Braltus
Response to Milestone 5 Report:
Quality and Clinical Data

BRALTUS
Tiotropium (as bromide) Powder for Inhalation
13 microgram

Table of Contents

Module 1

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)

Response:

The inclusion of the delivered dose has been included on the carton and label, see Module 1.3.3.

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.)

Response:

'Vcaps The Vegetarian Alternative empty hard capsule size 3 (Natural/Natural)' has been included in the DESCRIPTION section of the PI.

All recommendations have been accepted with the exception of the adoption of „Braltus Vcaps" as it appears to detract from the tradename, Braltus. Given that Vcaps is the vegetarian option, there is no risk of patients inadvertently eating animal based products.

The PI, CMI and PIL has been updated to include the statement 'Braltus and Spiriva both deliver 10 micrograms of tiotropium and are equivalent.'

A reformatted version of the PI has also been included in Module 1.3.1.

Provisional ARTG records (PARs):

Question 4

The sponsor is liaising with the GMP clearance branch to update the manufacturing address for [redacted]

Response:

The manufacturing address has been corrected on eBS, see PAR PM-2017-03103-1-5 (attached).

The address for [redacted] is:

[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)*

Response:

The manufacturing address for [redacted] is correct on the PAR.

It is understood that Quality Control covers the manufacturing step as listed in the in Module 3.2.P.3.1 of the submission dossier (Quality Control Testing (foreign particulate matter)).

The applicant does give permission for the manufacturing step to be changed on the PAR to 'Testing chemical and physical' to concur with the manufacturing steps listed on the GMP Clearance, if this is required.

The expiry date for [redacted] has been updated to 21/10/2021. This has been annotated on the PAR PM-2017-03103-1-1 (attached).

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.

Response:

The proposed 'Dear Healthcare provider' letter has been included as an Annex (HCP letter_AU) to this response document.

The proposed distribution list will be:

[redacted]

Module 5

Clinical Questions:

The Applicant notes the *second round comments on product documentation for the consideration of the PCES Delegate*. Any outstanding issues on product documentation will be addressed after receiving feedback from the TGA pharmacist on finalisation of the PI.

Errors of Fact or Omission

The quality and clinical evaluation reports have been reviewed:

1. Quality: There were no perceived errors identified.
2. Clinical Evaluation Report: see Annex – Clinical Evaluation Report_Errors of fact.

Date: TBC (proximate to launch)

DIRECT HEALTHCARE PROFESSIONAL COMMUNICATION

BRALTUS® tiotropium (as bromide) powder for inhalation, hard capsule, 13 micrograms

Delivered dose is 10 micrograms of tiotropium per capsule

Dosing guidance for BRALTUS® (bioequivalent to SPIRIVA®) –

Advice to minimise the risk of medication error between the two medicines

Dear Healthcare Professional,

The above referenced product, BRALTUS® tiotropium (as bromide) powder for inhalation, hard capsule 13 microgram has been registered in Australia based on established bioequivalence to the innovator product, Spiriva® (tiotropium) capsules.

The indication for BRALTUS is the same as that of SPIRIVA, for the long term maintenance treatment of bronchospasm and dyspnoea associated with chronic obstructive pulmonary disease (COPD) and for the prevention of COPD exacerbations

In agreement with the Therapeutic Goods Administration, Teva Pharma Australia Pty Ltd is sending this communication in order to highlight differences in how the active ingredient content is presented on the BRALTUS (tiotropium) label and Product Information compared to that of Spiriva (tiotropium) capsules.

- Should prescribers make a decision to switch patients between the originator product (SPIRIVA® - tiotropium bromide) and BRALTUS, it is important that the dosing instructions are correctly understood. This letter highlights the correct use of the new product.
- The pre-metered dose of tiotropium in BRALTUS (13 microgram) is lower than the pre-metered dose of SPIRIVA® (18 microgram), however the 'delivered doses' (i.e. dose delivered to the patient) of both products are the same (10 microgram).
- The BRALTUS outer carton includes information on both the pre-metered and delivered doses of tiotropium (13 microgram and 10 microgram respectively) whereas the SPIRIVA® carton states only the pre-metered dose of tiotropium (18 microgram).
- It is important to note that **both products provide the same delivered dose of tiotropium to the patient and the dosing regimen of one capsule, once daily, is the same with both products.**

Teva Pharma Australia Pty Ltd (ABN 41 169 715 664)

Level 1, 37 Epping Road, Macquarie Park, NSW 2113 AUSTRALIA / Locked Bag 2053, North Ryde NSW 1670

Phone +61 2 8061 9900 Fax +61 2 8061 9999 www.tevapharm.com

Further information

The recommended dose in adults (18 years and older) is one capsule taken once daily with the Zonda inhaler.

BRALTUS contains a smaller amount of tiotropium bromide in its capsules than the originator product SPIRIVA®, **but provides an equivalent amount of tiotropium (the delivered dose).**

The table below illustrates how the description of the products differ:

Variable	BRALTUS	SPIRIVA®
Active capsule contents*	16 microgram tiotropium bromide	22.5 microgram tiotropium bromide monohydrate
Tiotropium equivalent (pre-metered dose)	13 microgram tiotropium	18 microgram tiotropium
Delivered dose	10 microgram tiotropium	10 microgram tiotropium
Dosing regimen	One capsule, once daily	One capsule, once daily

*Please note that not all of this information in included in the package insert and the CMI.

It is important to note that if patients are being switched between SPIRIVA and BRALTUS, the dosing schedule of **one capsule, once daily remains the same and does not change.**

For further inquiries concerning this information, please contact Teva's Medical Information Department as follows: Email: Medinfo.Australia@tevapharm.com; Tel: 1800 288 382

Call for reporting

You are reminded to report any suspected adverse reactions directly to the TGA (Tel: 1800 020 653) or to Teva Pharma Australia via Email: safety.australia@tevapharm.com; Tel: 1800 288 382.

Yours faithfully,
Teva Pharma Australia Pty Ltd

Senior Medical Director

Teva Pharma Australia Pty Ltd (ABN 41 169 715 664)

Level 1, 37 Epping Road, Macquarie Park, NSW 2113 AUSTRALIA / Locked Bag 2053, North Ryde NSW 1670

Phone +61 2 8061 9900 Fax +61 2 8061 9999 www.tevapharm.com

PROVISIONAL ARTG RECORD

Label Name:	BRALTUS tiotropium (as bromide) 13 microgram dry powder for inhalation hard capsule	**Provisional ARTG Number:**	293317
Sponsor:	Teva Pharma Australia Pty Ltd	**Sponsor ID:**	61006
Agent:	Pharma To Market Pty Ltd	**Agent ID:**	53577

Approval Area: Drug Safety Evaluation Branch
RegistrationType: Registered
Provisional Registration Lapse Date:
Black Triangle Scheme Indicator: No
Black Triangle Scheme Lapse Date:
Charge Level: Registered Non-Biological Medicines - Lower Charge

Standard Conditions of Approval:

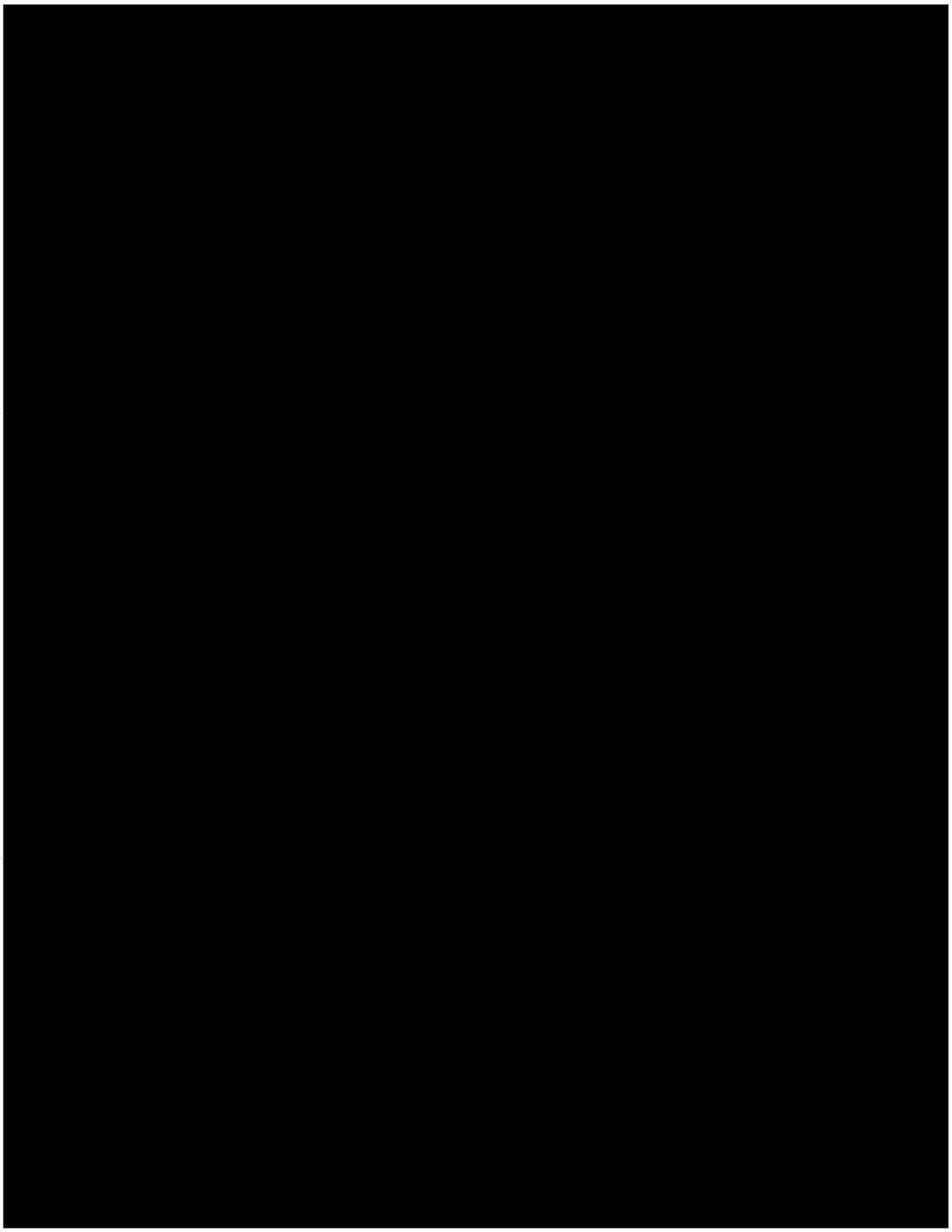
Conditions applicable to all therapeutic goods as specified in the document "Standard Conditions Applying to Registered or Listed Therapeutic Goods Under Section 28 of the Therapeutic Goods Act 1989" effective 1 July 1995.

Conditions applicable to the relevant category and class of therapeutic goods as specified in the document "Standard Conditions Applying to Registered or Listed Therapeutic Goods Under Section 28 of the Therapeutic Goods Act 1989" effective 1 July 1995.

MANUFACTURERS ASSOCIATED WITH ARTG ENTRY

MANUFACTURERS:

[redacted]



Summary of Comments on PAR PM-2017-03103-1-5.pdf

Page: 2

Number: 1 Author: Subject: Inserted Text Date: 13/08/2018 3:09:46 PM
21/10/2021

PRODUCT DETAILS

Product Name: BRALTUS tiotropium (as bromide) 13 microgram dry powder for inhalation hard capsule

Product ID: 591560

Product Status:

Product Type: Single Medicine Product

Grouping: No

Supplied In Australia:

ATC: Anticholinergics

Medicine Product Information: Package Insert
Consumer Medicine Information
Product Information
Primary Pack Label
Container Label

Non-standard Indications:

Indication	Provisionally Registered
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	No

Pack Size
30

Poison Schedule
(S4) Prescription Only Medicine

PRODUCT CONTAINER

Material	Closure	Container Condition	Time	Temperature	Condition
HDPE	Child resistant closure	Closed	24 Months	Store below 25 degrees Celsius	Store in Original Container

Shelf Life Additional Information: A shelf life of 24 months is proposed with a storage condition of Store below 25 degrees celsius

Container Type: Bottle

COMPONENT DETAILS

Product Name: BRALTUS tiotropium (as bromide) 13 microgram dry powder for inhalation hard capsule

Product ID: 591560

Component: BRALTUS tiotropium (as bromide) 13 microgram dry powder for inhalation hard capsule

Component ID: 500906

Dosage Form: Capsule, hard

Route of Administration: Inhalation

Visual Identification: BRALTUS capsules are colourless and transparent. The capsules contain a white powder.

COMPONENT FORMULATION

Active Ingredients	Quantity From	Quantity To	Category	Units	Additional Info
Tiotropium bromide	15.6		AAN	Microgram	
* Equivalent: tiotropium	13.0		AAN	Microgram	

Excipient Ingredients	Quantity From	Quantity To	Category	Units	Additional Info
lactose monohydrate	[redacted]		AAN	Milligram	

Animal Origin Species	Body Part	Part Text	Country	Endangered/Native
Bovine			Germany	No

Proprietary Ingredients	Quantity From	Quantity To	Category	Units	Additional Info
Vcaps The Vegetarian Alternative empty hard capsule size 3 (Natural/Natural)	1			Unit	Each capsule weighs 47.00 mg and is not ingested

Clinical Evaluation Report

Active substance: Tiotropium bromide

Product name: BRALTUS

Sponsor: Teva Pharma Australia Pty Ltd

Submission number: PM-2017-03103-1

eSubmission number:e002646

The errors of fact or omission identified in the evaluation report are summarized in the table below. The concerned section and paragraph have been identified and the correction has been proposed.

Section	Original text	Proposed text	Comments
Section 1.7.1. Formulation development (page 8 of 31)	"It has noted that the pilot PK study CLL11002 was a dose finding study..."	"It has noted that the pilot PK study CL11002 was a comparative bioavailability study"	Dose finding studies compare different strengths of a formulation comparing the efficacy/safety endpoints, but the mentioned study compares the bioavailability of the formulations regarding with PK endpoints
Section 3 (page 11 of 31)	The subsections "Distribution" and "Special populations" pharmacokinetic information which are present in the Spiriva HandiHaler Australian Product Information pharmacokinetics has been omitted.	It would be useful to also include information on "Distribution" and "Special populations".	
Section 3.1.1. (page 13 of 31)	Systemic bioequivalence. The AUC(0-t) units has not been included. The median Tmax should be used	For AUC(0-t) the units are pg*h/ml. The Test 1 median Tmax is 0.067 h, the	I would suggest to not include the SD of the median because the correct statistical descriptor is the inter-quartile rank, but is not usually reported.

	instead of mean Tmax as it represent better the endpoint.	Test 2 median Tmax is 0.067 and the Reference median Tmax is 0.033 h.	
Section 3.1.1. (page 15 of 31)	Safety "The aim of the study was not establish BE, rather to determine the right dose..."	Safety "The aim of the study was not establish BE, rather to determine the relative bioavailability..."	
Section 3.1.1. (page 17/18 of 31)	Safety "Cmax (3.67 vs 14.21) and AUC0-t (9.15 vs 35.03)..." "...inhalation techniques may also contribute..."	Safety "Arithmetic mean of Cmax (3.67 vs 3.64) and AUC0-t (9.15 vs 5.07)..." "inhalation techniques and adding placebo in the double dummy design"	The placebo lactose use concomitantly to the tiotropium, could compete with the tiotropium absorption and make the PK levels erratic.
Section 3.1.3. (page 18 of 31)	Study design "Wash out period was 10 days"	Study design "Real wash out period was 14 days"	It was reported in the final report of CLL13002 (page 56 of 161)
Section 5 (page 21 of 31)	"The pivotal BE demonstrated systemic bioequivalence of a 20 mcg dose of tiotropium"	"The pivotal BE demonstrated systemic bioequivalence of a 20 mcg delivered dose of tiotropium"	