioequivalent to the reference product.

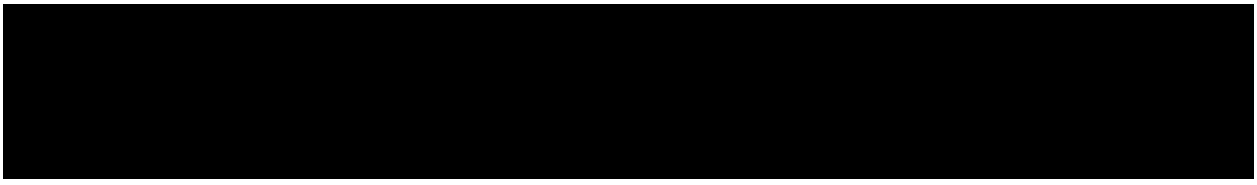
3. PLANNED RISK MINIMISATION ACTIVITIES

The sponsor has proposed a DHPC and an 'Information for the patient' as package insert. The sponsor has stated in the draft copy that the DHPC is developed to minimise the risk of medication error between the reference and the bioequivalent generic product. As there is no RMP provided for the product, it is unclear which specific risk the 'Information for the patient' targets. Consequently, this material is reviewed with assumed the purpose of providing instructions for adequate use.

4. ADEQUACY OF PROPOSED RISK MINIMISATION ACTIVITIES

No RMP has been required for evaluation for SPIRIVA by the TGA. Since its registration, no additional risk minimisation actions have been required for SPIRIVA by the TGA to mitigate any specific safety concerns. Consequently, no additional risk minimisation is considered necessary for BRALTUS to mitigate any safety concerns related to the use of tiotropium in the proposed indications. It is expected that the content in the PI for BRALTUS aligns with the content in the PI for SPIRIVA. This aspect is evaluated by the relevant area in the TGA.

The sponsor has advised in the PI that BRALTUS and SPIRIVA are bioequivalent. This bioequivalence is established between the use of BRALTUS with ZONDA device and the use of SPIRIVA with HANDIHALER device. Although the suggested inhalation technique is similar, there are significant differences between ZONDA device and HANDIHALER device:



[redacted]

The 'Information for the patient' is not considered additional risk minimisation as it is a package insert. As suggested in the draft PI, this leaflet provides instructions for adequate use of the product with its device. The leaflet appears to contain the same information as the draft CMI. It is noted that the inhalation technique required for BRALTUS is similar to that for SPIRIVA.

The evaluator has noted that unlike the instructions for use provided in the CMI for SPIRIVA, no instructions on cleaning with water have been provided for BRALTUS. It is unclear whether this is because the ZONDA device is not expected to be reused for more than 30 times and therefore, does not require water cleaning. The sponsor should provide clarification to whether ZONDA device can be cleaned and rinsed with water. Advice on/against water cleaning should be provided in both 'Information for the patient' and the CMI to ensure adequate maintenance of the device.

There is objection to other parts of the risk minimisation materials from the RMP perspective.

5. SPECIFIC ADVICE REQUESTED BY THE TGA DELEGATE

The delegate has made a specific request for advice[2] from the RMP evaluator on the following matter:

> *We (PCS) would prefer that the delivered dose was displayed in a more prominent location in addition to the metered dose. See below for an example:*
>
> *Braltus*
>
> *Tiotropium (as bromide) 13 microgram metered dose*
>
> *Tiotropium (as bromide) 10 microgram delivered dose*
>
> The RMP evaluator supports the proposed label change to show the delivered dose in addition to the metered dose to avoid confusion. However, it has been noted that the DHPC states '13 microgram' as 'pre-metered dose' whilst the label states '13 microgram' as 'metered dose'. It is recommended that the term is used consistently to avoid confusion.

6. EVALUATION OF EFFECTIVENESS OF ADDITIONAL RISK MINIMISATION ACTIVITIES

The proposed DHPC is the only additional risk minimisation activity. The sponsor has proposed to distribute the DHPC to [redacted]

[redacted]

The proposed [redacted] practitioners on the distribution list.

The sponsor should provide its implementation plan for the DHPC. The following aspects should be included:

a. Planned delivery time;
b. How the intended recipients are identified;
[redacted]