Therapeutic Goods Administration

Scientific Evaluation Branch

Pharmaceutical Chemistry Section

Milestone 5 Report: Quality Data

(Chemical Drug Substance, CTD Format Dossier)

New generic medicine (Type D)

(type of submission)

tiotropium bromide

(drug substance – polymorphic form if present)

BRALTUS

(proposed trade name)

13 microgram Dry Powder for Inhalation, hard capsules

(dose form and strengths)

Teva Pharma Australia Pty Ltd

(sponsor/distributor if appropriate)

PM-2017-03103-1-5

(submission number)

E18-211908

(Chemistry file number)

Milestone 3 evaluation report:	D18-10408790
Applicant's response to MS3:	e002646 - (0003)

Sections of this report require censoring prior to sending externally. Sections that should be removed are highlighted in yellow

PO Box 100 Woden ACT 2606 ABN 40 939 406 804
Phone: 02 6232 8444 Fax: 02 6203 1605 Email: info@tga.gov.au
http://www.tga.gov.au

Table of Contents

Introduction

The Sponsor's response to matters raised in the pharmaceutical chemistry milestone 3 report is evaluated in this report.

Module 1:

Trade name

Question 1

No objection to the trade name, BRALTUS, has been received from the clinical delegate.

Labels

Question 2

The sponsor has updated the labels to refer to the strength of the product as Tiotropium (as bromide) 13 micrograms, that is the metered dose. This is acceptable as the innovator product is described as the metered dose. However; ***as the innovator product is labelled as an 18 microgram metered dose which is claimed to be bioequivalent to the sponsor's 13 microgram metered dose product, it is considered that the sponsor should also include the delivered dose on the labels. A statement along the lines of 'Each capsule contains 13 micrograms of tiotropium (as bromide) and will deliver 10 micrograms of tiotropium' would be considered acceptable.***

The inclusion of the delivered dose on the label will also satisfy the preferred expression of the quantity or proportion of active ingredients by the dry powder inhaler, that is as the quantity *delivered* (refer TGO 91 Section 11(2)(h)).

The clinical delegate has been consulted regarding the labelling of the product and concurs that the delivered dose should be included on the labels (D18-10738217).

Product Information (PI)

Question 3

The PI has been amended to include 'Vcaps The Vegetarian Alternative empty hard capsule size 3 (Natural/Natural)' in the PI, however the previous (2011) version of the PI requires that ***this information is included in the 'DESCRIPTION' section of the PI where lactose monohydrate is also claimed as an excipient.***

The clinical delegate also recommends that the company consider referring to the capsules as 'Vcaps', e.g. 'Braltus Vcaps', instead of 'Braltus capsules' in order to emphasise that standard capsules (e.g. gelatin) are not available that Braltus is available only in Vcaps (D18-10863798). ***The PI should be updated to refer to 'Vcaps', particularly under the heading Presentation and Storage Conditions.***

Additionally, in order to avoid potential dosing confusion, it would be useful if the PI included a statement describing the delivered dose of Braltus and the reference product (see also the Clin. report D18-10738217). ***The sponsor should be asked to include the statement 'Braltus and Spiriva both deliver 10 micrograms of tiotropium and are equivalent' (or words to that effect) in the PI.***

(Note that the PI is not in the format introduced in 2018. Although it is preferred that the 'new' format is followed for new registrations, there is a transition period in effect and it is expected that the format of the PI will be revised prior to the end of this period.)

Provisional ARTG records (PARs)

Question 4

[redacted]

Question 5

The PARs have been corrected as requested. However, ***the manufacturing steps for*** [redacted] ***will need to be corrected once the manufacturing address has been corrected (see question 4).***

Module 3:

Drug Substance

Question 6

The DMF is considered acceptable to ensure the quality of the product (see D18-10385267).

Question 7

The sponsor has not added a microbial purity test to their drug substance specification as per the drug substance manufacturer's specification. However, data have been provided demonstrating absence in five batches and this will not be pursued on this occasion.

Question 8

The drug substance analytical methods used by the finished product manufacturer are identical to those used by the drug substance manufacturer. Method transfer studies have been provided for studies which do not use the Ph. Eur. method.

Question 9

The DMF holders' stability studies have been provided to support a re-test period of 12 months [redacted] This is acceptable.

Question 10

[redacted]

Drug Product

Question 11

A physical sample of the delivery device has been provided. This is acceptable.

Question 12

[redacted]

Question 13

[redacted]

Question 14

[redacted]

Question 15

[redacted]

Question 16

[redacted]

Question 17

The company states that due to the nature of setting up the test conditions the time spent under conditions of increased humidity can vary on separate occasions and this may affect the reproducibility of the results. Additionally, high humidity may affect the aerosol properties of a dry powder and is just as likely to affect the reference product as the proposed product.

The fine particle dose (FPD) of 3 reference and an additional 4 test batches emitted under high humidity conditions have been provided. Both the test and reference products are affected; [redacted] As previously noted 2 (of 6) of the test batches would fail the proposed specification for FPD.

[redacted]

The company states that the changes are not expected to have a significant impact of safety and efficacy because the impact is similar in both test and reference products.

Similar changes were not observed to the FPD of capsules stored under accelerated conditions (40 °C/75 % RH) for up to 6 months in the proposed container. Given that the capsules are available in packs of 30 only and are unlikely to be stored for significant periods outside of the container this will be accepted.

Question 18

Some changes were made to the device after the in vivo study to address the following points:

- [redacted]
- External colour changed to green

These changes were assessed in vitro to have no impact on the performance of the device.

Question 19

Holding times have been claimed based on actual holding times of the intermediates used in the registration batches. This is acceptable.

Question 20

[redacted]

Question 21

1. All tests have been included in the expiry specifications for regulatory testing purposes. This is acceptable.

2. Fine Particle Dose (FPD) and Mass Median Aerodynamic Diameter (MMAD) limits have been justified based on the batch used in the clinical studies. This is acceptable.

[redacted]

Question 22

The applicant has provided an assurance that the child resistant closure complies with TGO80. This is acceptable.

Question 23

The colour of the delivery device is different to that of the reference product and the sponsor has provided a clinical justification for the colours used. There are no objections to the proposed colours from a clinical perspective (refer D18-10863798). This is acceptable.

Question 24

The in-use stability data demonstrate stability of the product for up to 60 days. This is acceptable.

Question 25

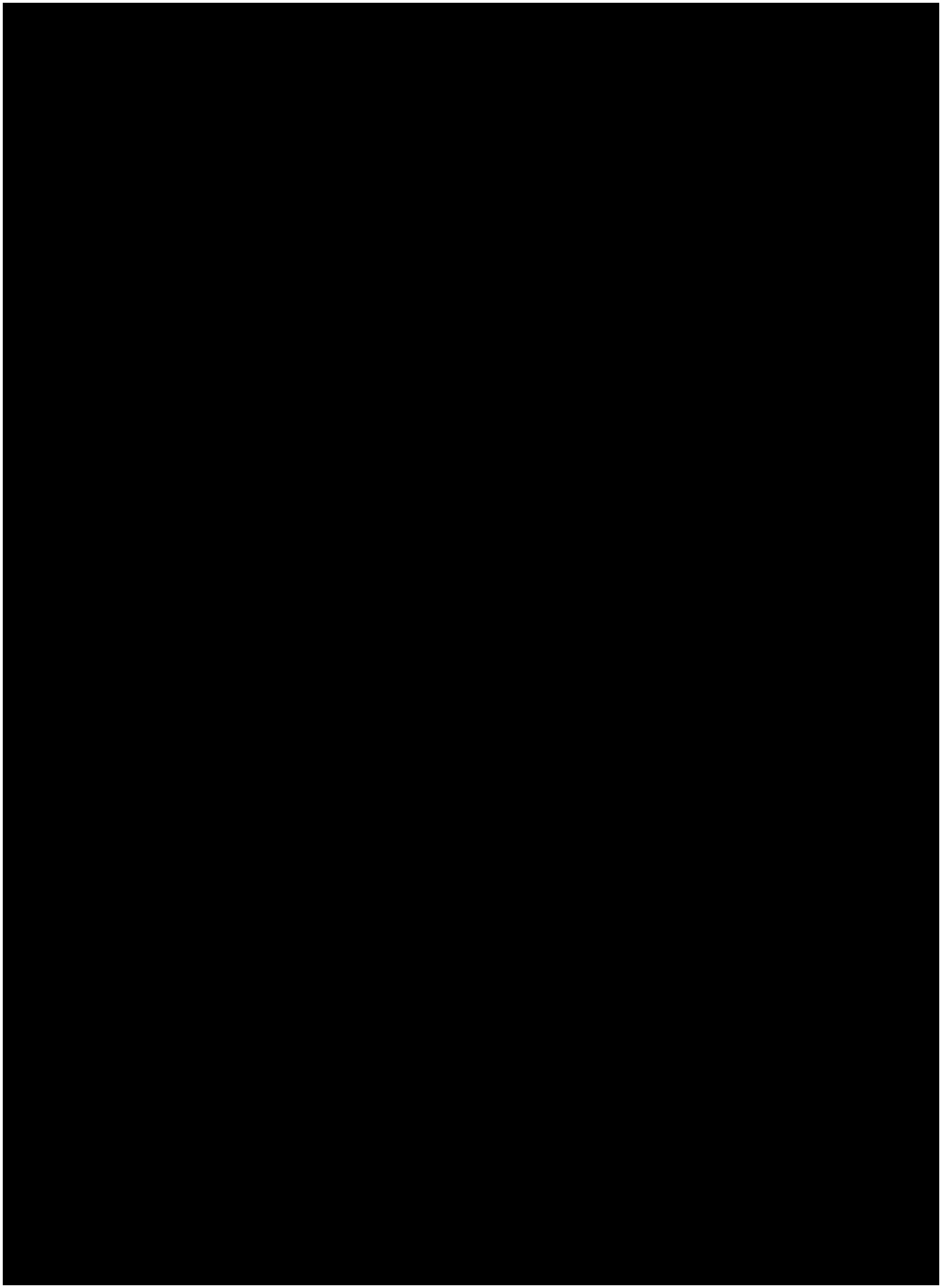
The photo stability studies provided with the initial study were conducted under ICH conditions. [redacted] an additional storage condition will not be pursued on this occasion.

Question 26

The sponsor has completed the characterization of Spiriva products sourced from Europe and Australia to justify the use of the overseas reference product in the bioequivalence study (refer 5.3.b of the MS3 report). The previously provided document has been reissued and contains testing results for an additional 3 Spiriva Australia and 3 Spiriva Europe batches [redacted]

The following additional aspects are provided:

[redacted]



[redacted]

Question 27

Bioequivalence study CLL13002 involved a single dose of two capsules and it was unclear why two capsules should be considered acceptable as the PI recommends a single capsule per day. The sponsor has provided a justification, which from a pharmaceutical chemistry perspective, appears reasonable (refer to Milestone 3 report D18-10408790). There are no clinical objections to the proposed colour and/or presentation (D18-10863798). This is accepted.

Question 28

The justification for choosing 90.20% confidence intervals for the pooled samples in the bioequivalence study are considered acceptable (see D18-10415848 and D18-10476682).

It is noted that a Dear Healthcare provider letter has been provided (e002646 (0003) - Response to request for information - Annexes) and appears to be the one approved for distribution in Ireland. ***The proposed version for distribution in Australia should be provided as well as the proposed distribution list***.

The contents of the DHCP letter will be referred for clinical and/or RMP comment.

Evaluator's recommendation

Approval is not recommended from a pharmaceutical chemistry and biopharmaceutics perspective at this stage for the following reasons. If the Sponsor was to satisfactory address the outstanding matters then approval could be recommended

- Due to concerns related to the statement of active for the proposed product compared to the innovator product, and the potential for mis-dosing of the product;
    - The labels should be updated to state the delivered dose, as outlined on page 3
    - A statement declaring equivalence between the product and the reference product, as outlined on page 3 of this report, in the Product Information (and CMI).
- The Product Information should be updated to include full list of excipients under the 'Description' heading and reference to (vegetarian) 'capsules' should be to be updated to 'Vcaps' throughout the PI, as discussed on page 3 of this report.
- The DCHP letter that is intended to be distributed in Australia should be provided for review as well as where and to whom the DHCP letter will be distributed.

[redacted]

    - The Provisional ARTG Record will need to be updated accordingly once the clearance has been amended

The Sponsor is requested to check the Provisional ARTG Records (PARs) for accuracy and advise the TGA of any errors.

The Sponsor is reminded to ensure valid GMP Clearances are available at the time of the Delegate's decision.

[redacted]