



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Tiotropium

Proprietary Product Name: Braltus

Sponsor: Teva Pharmaceuticals Pty Ltd

June 2019

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<https://www.tga.gov.au>>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Common abbreviations

Abbreviation	Meaning
ADR	Adverse drug reaction
AE	Adverse event
AUC _{0-t}	Area under the drug concentration versus time curve until last measurable sampling time point
BE	Bioequivalence
CI	Confidence interval
C _{max}	Maximum measured concentration of drug
COPD	Chronic obstructive pulmonary disease
CV	Coefficient of variation
DHPC	Direct healthcare professional communication
DPI	Dry powder inhaler
EU	European Union
GMP	Good Manufacturing Practice
HCP	Health care provider
HPLC	High performance liquid chromatography
ICH	International Council on Harmonisation
LLQ	Lower limit of quantification
PI	Product Information
PK	Pharmacokinetic(s)
PD	Pharmacodynamic(s)
SAE	Serious adverse event
SD	Standard deviation
TGA	Therapeutic Goods Administration
t _{max}	Time to observe maximum drug concentration

Abbreviation	Meaning
$t_{1/2}$	Half life
XPRD	X-ray powder diffraction

I. Introduction to product submission

Submission details

Type of submission: New generic medicine

Decision: Approved

Date of decision: 31 October 2018

Date of entry onto ARTG: 15 November 2018

ARTG number: 293317

, Black Triangle Scheme No

Active ingredient: Tiotropium (as bromide)

Product name: Braltus

Sponsor's name and address: Teva Pharma Australia Pty Ltd

Locked Bag 2053

North Ryde BC NSW 1670

Dose form: Hard capsule

Strength: 13 µg

Container: Bottle

Pack size: 30

Approved therapeutic use: *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.*

Route of administration: Inhalation

Dosage: One capsule daily

Product background

This AusPAR describes the application by Teva Pharma Australia Pty Ltd (the sponsor) to register Braltus tiotropium bromide 13 µg for the following indication:

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.

This is a medicine therapeutically equivalent to Spiriva. This indication is the same as the TGA approved indication for Spiriva tiotropium 18 µg, powder for inhalation blister pack (ARTG 81525)

Tiotropium is a long-acting, specific anti-muscarinic (anticholinergic) agent.

The delivery device to be used with Braltus is called the Zonda device, and the device used for Spiriva is called a Handihaler device.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 15 November 2018

At the time the TGA considered this application; a similar application had been considered in the European Union (EU) via the decentralised procedure and had received a positive opinion on 24 June 2016.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Registration time line

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 1: Registration timeline for submission PM-2017-03103-1-5

Description	Date
Submission dossier accepted and first round evaluation commenced	9 October 2017
First round evaluation completed	10 April 2018
Sponsor provides responses on questions raised in first round evaluation	12 June 2018
Second round evaluation completed	14 August 2018
Delegate's Overall benefit-risk assessment.	19 September 2018
Sponsor's response to Delegate's Overall benefit-risk assessment	28 September 2018
Registration decision (Outcome)	31 October 2018
Completion of administrative activities and registration on ARTG	15 November 2018

Description	Date
Number of working days from submission dossier acceptance to registration decision*	224

*Statutory timeframe for standard applications is 255 working days

Evaluations included under Quality findings incorporate both the first and second round evaluations.

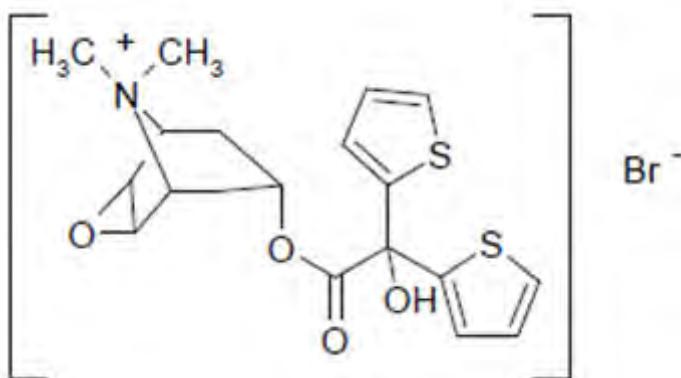
To establish therapeutic equivalence for orally inhaled products, the TGA uses the EU guidance framework.¹ This involves a stepwise approach involving psychochemical, pharmacokinetic, pharmacodynamic and clinical studies. It is a joint evaluation by the chemistry (quality) and clinical streams.

III. Quality findings

Drug substance (active ingredient)

Tiotropium bromide is made by chemical synthesis. There are known polymorphs of tiotropium bromide; the stated polymorphic form is manufactured consistently.

Figure 1: Structure of tiotropium bromide



Tiotropium bromide; methanol solvate is used in the manufacture of the product. It is dissolved and spray dried with lactose.

The drug substance is appropriately controlled by acceptable tests and limits for appearance, identity (high performance liquid chromatography (HPLC), bromides and X-ray powder diffraction (XPRD)), assay, related substances, heavy metals, water content, residual solvents and sulphated ash. Related substances and residual solvents have been controlled according to the International Council on Harmonisation (ICH) guidelines. The specifications are compliant with the British Pharmacopoeia monograph.

¹ CPMP/EWP/4151/00 Rev 1 Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for use in the treatment of asthma in children and adolescents

Excipients

Lactose monohydrate

Lactose monohydrate is the only excipient used in the drug product. Particle size was determined to be a critical parameter and as such is controlled.

Drug product

The proposed drug product consists of a capsule containing a blend of tiotropium bromide and lactose monohydrate and a single dose inhaler device. There is 13 µg tiotropium (as bromide) in each capsule. When used with the supplied inhaler device it is designed to deliver 10 µg tiotropium to the patient.

The capsules are packed in high density polyethylene (HDPE) bottles with a child resistant cap containing a desiccant. The bottles contain 30 capsules. The inhaler device is designed to only be used with this product and is to be discarded after 30 uses.

The manufacturing process involves spray drying the drug substance with lactose and filling the blend in empty capsule shells.

The finished product is appropriately controlled using the finished product specifications. The specifications include acceptable tests and limits for appearance, identity (HPLC and ultra violet), assay, content uniformity, water content, degradation products, mean delivered dose, uniformity of delivered dose, aerodynamic particle size, foreign particulate matter, amorphous content and microbial purity. All individual degradation products are controlled according to the ICH identification threshold (not more than (NMT) 1.0%), except for impurity G which has been qualified based on levels found in the reference product.

A shelf life of 24 months when stored below 25°C is recommended in the proposed container closure.

Biopharmaceutics

Section 5.2 of the guideline; outlines when *in vitro* data are sufficient to establish therapeutic equivalence for metered dose inhalation medicines. The target delivered dose of the test and reference products were similar, however, all of the criteria were not satisfied for the test product and so pharmacokinetic studies have been provided to demonstrate therapeutic equivalence. In these studies, 2 capsules of both the test and reference products are administered to healthy subjects (AUC_{0-t} ,² 101.3% to 111.6%; C_{max} ,³ 87.3% to 106.6%). These have been assessed in detail by the clinical evaluator.

IV. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

V. Clinical findings

A summary of the clinical findings is presented in this section.

² AUC_{0-t} : Area under the drug concentration versus time curve until last measurable sampling time point

³ C_{max} : Maximum measured concentration of drug

Introduction

Dosage forms and strengths

New medicine (Braltus)

Dosage form: Tiotropium bromide as powder for inhalation in a Zonda device.

Each hard Braltus capsule contains 13 µg tiotropium, equivalent to 15.6 µg tiotropium bromide and the excipient lactose monohydrate (which contains milk protein).

Reference medicine (Spiriva)

Dosage form: Tiotropium bromide monohydrate as powder for inhalation in a Handihaler device. Each hard gelatine Spiriva capsule contains 18 µg tiotropium, equivalent to 22.5 µg tiotropium bromide monohydrate and the excipient lactose monohydrate (which contains milk protein).

Figure 2: Zonda and Handihaler Dry Powder Inhaler devices



Formulation

Formulation development

The manufacturer utilised a spray dried formulation of tiotropium/lactose to achieve a stable form of tiotropium bromide

Active ingredient: Tiotropium 13 µg, equivalent to 15.6 µg of tiotropium bromide.

The quantity of active ingredient in the capsule is different to the innovator product Spiriva that contains 18 µg tiotropium, equivalent to 22 µg tiotropium bromide monohydrate. However, the delivered dose for both Braltus and Spiriva is the same at 10 µg. This was attributed to the manufacturing technique which resulted in a more efficient delivery of the delivered dose of tiotropium while achieving equivalent aerodynamic particle size distribution.

Excipients

Lactose monohydrate: 18 mg/capsule. This is quantitatively different to amount in the capsule of the same excipient in the innovator product.

Contents of the clinical dossier

The dossier was confined to bioequivalence comparison of the proposed and registered dose form, and contained the following:

- Bioequivalence studies
- Literature references.

Paediatric data

Paediatric data was not included in the dossier. Paediatric data is not required for establishing bioequivalence for generic medications.

Guidance

The relevant TGA adopted guidelines referred for the purpose evaluation of bioequivalence are:

- CPMP/EWP/QWP/1401/98 Rev. 1: Guideline on the investigation of bioequivalence.
- CPMP/EWP/239/95 final: Note for guidance on the clinical requirements for locally acting products containing known constituents.
- CPMP/ICH/363/96 Note for Guidance for statistical principles for clinical trials.
- CPMP/EWP/4151/00 Rev. 1 Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for the use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for the use in the treatment of asthma in children and adolescents.
- CHMP/EWP/2922/01 Rev.1 Guideline on the clinical investigation of medical products for the treatment of asthma. TGA standards and guidelines for prescription medicines: <http://www.tga.gov.au/publication/australian-regulatory-guidelines-prescription-medicines-argpm>. Local guidance 15 and 17.

The TGA uses a stepwise approach to the assessment of bioequivalence of inhaled medications. This includes reviewing information about physiochemical properties (quality), device (quality and clinical), pharmacokinetics, pharmacodynamics and where relevant; clinical studies.

The sponsor has stated that the guideline on the investigation of bioequivalence;⁴ and CPMP/EWP/4151/00 Rev. 1,⁵ were referred during product development.

Good clinical practice

The sponsor states that the clinical study reports in the submission state the studies complied with CPMP/ICH/135/95 Note for Guidance on Good Clinical Practice (as annotated with TGA comments).

Pharmacokinetics

Absorption

Tiotropium (as stated in Australian Spiriva PI).

⁴ CPMP/EWP/QWP/1401/98 Rev. 1: Guideline on the investigation of bioequivalence

⁵ CPMP/EWP/4151/00 Rev. 1 Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for the use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for the use in the treatment of asthma in children and adolescents

It is expected from the chemical structure of the compound that tiotropium is poorly absorbed from the gastro-intestinal tract. This was confirmed in a study in young healthy volunteers, with a low bioavailability of 2 to 3% for oral solutions. Food is not expected to influence the absorption of tiotropium for the same reason.

Following inhalation in young healthy volunteers, the absolute bioavailability was 19.5% that suggests that around 20% of inhaled drug reaches the lung. Being a dry powder inhaler (DPI), the rest of the inhaled powder would be deposited in upper airway and swallowed following inhalation.

Maximum tiotropium plasma concentrations were observed 5 to 7 minutes after inhalation (short t_{max}). At steady state, peak tiotropium plasma concentrations in patients with COPD were 12.9 pg/mL and decreased rapidly in a multi-compartmental manner. Steady state trough plasma concentrations were 1.71 pg/mL.

Metabolism

Metabolism does not occur to any great extent in young healthy volunteers. Approximately 74% of tiotropium is excreted in urine as unchanged after an intravenous dose.

Excretion

The effective half-life of tiotropium ranges between 27 to 45 hours following inhalation by patients with COPD. Total clearance was 880 mL/min after an intravenous dose in young healthy volunteers. Following inhalation of tiotropium by patients with COPD, urinary excretion is 7% (1.3 µg) of the unchanged dose over 24 hours, the remainder being mainly non-absorbed drug in the gut that is eliminated via the faeces. The renal clearance of tiotropium exceeds the creatinine clearance, indicating secretion into the urine. After chronic, once daily inhalation by patients with COPD, pharmacokinetic steady state was reached by Day 7, with no accumulation thereafter. Tiotropium demonstrates linear pharmacokinetics in the therapeutic range independent of the formulation.

Studies providing pharmacokinetic data

Study CLL11002

Primary objective: To assess the bioavailability of two different dry inhalation powder products, administered as test drugs (Test 1: Tiotropium 12 µg inhalation powder and Test 2: Tiotropium 18 µg inhalation powder), compared to reference drug (Spiriva 18 µg inhalation powder).

Secondary objective: To assess the safety of the preparations on the basis of adverse events and/or adverse drug reactions.

This was an open label, monocentric, randomised, single dose, three-period, crossover trial.

12 healthy subjects were recruited. A wash-out period of 7 days was observed between the subsequent study periods.

Subjects were administered with one oral inhalation (single dose) of 12 µg tiotropium (Test 1), 18 µg tiotropium (Test 2) and reference drug Spiriva. Drugs were administered under fasting conditions in 3 study periods, which was followed by blood samplings for analysis. Blood sampling was done at pre-dose and 0:02, 0:04, 0:06, 0:08, 0:10, 0:15, 0:30, 0:45, 1:00, 1:30, 2:00, 4:00, 6:00, 9:00, 12:00, 15:00 and 24:00 hours after the inhalation.

As the plan was to conduct descriptive statistics, no power calculation was performed to assess sample size. Twelve subjects completed all study periods according to the protocol.

To assess bioavailability, 90% confidence interval (CI) was calculated for intra-individual ratios of primary endpoints and was compared within acceptance ranges of 80 to 125%.

The sponsor states that these analyses were performed for the estimation of sample sizes for pivotal study. The effective half-life of tiotropium is 27 to 45 hours; hence, a wash out period of 7 days is not considered as adequate.

Tiotropium assay: The method of assay was liquid chromatography with a reversed phase column and tandem mass spectrometry detection (LC/MS/MS).

Primary endpoints: $AUC_{(0-t)}$ and C_{max} of tiotropium.

Secondary endpoint: t_{max} of tiotropium.

A descriptive and comparative statistical evaluation was performed for all study endpoints.

Safety outcome measures were adverse events (AEs) and/or adverse drug reactions (ADRs) during the study period.

Study CLL12003

This study was conducted to assess relative bioavailability of the test product (Braltus), in comparison with the reference product (Spiriva).

Primary objective: To assess the systemic exposure of one pre-dispensed test formulation containing 13 μ g tiotropium (as tiotropium bromide) Test, compared to Reference product (Spiriva) 18 microgram, inhalation powder.

Secondary objective: To evaluate AEs and assess safety of products.

Study design: Monocentric, randomized, single dose, double blind, double dummy, 3 way, semi replicate, crossover study in a two stage design with one interim analysis.

Wash-out period of 10 days was observed between study periods.

The primary endpoints in the present trial were $AUC_{(0-t)}$ and C_{max} of tiotropium.

The key secondary endpoint was t_{max} of tiotropium.

The trial was planned to be performed according to a two-stage design, with an interim analysis to determine whether bioequivalence has been established, and also to reconsider number of subjects required.

- Test product: Tiotropium 10 μ g delivered dose inhalation powder. 15.6 μ g tiotropium bromide equivalent to 13 μ g tiotropium per inhalation. The delivered dose is 10 μ g tiotropium. Device: Zonda inhaler.
- Reference product: Spiriva 18 μ g, inhalation powder. 22.5 μ g tiotropium bromide monohydrate equivalent to 18 μ g tiotropium per inhalation. The delivered dose is 10 μ g tiotropium. Device: Handihaler.

Study 3: CLL 13002 (Pivotal study)

Primary objective: To assess the systemic exposure of test formulation containing 13 μ g tiotropium with Zonda device (Test) compared to reference product Spiriva 18 μ g tiotropium inhalation powder with Handihaler device.

Secondary objective: To investigate safety of the preparations.

Study design: Monocentric, randomized, single dose, open, 3 way, semi replicate, crossover study in a two stage design with one interim analysis and sample size reassessment.

Healthy subjects were recruited. Wash out period was 10 days.

The trial was planned to be performed according to a two-stage design.

An interim evaluation of results was performed after the first 18 subjects completed all study periods. The interim evaluation of the results of the first 18 subjects revealed that a total sample size of 30 subjects (including the first group of 18 subjects) was needed for reaching a power of 90% for proving bioequivalence of both products. Therefore, 12 additional subjects were randomized in the 2nd stage of the trial.

The study used a higher dose (two capsules of test and reference products, that is, 20 µg of delivered dose) of tiotropium to achieve higher systemic concentration of tiotropium as in the previous studies many values were stated as below the lower limit of quantification (LLQ) of 0.5 pg/ml. In addition, the assay liquid chromatography with a reversed phase column and tandem mass spectrometry detection (LC/MS/MS) was improved and LLQ lowered from 0.5 to 0.2 pg/ml.

Evaluator's conclusions on pharmacokinetics

The absorption characteristics of tiotropium indicate a near complete absorption from the lung, which suggest that the pharmacokinetic (PK) parameters that were measured in these studies could be considered as surrogate measures of lung deposition. The PK parameters that were estimated in the pivotal study are within the acceptable range to establish bioequivalence.

In Studies CLL 11002 and CLL 12003, the sponsor was unable to demonstrate bioequivalence (BE) because of problems with high variability of the PK variables. Problems with assay and timing of the PK sampling around C_{max} would have contributed and were addressed in the third and pivotal study.

The pivotal study used a three way cross over design. This is appropriate and consistent with the guidelines.

Charcoal block was not utilised in the pivotal BE study. The sponsor has substantiated this approach by providing literature based evidence that suggest tiotropium is not absorbed in the gastrointestinal tract due to its electrical charge and hence its systemic availability is negligible. Moreover, the shorter mean t_{max} for tiotropium of (5 to 7 minutes) and higher C_{max} suggest systemic levels measured could be used as surrogate markers of lung deposition. In view of these facts, the sponsor's approach of not using charcoal block is considered acceptable.

The reference product and the device were manufactured in Germany and are not the same as that registered in Australia. The sponsor has provided studies that compared flow characteristics of Spiriva inhalers that are TGA registered and those that are registered in EU (used in studies in this submission). The quality report will be referred to ascertain comparability.

Pharmacodynamics

No studies to assess pharmacodynamic parameters were required as the PK studies were sufficient to establish bioequivalence.

Efficacy

Studies providing efficacy data

No studies to assess clinical efficacy and safety were required as the physiochemical and PK studies were sufficient to establish therapeutic equivalence.

Evaluator's conclusions on efficacy

The sponsor has not addressed whether the tiotropium bromide salt or tiotropium bromide monohydrate salt would have any difference in efficacy.

The pivotal bioequivalence study demonstrated systemic bioequivalence using a 20 µg delivered dose of tiotropium. This is likely to correlate with pulmonary delivery thus clinical efficacy and safety. Thus, extrapolation from the innovator in this regard is acceptable.

Tiotropium has a wide therapeutic index and there is a single dose recommendation for this product.

First round recommendation regarding authorisation

Further information is required before this application would be considered satisfactory for approval:

1. Is there any potential difference in metabolism, stability or receptor binding of the monohydrate form of tiotropium bromide versus tiotropium bromide?
2. Are the European and Australian reference product of acceptable comparability to accept the bioequivalence studies?
3. Is the handling of both devices the same?
4. Will patients need education to handle the new device?
5. What are the potential clinical consequences related to increased quantity of lactose as an excipient?

Since drug delivery from a dry powder inhaler (DPI) is largely dependent on flow rate that is required to activate the device, the flow rate characteristics in the targeted patient population is critical. The quality evaluation report on *in vitro* measures that assess flow characteristics in COPD patients will be examined to assess comparability in that aspect.

Clinical questions and second round evaluation

Pharmacokinetics

1. ***Please clarify the rationale for using two reference groups with the same dose in the pivotal Study CLL 13002.***

Sponsor's response

Two reference groups were included as a partially replicated study design was adopted for Study CLL13002 that facilitates estimation of intra-subject variability. Intra subject variability was 22.40% for C_{max} and 11.92% for AUC_{0-t} . Extent of variability in those results does not affect the bioequivalence limits established for this product which was the accepted range of 80.00 to 125.00%.

Evaluator's comment

Partial replicated study design with repeating reference product and scaling the bioequivalence for reference variability is an accepted methodology for drugs with high within subject variability. Orally inhaled products are known to have higher inherent

intra-subject variability. Sponsor's response is adequate and is in accordance with guideline on the investigation of bioequivalence.⁶ The intra-subject variability is less than 30% and hence the accepted CI range is suited for this study.

2. *The delivered dose is 10 mcg (same as Spiriva), in spite of the lower dose (13 µg versus 18 µg) in Braltus capsule. Please clarify how this is achieved?*

Sponsor's response

[Information redacted]. The sponsor claims that the difference in formulation of Braltus enables improved aerodynamic characteristics and thus greater efficiency. This is the reason for the same delivered dose achieved from Braltus for a lower quantity of tiotropium (13 µg), compared to Spiriva (18 µg).

Evaluator's comment

The sponsor's response is adequate. From a clinical perspective, the pivotal clinical study demonstrated comparable bioavailability and bioequivalence. No efficacy data was submitted. Considering the short t_{max} and high C_{max} , the bioequivalence data are considered as surrogate measures of lung disposition/efficacy of tiotropium.

Efficacy

3. *Please describe any impact that the extra quantity of lactose may have on efficacy and safety.*

Sponsor's response

The extra quantity of lactose in the tiotropium formulation is not considered to have an impact over safety. With the once daily administration, the maximum daily lactose exposition would be 17.74 mg, compared to 5.5 mg from Spiriva.

The sponsor has listed few inhalers that are approved in EU for the treatment of asthma and COPD that contain greater quantity of lactose/dose, when compared to Braltus. These are Foradil 12 µg (formoterol fumarate dehydrate as active pharmaceutical ingredient (API)) with 25 mg lactose/capsule. Foradil is administrated twice daily, thus the daily exposure is 50 mg of lactose. Onbrez breezehaler 150 µg (indacaterol as API contains 24.8 mg of lactose/capsule, with a daily exposure of 49.6 mg of lactose. Onbrez is approved by TGA for the indication of treatment of COPD.

The bioequivalence demonstrated in the study in terms of the rate and extent of absorption suggests that the excess amount of lactose has not interfered with lung disposition and thus efficacy. The adverse events reported from the BE study was in line with known safety profile of tiotropium.

Evaluator's comments

The sponsor's response is adequate. Lactose, as an excipient has been used in many other TGA approved DPIs used for similar indications. Based on the surrogate measures from BE study, the quantitative difference between the test and reference products does not appear to affect drug delivery and efficacy. No evidence of increased bronchial irritability and/or paradoxical bronchospasm was noted in subjects in Braltus group, compared to Spiriva group. Hence, from a clinical perspective, it does not appear to be an issue. PI and consumer medicine information (CMI) contain statements that clearly state the presence of lactose in the product.

⁶ CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** Guideline on the investigation of bioequivalence.

The sponsor has also provided a vegetarian option for capsules. The proprietary ingredient name is Vcaps, Proprietary Ingredient ID 10127. Vcaps are a new alternative to animal gelatine capsules. They are composed of inert vegetable cellulose. The quality evaluators' comments need to be referred for comparability of drug delivery between Vcaps and Braltus capsules.

4. Please describe the impact of different salt of tiotropium on efficacy and safety.

Sponsor's response

Tiotropium bromide methanol solvate is used in the manufacture of tiotropium dry powder inhaler. During manufacture it is transformed to tiotropium bromide. Therefore, tiotropium bromide is the API in the finished product which will reach the receptor in the bronchial smooth muscle. Similarly, tiotropium salt in the reference product is in the monohydrate form and the active drug that is delivered to the lung is tiotropium. Absolute solubility of tiotropium spray dried matrix (test) and tiotropium bromide monohydrate (reference) assessed by *in vitro* tests were comparable.

The dissolution profiles (extent and rate) across formulations were performed in a media that simulated lung fluid. Phosphate buffered saline at pH7.4 was chosen as the media. Both the test and reference drugs were dissolved in this media until saturation was achieved (approximately 25 to 30 mins).

Figure 3: Comparison of mean dissolution profile of fine particles of tiotropium between Braltus and Spiriva (as% dissolved of the fine fraction)



Evaluator's comment

Overall, the rate of dissolution of API in PBS appears comparable. The quality evaluator's report needs to be referred for final comments.

5. Comparability of Australian and European reference products.

Figure 4: Device comparison across reference products (Handihaler) and test product (Zonda inhaler)

[Information redacted]

Evaluator's comment:

From a clinical perspective, the similarity between devices is expected to be comparable for patients during transition from Braltus to Spiriva or vice versa.

The sponsor has performed *in vitro* studies to compare physical characteristics between EU and Australian reference products. The quality evaluator's concluded that these were acceptable.

PI and CMI

6. ***In spite of the same delivered dose, the lower dose in capsule (13 µg) of Braltus, compared to 18 µg in Spiriva raises the potential for medication errors (over dosage), when attempting to achieve the same dose. Please comment on risk mitigation strategies adopted in PI, CMI and label to address the difference in tiotropium dose in capsules in Braltus, compared to Spiriva.***

Sponsor's response

The dosage and administration section of PI has instructions to take one capsule once daily, rather than based on active drug content and/or delivered dose. Outer packaging and the container label also contains instructions to take one capsule as the recommended dose. The sponsor also states that the summary of bioequivalence study in the PI will be referenced, in case of any further queries. The sponsor has mentioned that the proposed educational material for health care providers (HCPs) will be aimed at providing information related to the bioequivalence between Braltus and Spiriva; in spite of the difference in the quantity of API. The sponsor has also mentioned their willingness to provide information about bioequivalence study in the CMI. The evaluator considers that this will be beyond the scope of CMI document.

Evaluator's comment

The indication expressed as 'one capsule once daily' instead of the quantity of API will clarify that the recommended dosages are identical between Braltus and Spiriva. However, the actual quantity of API will still be displayed on the carton and label and hence there is a potential for dosage errors. As recommended in the first round, the evaluator considers the inclusion of a statement in CMI as necessary: *Braltus is equivalent to Spiriva, with the same dosage of one capsule to be taken once daily. Do not take these drugs together.*

Second round benefit-risk assessment

- From a clinical perspective, the sponsor has adequately justified the difference in excipients and it does not seem to be having an impact on bio-equivalence between test and reference products. The quality evaluator's comments needs to be referred for comparability of physiochemical properties between test and reference products in order to determine the therapeutic equivalence between Spiriva and Braltus.
- The comparability of physical appearance of Spiriva and Braltus devices indicate that it is unlikely to have difficulty with handling for patients, when switching from one device to the other. However, the quality evaluator's comments related to comparability of critical dimensions and flow characteristics between devices need to be referred for final impression.
- The increased quantity of lactose does not appear to have significant clinical consequences related to API delivery and/or patient safety.

At this point in time, based on the clinical data in this submission, the evaluator has no major objections for recommendation of Braltus DPI for authorisation.

VI. Pharmacovigilance findings

Risk management plan

The Risk Management Plan (RMP) evaluation section provided advice that an RMP evaluation was not required for this generic submission. Consequently, no RMP has been submitted for evaluation. However, the RMP team was consulted to review the labelling and health care professional communication during the evaluation.

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).

As requested, the focus of the RMP review was on the adequacy of the proposed DHPC and package insert, with the understanding that the product that is considered to be therapeutically equivalent to the reference product.

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. The suggested inhalation techniques were similar for both products. However there were some 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. The 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 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:

1. planned delivery time frame;
2. how will the list of individual recipients be obtained to ensure the intended recipients are included; and
3. 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 advice⁷ from the RMP evaluator on the following matter:

The quality evaluator 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.

Proposed 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.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Background

Tiotropium is a long acting muscarinic agonist. It acts in the airway as a bronchodilator.

The innovator medicine is Spiriva (made by Boehringer Ingelheim). The innovator contains tiotropium bromide monohydrate as powder for inhalation in a Handihaler device. Each hard gelatine Spiriva capsule contains 18 µg tiotropium, equivalent to 22.5 µg tiotropium bromide (monohydrate) and the excipient lactose monohydrate.

Braltus contains tiotropium bromide as powder for inhalation in a Zonda device. Each hard Braltus capsule contains 13 µg tiotropium, equivalent to 15.6 µg tiotropium bromide and the excipient lactose monohydrate.

One inhalation of Braltus delivers the same dose as one inhalation on Spiriva. The lower dose of active drug in the Braltus capsule/device is due to a difference in the way the product is manufactured, which leads to more efficient drug delivery. The active drug

⁷ TGA Delegate request

reaching the lung with both devices is tiotropium bromide. The two devices have comparable air flow resistance and flow rate and a 4 Kpa pressure drop.

Tiotropium (Spiriva) was first registered in Australia in 2002. It is widely used in the management of COPD. Tiotropium is also available as a Respimat inhaler at a dose of 2.5 µg /inhalation. This is not bioequivalent to Spiriva.

Braltus has been approved in the EU in 2016.

Quality

The chemistry clearance document was provided.

There were no concerns with the drug substance specifications of the API manufacturer, the drug substance specifications of the finished product manufacturer, finished product specifications or shelf life.

The labelling was compliant with Therapeutic Goods Order 91; however suggestions were made to avoid medication confusion.

Good Manufacturing Practice (GMP) clearances were valid until 29 March 2019.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Pharmacology

The following studies were submitted.

Study CLL1102

This was a study to assess the bioavailability of two different inhalation powders, test 1 tiotropium 12 µg inhalation powder, and test 2 tiotropium 18 µg inhalation powder relative to the reference, Spiriva. The inhalation device used was the monodose device (not Zonda).

This was an open labelled, randomised, single dose, three period cross over study. Twelve subjects were recruited. The main endpoints were AUC, C_{max} , t_{max} and adverse events.

Neither inhalation formulation was bioequivalent to the reference inhaler. The upper 90% CI AUC of both formulations was over 125%. The lower 90% CI was less than 80% for both formulations. There was a high CV.

The results of this study assisted in the design of subsequent bioequivalent studies.

Study CLL12003

This study used a 13 µg dose of tiotropium in the Zonda inhaler. The design was a monocentric, randomized, single dose, double blind, double dummy, 3 way semi-replicate cross over study in a two stage design with one interim analysis. There was a wash out period of 10 days between doses. The primary endpoints were AUC and C_{max} . t_{max} was a secondary endpoint. This study used a wider confidence interval for bioequivalence based on the high CV of endpoints in Study CLL102. At the end of stage 1 of this study, the upper 90% CI for AUC was well above the specified range, and the upper and lower CI for C_{max} were beyond the specified range, stage 2 was not performed.

Study CLL13002

This study was similar to Study CLL12003, however the methodology was improved. It used a larger sample size (30 patients), higher dose of tiotropium (2 puffs) and an improved assay for tiotropium with lower LLQ. After the second phase of the study, the upper and lower confidence intervals for the AUC and C_{max} were within the acceptable range of 80 to 125%. Thus, the test product Braltus was considered bioequivalent to Spiriva.

None of these studies utilised a charcoal block or AUC0-30min. This was considered appropriate for tiotropium due to the near complete absorption from the lung and minimal absorption from the gastrointestinal tract (GIT).

The clinical evaluator had the following comments in relation to the PI:

1. With the difference in the quantity of API between Braltus and Spiriva, sponsor needs to mention at the beginning of the PI under the section: Name of the medicine: Braltus is a generic product of Spiriva (See *Braltus pharmacokinetic profile* under *Pharmacology*).
2. Describe about the comparability (therapeutic equivalence) of Braltus to Spiriva under '*Braltus pharmacokinetic profile*' heading as: The comparability of Braltus and Spiriva was made on the basis of findings related to their physiochemical, flow geometry, particle size and distribution and systemic bioequivalence study.
3. The sponsor needs to describe the Vcaps Braltus capsules in the presentation and storage section as:

'Each hard Braltus capsule contains and the excipient lactose monohydrate (which contains milk protein). Braltus is provided as Vcaps; a vegetarian alternative empty hard capsule size 3.

4. Under the dosage and administration section, for the benefit of Healthcare Practitioners, the sponsor needs to mention the availability of Braltus Vcaps as a vegetarian alternative.

The sponsor made changes to the PI as a result of the clinical evaluator's requests.

Risk management plan

An RMP evaluation was requested by the Delegate in view of the concerns about medication confusion with the different amount of medicine in the capsule and on the label for Braltus and Spiriva.

Recommendations of the RMP evaluator

The RMP evaluator had the following 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. The suggested inhalation techniques were similar for both products. However there were some 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 DHPC information 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 information. The following aspects should be included:

1. planned delivery time frame;
2. how will the list of individual recipients be obtained to ensure the intended recipients are included; and
3. 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 from the RMP evaluator on the following matter:

The quality evaluator 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 Dear HPC information 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.

Risk-benefit analysis

Delegate's considerations

The Delegate is satisfied that the delivered dose of the Spiriva and Braltus inhaler is bioequivalent and that Braltus could be considered therapeutically equivalent to Spiriva.

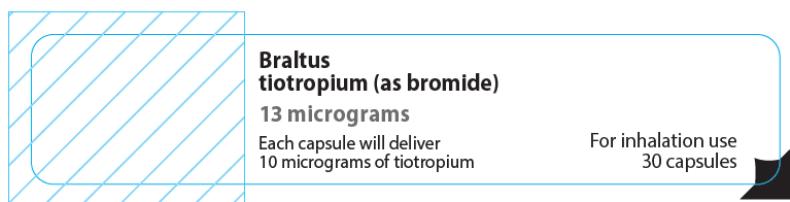
However, before this application can be approved, the following changes are required to the labelling, product information and health care provider letter to provide clarity over the differences in the two products.

Label

The Delegate has reviewed the labels on the carton and device that were sent in with the post second round evaluation response.

In relation to the carton, both the metered dose and delivered dose need to be clear (similar to this label below from the bottle).

Figure 5: Label for bottle for Braltus capsules



In relation to the bottle, it is unclear how each of the three labels will be displayed. Could the sponsor please clarify this?

Product Information

From version 13082018 v0.3:

- (page 4), Braltus pharmacokinetic profile:

For inhaled products, the amount of drug delivered is dependent upon the formulation and the device used. Please include the trade name and the name of the delivery device for the reference product.

- (page 19 and 1) Name

Please include the statement: 'Braltus is a generic version of Spiriva' and relocate the statement 'Braltus and Spiriva both deliver 10 micrograms of tiotropium bromide' from the Dosage and administration section to the name of medicine section. The Delegate acknowledges that this is not a usual requirement for a generic. However, Braltus has a number of features not typical of a generic.

- (Page 1 and 20) Vcaps

The description of the Vcap under presentation and description remains confusing. It reads as the Vcaps are an excipient. Please clarify that the outer capsule is known as a Vcap and describe what it is made of. Please clarify if the capsule shell is inhaled or remains in the device.

Health care provider letter

Please use metered dose rather than pre-metered dose for consistency.

Please respond to the RMP evaluator's recommendations.

CMI

Please respond to the RMP evaluator's recommendations.

Request for ACM advice

This submission was not referred to the ACM.

Response from sponsor***Label***

The sponsor has updated the labels to refer to the strength of the product as tiotropium (as bromide) 13 µg, 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 µg metered dose which is claimed to be bioequivalent to the sponsor's 13 µg 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 to TGO 91 Section 11(2)(h)).

The Delegate has been consulted regarding the labelling of the product and concurs that the delivered dose should be included on the labels.

Sponsor response:

The inclusion of the delivered dose has been included on the carton and label.

Product Information

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', for example 'Braltus Vcaps', instead of 'Braltus capsules' in order to emphasise that standard capsules (for example gelatin) are not available that Braltus is available only in Vcaps. 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. 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.)

Sponsor 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 have 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 been included in this response.

Advisory committee considerations⁸

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Braltus tiotropium (as bromide) 13 microgram powder for inhalation in hard capsule indicated for:

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.

Specific conditions of registration applying to these goods

- The actual date of commencement of supply is to be notified to the Head, Prescription Medicines Authorisation Branch, TGA. Should it be decided not to proceed to supply, notification to this effect should be provided.
- Post marketing reports are to be prepared annually until the period covered by such reports is not less than three years from the date of this approval letter. No fewer than three annual reports are to be prepared. The reports are to at least meet the requirements for Periodic Safety Update Reports (PSURs) as described in the European Medicines Agency's *Guideline on good pharmacovigilance practices (GVP) Module VII Periodic Safety Update Report* (Rev 1), Part VII.B. *Structures and processes*. Reports are to be submitted to the TGA only when requested in writing by the TGA. When requested, reports must be provided to the TGA within ten (10) calendar days. Preparation of the report must be completed within ninety calendar days of the datalock point for that report. An annual report may be made up of two PSURs each covering six months. Note that submission of a PSUR does not constitute an application to vary the registration.

⁸ The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines. The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

Attachment 1. Product Information

The PI for Braltus approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

Therapeutic Goods Administration

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<https://www.tga.gov.au>