

From: [REDACTED]
To: [REDACTED]
Cc: [REDACTED]
Subject: PM-2017-03103-1-5 - BRALTUS - Approval Document [SEC=UNCLASSIFIED]
Date: Wednesday, 31 October 2018 3:03:31 PM
Attachments: [EU5 S25 Approval document - tiotropium bromide BRALTUS - PM-2017-03103-1-5 \(Type D - new generic medicine\) - Teva Pharma Australia Pty Ltd - 31 October 2018.pdf](#)

Dear [REDACTED]

Find attached approval document for above submission for your consideration.

Note:

- Further enquiries should be made to the ARTG team.
- In line with the Government's digital transition policy, decision letters will now be signed electronically. **Where a letter has been signed electronically, hardcopy / paper copy will no longer be sent by post.** The decision letter for this submission has been signed electronically.

I will appreciate an email acknowledging receipt of this correspondence.

Do not hesitate to contact me if you have any questions on this matter.

Thank you

Regards

[REDACTED]

[REDACTED]

Prescription Medicines Authorisation Branch

[REDACTED]

Therapeutic Goods Administration

Department of Health
PO Box 100
Woden ACT 2606 Australia
www.tga.gov.au

This response is general information given to you without prejudice; it is not binding on the TGA and you should get your own independent legal advice to ensure that all of the legislative requirements are met.



Australian Government

Department of Health
 Therapeutic Goods Administration

The Managing Director
 Teva Pharma Australia Pty Ltd
 Locked Bag 2053
 NORTH RYDE BC NSW 1670

Submission No: PM-2017-03103-1-5
Clinical File: E17-28755
Chem File: E18-211908
RMP File: E18-343944
PI/CMI File: E18-357080

Attention: [REDACTED]
Senior Regulatory Affairs Associate

Dear Sir/Madam

I refer to the submission dated 30 August 2017, submitted on your behalf by [REDACTED] for the registration of the new generic medicine, BRALTUS containing tiotropium (as bromide) in the Australian Register of Therapeutic Goods (ARTG) under the provisions of the *Therapeutic Goods Act 1989* (the Act).

Evaluation of the submission (PM-2017-03103-1-5) under section 25 of the Act has now been completed and under section 25AB of the Act I am notifying you of my decision under subsection 25(3) of the Act to **approve the registration** of:

BRALTUS tiotropium (as bromide) 13 microgram powder for inhalation in hard capsule

The approved indications for this therapeutic good are:

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.

The application for registration of the generic tiotropium 13 microgram (as bromide) powder for inhalation in hard capsule delivering tiotropium 10 microgram included data that established to the TGA's satisfaction that the product can be considered bioequivalent to SPIRIVA tiotropium 18 micrograms (as bromide monohydrate) powder for inhalation (in hard capsule) delivering tiotropium 10 microgram sponsored by Boehringer Ingelheim Pty Ltd.

This approval is based on the evaluation of the information and data provided with the original letter of application and with any subsequent correspondence and submissions relating to the application.

Before the good can be included in the Register, you are required to provide a certificate required under subsection 26B(1) of the Act.

The patent certificate can be downloaded via the TGA website (<http://www.tga.gov.au/about/international-usa-fta.htm>). You should send the completed and signed certificate quoting the submission number to the attention of Application Support Team, Prescription Medicines Authorisation Branch, TGA at the address on the footer of this letter. Alternatively, please send a copy by return facsimile message to (02) 6232 8140 or email ast.application.support.team@tga.gov.au. As noted above, a Certificate of Registration can only be issued after receipt of the completed and signed patent certificate.

The text of the Product Information (PI) as set out in the version (16102018 v 0.5) provided with your email correspondence of 17 October 2018 and presented at **Attachment 1** is approved under subsection 25AA(1) of the Act.

For the product approved in this submission, the:

- Product Information document approved by the TGA must be lodged with the TGA **within 2 weeks** of the date of registration of the product, and
- related Consumer Medicine Information (CMI) document must be lodged with the TGA prior to supply of the product.

The documents must be lodged in the TGA eBusiness Services system (eBS) - information on how to lodge these documents is available at www.ebs.tga.gov.au.

Note that documents lodged must be in text PDF format – please be aware that scanned PDF documents will not be accepted by the system.

Registration commences on the day specified in the ARTG. ARTG Certificates will be available for downloading from the eBS Web Site (<https://www.ebs.tga.gov.au/>) the day following the entry being written to the ARTG; however, the therapeutic product cannot be written to the ARTG until the Sponsor has furnished the TGA with the appropriate patent certificate.

The good must conform to the manufacturing and product details provided at **Attachment 2**. These details will be included among those in the computerised database of the ARTG.

Supply of the approved therapeutic good is not permitted until it is registered.

You must ensure that the name and contact details of the person responsible for fulfilling your pharmacovigilance reporting requirements have been provided to the TGA and remain correct. Any change to the pharmacovigilance contact person details must be notified within 15 calendar days. Further information regarding your pharmacovigilance obligations can be found in the Australian requirements and recommendations for pharmacovigilance responsibilities of sponsors of medicines (see <https://www.tga.gov.au/australian-requirements-and-recommendations-pharmacovigilance-responsibilities-sponsors-medicines>).

If you have not already done so, please provide a Certified Product Details (CPD) document which includes the finished product release and expiry specifications and the approved test methods for the finished products within one month of the date of this letter (see <http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm>). The CPD document should be submitted in an electronic format, either on disc or as attachment in an email, to evaluation.support@tga.gov.au.

Conditions of Registration

Under subsection 28(2B) of the Act I am imposing the following conditions on registration in relation to this product:

- a. Conditions applicable to all registered 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 (see **Attachment 3**);
- b. Conditions applicable to specific classes of registered therapeutic goods as specified in the *Standard Conditions Applying to Registered or Listed Therapeutic Goods under Section 28 of the Therapeutic Goods Act 1989* effective 1 July 1995 (see **Attachment 3**);
- c. Conditions listed in **Attachment 4**.

As part of the standard conditions of registration applying to all registered therapeutic goods it should be noted that, no changes can be made to the goods without the prior approval of the TGA.

Under paragraph 30(2)(c) of the Act, refusal or failure to comply with a condition of registration to which inclusion of the medicine in the ARTG is subject may result in the suspension or cancellation of registration.

Other Matters

- a. In accordance with regulation 9A of the Therapeutic Goods Regulations 1990 (the Regulations), a patient information document (Consumer Medicines Information - CMI) must be supplied with the goods and be provided to a person to whom the goods are to be administered or otherwise dispensed in such a manner as defined by the subregulation 9A(2). The format of the CMI is set out in Schedule 12 of the Regulations. The CMI (BRALTUS ZONDA V0.4) submitted with your email correspondence of 28 September 2018 is considered to meet the format as set out in Schedule 12.

There is a continuing obligation to ensure that at all times the CMI complies with the statutory requirements, including consistency with the PI. If the related CMI document needs to be changed as a consequence of the change to the approved PI, it must be lodged with the TGA **within 2 weeks** of the date of the changed PI. In the case of changes relating to the safety or safe use of the product, more rapid change of the CMI may be warranted.

- b. The labels for this product have not been checked for consistency with any State and Territory labelling requirements that may be applicable. You should ensure compliance with such requirements.
- c. If your product contains an active or excipient that is produced by a genetically modified organism, the Office of the Gene Technology Regulator should be informed when supply commences. The address is:

The Office of the Gene Technology Regulator
GPO Box 9848
Canberra ACT 2601

- d. The National Director of Pharmaceutical Services, Department of Veterans' Affairs, would like to be provided with a copy of the approved PI for this product. Please consider providing a copy to:

National Director of Pharmaceutical Services
Department of Veterans' Affairs
GPO Box 9998
In Your Capital City

Request for reconsideration of an initial decision

This decision is a reviewable initial decision under section 60 of the Act. Under section 60, a person whose interests are affected by a 'reviewable' initial decision, can seek reconsideration of the initial decision.

As this document constitutes written notice of the making of an initial decision being given by the Secretary, a request for reconsideration of this initial decision must be given to the Minister within 90 days and be accompanied by any information that you wish to have considered. A request for reconsideration given to the Minister outside the statutory 90 day reconsideration period cannot be accepted.

The Minister may either personally undertake a request for reconsideration of an initial decision or delegate to an officer of the Department with the appropriate delegation.

Under section 60(3A) of the Act, the Minister (or the Minister's delegate) is not able to consider any information provided after the notification is made of a request for reconsideration of an initial decision unless the information is provided in response to a request from the Minister (or the Minister's delegate), or it is information that indicates that the quality, safety or efficacy of the relevant therapeutic goods is unacceptable.

Guidelines for requesting reconsideration of an initial decision

A request for reconsideration should be made in writing, signed and dated by the person requesting reconsideration, should be titled "**<insert person/company name> - Request for Reconsideration Under Section 60 of the *Therapeutic Goods Act 1989***" and should include the following:

- a copy of the initial decision notification letter (or other evidence of notification);
- identify, and describe with as much specificity as possible, which component(s) of the initial decision should be reconsidered and set out the reasons why reconsideration is requested;
- any information/documentation in support of the request, clearly labelled to correspond with (any or each of) the reasons why reconsideration is requested; and
- an email address nominated for the purposes of receiving correspondence in relation to the request for reconsideration.

All requests for reconsideration should be given to the Minister by email:

Email: **'minister.hunt.DLO@health.gov.au'** and copied to **'decision.review@health.gov.au'**

Requests for reconsideration that include dossiers (or similar bulk material) that cannot easily be attached to the request given first by email, may then be submitted on a USB drive or CD sent by express post or registered mail to:

Mail: **Minister for Health**
Suite M1 40
c/- Parliament House
CANBERRA ACT 2600

Subject to the *Administrative Appeals Tribunal Act 1975* (AAT Act), if you are dissatisfied with the decision upon reconsideration by the Minister (or the Minister's delegate), you can apply to the Administrative Appeals Tribunal (AAT) for a review of that decision upon reconsideration.

NOTE: This initial decision remains in effect unless and until it is revoked or revoked and substituted by the Minister (or the Minister's delegate) as a result of a request for reconsideration under section 60 of the Act OR is set aside, varied or remitted by the AAT or is otherwise overturned or stayed.

Yours sincerely,

Signed and authorised by

[Redacted Signature]

Delegate of the Secretary

[Redacted Name]

Prescription Medicines Authorisation Branch

Email:

[Redacted Email Address]

31 October 2018

Attachments

1. Approved Product Information for BRALTUS.
2. Manufacturing and Product Details to which the Good Must Conform.
3. *Standard Conditions Applying to Registered or Listed Therapeutic Goods Under Section 28 of the Therapeutic Goods Act 1989.*
4. Specific Conditions Applying to this Therapeutic Good.

AUSTRALIAN PRODUCT INFORMATION – BRALTUS® (TIOTROPIUM [AS BROMIDE]) POWDER FOR INHALATION, HARD CAPSULE

1 NAME OF THE MEDICINE

Tiotropium (as tiotropium bromide)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

BRALTUS® tiotropium (as bromide) powder for inhalation, hard capsule. The drug product must be inhaled with the ZONDA® device.

BRALTUS is a generic version of SPIRIVA. Each capsule of BRALTUS and SPIRIVA delivers 10 micrograms of tiotropium and are equivalent.

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

Excipient(s) with known effect: lactose monohydrate.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

BRALTUS powder for inhalation in capsules.

Each hard BRALTUS capsule contains 13 micrograms tiotropium, equivalent to 15.6 micrograms tiotropium bromide.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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.

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended dosage of BRALTUS is inhalation of the contents of one capsule, once daily with the ZONDA device, at the same time each day (see ZONDA instructions for use, in the patient information leaflet provided in each pack of BRALTUS).

The delivered dose (the dose that leaves the mouthpiece of the ZONDA inhaler) is 10 micrograms of tiotropium per capsule.

BRALTUS capsules must not be swallowed.

Do not place a BRALTUS capsule directly into the mouthpiece.

Special populations:

Elderly patients can use BRALTUS at the recommended dose.

Renally impaired patients can use BRALTUS at the recommended dose. However, as with all predominantly renally excreted drugs, tiotropium use should be monitored closely in patients with moderate to severe renal impairment (see Section 5.2 Pharmacokinetic properties).

Hepatically impaired patients can use BRALTUS at the recommended dose.

Paediatric population:

There is no experience with tiotropium in infants, children or adolescents and therefore should not be used in this age group.

Method of administration:

To ensure proper administration of the medicinal product, the patient should be trained in the use of the inhaler by either the prescribing physician or by other healthcare professionals.

The ZONDA inhaler is especially designed for BRALTUS capsules; patients must not use it to take any other medication.

BRALTUS capsules must only be inhaled using the ZONDA inhaler. Patients must not use any other inhalers to take BRALTUS capsules.

The ZONDA inhaler should only be used with the bottle of capsules provided. Do not reuse the inhaler for another bottle of capsules. Discard the ZONDA device after 30 uses.

The capsule shell is not inhaled and remains in the device.

4.3 CONTRAINDICATIONS

BRALTUS is contraindicated in patients with a history of hypersensitivity to tiotropium bromide, atropine or its derivatives, e.g. ipratropium or oxitropium or to any other component of this product (see Section 6.1 List of excipients).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Tiotropium, as a once daily maintenance bronchodilator, should not be used for the treatment of acute episodes of bronchospasm, i.e. rescue therapy.

Immediate hypersensitivity reactions may occur after administration of tiotropium.

As with other anticholinergic drugs, tiotropium should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction. In a meta-analysis of placebo-controlled trials, tiotropium was associated with a non-significant increase in the risk of urinary retention, and a significant increase in the risk of micturition difficulties.

Inhaled medicines may cause inhalation-induced bronchospasm.

Tiotropium should be used with caution in patients with recent myocardial infarction <6

months; any unstable or life threatening cardiac arrhythmia or cardiac arrhythmia requiring intervention or a change in drug therapy in the past year; hospitalisation of heart failure (NYHA Class III or IV) within the past year. These patients were excluded from the clinical trials and these conditions may be affected by the anticholinergic mechanism of action.

As with all predominantly renally excreted drugs, tiotropium use should be monitored closely in patients with moderate to severe renal impairment (creatinine clearance of ≤ 50 mL/min) (see Section 5.2 Pharmacokinetic properties). Tiotropium should be used only if the expected benefits outweigh the potential risk. There is no long term experience in patients with severe renal impairment.

Patients must be instructed in the correct administration of tiotropium. Care must be taken not to allow the powder or spray to enter into the eyes. Eye pain or discomfort, blurred vision, visual halos or coloured images in association with red eyes from conjunctival congestion and corneal oedema may be signs of acute narrow-angle glaucoma. Should any combination of these symptoms develop specialist advice should be sought immediately. Miotic eye drops are not considered to be effective treatment.

Dry mouth which has been observed with anticholinergic treatment, may in the long term be associated with dental caries.

An increase in anticholinergic effects may occur with increasing age.

BRALTUS should not be used more frequently than once daily (see Section 4.8 Overdose).

BRALTUS capsules are to be used only with the ZONDA[®] device (see Section 4.2 Dose and method of administration).

This product contains 18 mg of lactose monohydrate per capsule. The excipient lactose may contain trace amounts of milk proteins. Care should be taken with those with severe hypersensitivity or allergy to milk protein.

Use in hepatic impairment

There are no data on the use of tiotropium in patients with hepatic impairment. As tiotropium is primarily cleared by renal mechanisms, no dosage adjustment is recommended. However patients should be monitored closely.

Use in renal impairment

Renally-impaired patients can use BRALTUS at the recommended dose. However, as with all predominantly renally excreted drugs, BRALTUS use should be monitored closely in patients with moderate to severe renal impairment. For patients with moderate to severe renal impairment - see Section 5.2 Pharmacokinetic properties.

Use in the elderly

Elderly patients can use tiotropium at the recommended dose. Renal clearance of tiotropium is likely to be slower in elderly patients (see Use in Renal Impairment).

Paediatric use

The safety and effectiveness of tiotropium in paediatric patients or adolescents under 18 years of age has not been established. Therefore, BRALTUS should not be used in these patients.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Although no formal drug interaction studies have been performed, tiotropium has been used concomitantly with other drugs which are commonly used in the treatment of COPD, including sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids without clinical evidence of drug interactions.

Common concomitant medications (LABA, ICS and their combinations) used by patients with COPD were not found to alter the exposure to tiotropium.

Limited information about co-administration of other anticholinergic medicines with tiotropium is available from a clinical trial. The concomitant use of tiotropium with other anticholinergic agents (e.g. glycopyrronium, aclidinium, umeclidinium, ipratropium) is expected to have additive anticholinergic effects. Acute single dose administration of ipratropium bromide monohydrate after 19 days of tiotropium treatment in healthy volunteers (n=35) was not associated with relevant changes in vital signs or electrocardiographic findings. Adverse events were reported by 3 (9%) of subjects in the study during ipratropium treatment with tiotropium compared to 1 (3%) during placebo treatment with tiotropium. Ipratropium was associated with a 16% decrease in salivary secretions in healthy volunteers. Chronic co-administration of other anticholinergic medicines with tiotropium has not been studied and is therefore not recommended.

4.6 FERTILITY, PREGNANCY AND LACTATION**Effects on fertility**

Clinical data on fertility are not available for tiotropium. Tiotropium (as bromide) did not affect the fertility of male or female rats when administered by inhalation at doses up to 2 mg/kg (750x the maximum recommended human daily dose of 22.5 µg, based on body surface area).

Use in pregnancy – Pregnancy Category B1

There is a limited amount of data from the use of tiotropium in pregnant women. Reproductive toxicity studies with tiotropium bromide administered by inhalation to rats and rabbits at doses up to 2.0 and 0.5 mg/kg/day, respectively, produced no evidence of fetal malformations. These doses correspond to 750x and 400x the maximum recommended human daily dose of 22.5 microgram based on body surface area. Animal studies do not suggest direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant doses.

As a precautionary measure, it is preferable to avoid the use of tiotropium during pregnancy.

Use in lactation

Clinical data from lactating women exposed to tiotropium are not available. Based on studies in lactating rats, a small amount of tiotropium is excreted in breast milk.

Therefore, tiotropium should not be used in lactating women unless the expected benefit outweighs any possible risk to the infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. The occurrence of dizziness or blurred vision may influence the ability to drive and use machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Many of the listed undesirable effects can be assigned to the anticholinergic properties of tiotropium.

Adverse drug reactions were identified from data obtained in clinical trials and spontaneous reporting during post approval use of the drug. The clinical trial database includes 9,647 tiotropium patients from 28 placebo-controlled clinical trials with treatment periods ranging between four weeks and four years, contributing 12,469 person years of exposure to tiotropium.

Frequency is defined using the following convention:

Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

System Organ Class / MedDRA Preferred Term	Frequency
<u>Metabolism and nutrition disorders</u>	
Dehydration	Not known
<u>Nervous system disorders</u>	
Dizziness	Uncommon
Headache	Uncommon
Taste disorder	Uncommon
Insomnia	Rare
<u>Eye disorders</u>	
Vision blurred	Uncommon
Glaucoma	Rare
Intraocular pressure increased	Rare
<u>Cardiac disorders</u>	
Atrial fibrillation	Uncommon
Palpitations	Rare
Supraventricular tachycardia	Rare
Tachycardia	Rare
<u>Respiratory, thoracic and mediastinal disorders</u>	
Cough	Uncommon
Dysphonia	Uncommon
Pharyngitis	Uncommon
Epistaxis	Rare
Bronchospasm	Rare
Laryngitis	Rare
Sinusitis	Rare
<u>Gastrointestinal disorders</u>	
Dry Mouth, usually mild	Common
Constipation	Uncommon
Oropharyngeal candidiasis	Uncommon
Gastroesophageal reflux disease	Uncommon
Dysphagia	Rare
Gingivitis	Rare
Glossitis	Rare
Stomatitis	Rare
Nausea	Rare

Intestinal obstruction, including ileus paralytic	Rare
Dental caries	Very Rare
<u>Skin and subcutaneous tissue disorders, immune system disorders</u>	
Rash	Uncommon
Pruritus	Rare
Angioneurotic oedema	Rare
Urticaria	Rare
Hypersensitivity (including immediate reactions)	Rare
Skin infection/skin ulcer	Not known
Dry skin	Not known
Anaphylactic reaction	Not known
<u>Musculoskeletal and connective tissue disorders</u>	
Joint swelling	Not known
<u>Renal and urinary disorders</u>	
Urinary retention (usually in men with predisposing factors)	Uncommon
Dysuria	Uncommon
Urinary tract infection	Rare

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

High doses of tiotropium may lead to anticholinergic signs and symptoms.

However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 282 micrograms tiotropium in healthy volunteers. Additionally, no relevant adverse effects, beyond dry mouth, were observed following 7 day dosing of up to 141 micrograms tiotropium in healthy volunteers. In a multiple dose study in COPD patients, with a maximum daily dose of 36 micrograms tiotropium over four weeks, no significant undesirable effects were observed.

Acute intoxication by inadvertent oral ingestion of tiotropium powder is unlikely, due to low oral bioavailability.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Other drugs for obstructive airway diseases, inhalants, anticholinergics; ATC code: R03BB04

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Tiotropium is a long-acting, specific antimuscarinic (anticholinergic) agent. It has similar affinity to the muscarinic receptor subtypes M₁ to M₅ (K_D 5-41 pM). In the airways, inhibition by tiotropium of M₃-receptors at the smooth muscle results in relaxation. The competitive and

reversible nature of antagonism was shown with human and animal origin receptors. In non-clinical *in vitro* as well as *in vivo* studies, bronchoprotective effects were dose dependent. Bronchoprotective effects lasting at least 24 hours were observed in some of the *in vivo* studies. The long duration of effect of tiotropium is likely to be due to its slow dissociation from M₃-receptors. Tiotropium exhibited a significantly longer dissociation half-life from M₃ receptors than ipratropium.

Tiotropium, a N-quaternary anticholinergic agent, is topically (broncho-) selective when administered by inhalation. The high potency (IC₅₀ approximately 0.4 nM for M₃) and slow receptor dissociation is associated with a significant and long-acting bronchodilation in patients with chronic obstructive pulmonary disease (COPD). The bronchodilation following inhalation of tiotropium is primarily a local effect on the airways, not a systemic one.

Cardiac electrophysiology

In a dedicated QT study involving 53 healthy volunteers, a dispensed dose of 18 micrograms of tiotropium and a dispensed dose of 54 micrograms of tiotropium over 12 days did not significantly prolong QT intervals of the ECG.

The pharmacokinetic studies conducted using BRALTUS (13 micrograms tiotropium) have demonstrated bioequivalence to the reference product containing a dispensed dose of 18 micrograms tiotropium (see ***BRALTUS pharmacokinetic profile***).

Clinical trials

The reported clinical studies are those of the innovator reference product. Bioequivalence has been demonstrated between BRALTUS (13 micrograms tiotropium) and the innovator reference product (18 micrograms tiotropium). *In vitro* studies have demonstrated that the same delivered dose of tiotropium is obtained from BRALTUS (13 micrograms tiotropium) in combination with the ZONDA device when compared against the innovator inhalation product (18 micrograms tiotropium).

Additionally, an investigation was conducted to assess inspiratory flow rates achieved using the ZONDA device. Two separate studies were performed, the first one in COPD patients and the second one in Healthy Volunteers, using the inhalation device of the innovator product compared to the ZONDA device.

Inhalation profile study in COPD patients

A total of 50 patients with moderate (FEV₁ (forced expiratory volume in 1 second) = 50-79% predicted) (n =26), severe (FEV₁ = 30-49% predicted) (n=18) or very severe ((FEV₁<30% predicted) (n = 6) COPD were randomised and completed the study comparing the ZONDA device and the innovator's dry powder inhaler. Each participant was asked to carry out two inhalations through each dry powder inhaler. The peak inhalation flow, maximum pressure change, inhalation volume, time of inhalation, time to reach the PIF (T_{peak} in sec) and the acceleration rate were measured. The study was conducted with empty capsules.

The majority of patients were able to achieve peak flow rates between 30 and 60 L/min for both devices. The inhalation parameters of the ZONDA device were significantly higher (p<0.001) than those of the innovator reference product with respect to peak inhalation flow,

pressure change and acceleration rate.

Inhalation profile study in Healthy Volunteers

Fifty healthy volunteers (26 females and 24 males) completed an open label, randomised study using a ZONDA device and the innovator dry powder inhaler. Their ages ranged from 20 to 55 years and their FEV₁ % predicted values ranged from 80.0% to 118.0%. The study was conducted with empty capsules. The results show that the numerical differences in the inhalation parameters of the ZONDA and the innovator's dry powder inhaler are only small and not likely to affect the emitted dose. All peak inhalation flows were above 30L/min and with the inhaled volumes being greater than 1 litre, there would not be any issues for both devices with respect to dose emission, therefore concluding that pharmacokinetic crossover studies would be consistent for both devices.

Clinical efficacy

The pivotal clinical development program consisted of four one-year randomised, double-blind studies; two placebo-controlled and two with an active control (ipratropium) in 1456 COPD patients, 906 of which received tiotropium. The studies assessed lung function in terms of forced expiratory volume in one second (FEV₁), forced vital capacity (FVC) and peak expiratory flow rate (PEFR). Health outcome measures including dyspnoea, exacerbations, hospitalisations and health-related quality of life (as measured by the St George's Respiratory Questionnaire, SGRQ) were also assessed. In addition, the development program included two large trials of six months duration which compared the bronchodilator efficacy and safety of tiotropium, with salmeterol inhalation aerosol and placebo in patients with COPD. These two studies randomised a total of 1207 patients, with approximately one-third treated with tiotropium.

Lung function

Overall results from the four one-year studies demonstrated that tiotropium, administered once daily, provided significant improvement in lung function (FEV₁ and FVC) within 30 minutes following the first dose and that this improvement was maintained for 24 hours. Pharmacodynamic steady state was reached within one week, with near maximal bronchodilation observed by the third day. Tiotropium significantly improved morning and evening PEFR as measured by the patient's daily recordings. The bronchodilator effects of tiotropium were maintained throughout the one-year period of administration with no evidence of tolerance.

In the two one-year, randomised, double blind, placebo-controlled studies, 550 patients received tiotropium once daily and 371 patients received placebo. Mean differences in FEV₁ between tiotropium and placebo were highly statistically significant at all time points ($p < 0.0001$). The mean trough FEV₁ at Day 92 (defined as the primary efficacy endpoint) was 0.14 L greater following tiotropium than placebo ($p < 0.0001$) and remained significantly different from placebo throughout the one year observation period ($p < 0.0001$). The FVC response generally paralleled that of FEV₁.

In the two one-year, randomised, double blind, ipratropium-controlled studies, 356 patients received tiotropium once daily and 179 patients received ipratropium, 2 puffs of 20

micrograms, four times a day. Mean differences in trough FEV₁ between tiotropium and ipratropium were highly statistically significant at all time points ($p < 0.0001$). The mean trough FEV₁ on Day 92 was 0.14 L greater following tiotropium than ipratropium ($p < 0.0001$). The FVC response generally paralleled that of FEV₁.

Long-term clinical trials (6 months and 1 year)

Dyspnoea, Exercise tolerance

In the one-year trials, tiotropium significantly improved dyspnoea in patients, as evaluated using the Mahler Transitional Dyspnoea Index (TDI) and patient daily reported symptoms. Following treatment with tiotropium, the dyspnoea score improved significantly when compared to placebo, with changes in each domain, as well as the focal score, being highly statistically significant over one year ($p < 0.0002$). The proportion of patients treated with tiotropium who achieved a TDI focal score change of at least 1 point over the one-year period, representing a clinically meaningful difference, was statistically greater than the proportion of patients treated with placebo ($p < 0.0001$).

When compared to ipratropium, patients treated with tiotropium exhibited significantly less dyspnoea at each time point, and the proportion of patients achieving a difference of 1 point in the TDI focal score was significantly greater in the tiotropium group.

The impact of improvement in dyspnoea on functional activities was investigated in two randomised, double-blind, placebo-controlled, parallel group studies in 433 COPD patients. The studies investigated whether six weeks treatment with tiotropium once daily improves exercise tolerance in patients with COPD as measured by symptom-limited exercise endurance time (ET) during constant work rate cycle ergometry at 75% of maximal work capacity. Results demonstrated that tiotropium significantly improved ET by 20% to 28% compared with placebo. Increases in ET (seconds) are shown in Table 1.

Additionally in these trials, tiotropium demonstrated significant reductions in lung hyperinflation at rest and significant reductions in lung hyperinflation and dyspnoea during constant work rate cycle exercise.

Table 1: Endurance time (ET) after 42 days treatment with tiotropium vs placebo in patients with COPD

Study	Pre-treatment	Adjusted mean ET		Treatment Difference	p-value
	Baseline ET	Tiotropium	Placebo	tio – placebo at 42 days	
Trial A	492	640	535	105	0.0098
Trial B	537	741	577	164	0.0002

Health related quality of life

The SGRQ was the primary instrument used to evaluate disease-specific health related quality of life, with the impact domain stated as the primary endpoint. Tiotropium was significantly more effective than both placebo and ipratropium in improving health-related quality of life based on the SGRQ. The percentages of patients in the tiotropium groups who demonstrated

a clinically meaningful improvement (pre-specified criteria of 4 units) over baseline were significantly greater than those in the placebo and ipratropium groups.

Tiotropium was more effective than placebo in each domain. Generally, the difference between the treatment groups increased between baseline and the last treatment visit. For the primary measure, Impacts score, the difference between the two treatment groups ranged from 1.8 to 4.0 and was statistically significant ($p < 0.05$) on all test days.

A significantly greater ($p < 0.05$) percentage of patients in the tiotropium group showed a clinically meaningful improvement (drop of 4 units) in the Impacts score from six months through to the end of the study and for Total score from three months through to the end of the study.

Tiotropium was also shown to be more effective than ipratropium in improving health-related quality of life using the SGRQ. For Impacts score, the difference between the two treatment groups in the mean score ranged from 0.6 at 8 days to 4.3 at 364 days and was statistically significant from three months through the end of the study. Statistically significant differences between tiotropium and ipratropium were also noted for the Total score on four of six test days.

A significantly greater ($p < 0.05$) percentage of patients in the tiotropium group showed clinically meaningful improvement (difference greater than 4 units) in both Impacts and Total scores over ipratropium after six months.

Two trials of six months duration compared the bronchodilator efficacy and safety of tiotropium once daily with salmeterol inhalation aerosol (50 micrograms twice daily) and placebo in patients with COPD. In one study, designed to evaluate the 12-hour duration of action, when the effects over time for tiotropium and salmeterol were compared, the mean trough FEV_1 in the tiotropium group was significantly higher than that in the salmeterol group ($p < 0.05$), beginning on day 57. The difference between tiotropium and salmeterol for trough, average and peak FEV_1 response was statistically significant ($p < 0.05$), except for trough response on day 15, and average and peak FEV_1 response on day 1. At the end of the study, trough FVC had improved in the tiotropium group significantly above the placebo ($p < 0.001$) and the salmeterol ($p < 0.01$) groups. At the end of the combined six months trials, the improvement in TDI focal scores for tiotropium above placebo was 1.1 units ($p < 0.001$), which was both statistically and clinically significant, and for salmeterol above placebo was 0.7 units ($p < 0.05$), which was not clinically significant.

COPD exacerbations

In the analysis of the pooled data from the four one-year studies, tiotropium significantly reduced both the number of COPD exacerbations and the number of hospitalisations associated with COPD exacerbations. In addition, time to first COPD exacerbation and to first hospitalisation associated with a COPD exacerbation was significantly prolonged.

In the placebo-controlled trials, the percentage of patients with at least one exacerbation during the treatment period was 36% in the tiotropium group and 42% in the placebo group ($p = 0.03$); at least one hospitalisation for exacerbation occurred in 5.5% and 9.4% of patients

respectively ($p=0.019$). The number of exacerbations and hospitalisations associated with exacerbations (expressed as events per 100 patient years) were significantly fewer for patients treated with tiotropium compared to placebo ($p=0.045$ and $p=0.019$ respectively). Patients on tiotropium also spent significantly fewer days in hospital for exacerbations compared to placebo ($p=0.023$). The time to first exacerbation was significantly delayed in the tiotropium group relative to placebo ($p=0.011$). Overall, these data indicate that therapy with tiotropium is associated with a delayed onset and a lower incidence of COPD exacerbations.

In the ipratropium-controlled trials, the percentage of patients with an exacerbation during the treatment period was 35% in the tiotropium group and 46% in the ipratropium group, a difference that was statistically significant. A similar trend was seen for hospitalisations for exacerbation (7.3% vs. 11.7%; $p=0.108$). The number of exacerbations and exacerbation days impacted by these events was also less in the tiotropium group compared to ipratropium ($p=0.006$ and $p=0.002$, respectively). A similar trend was observed for hospitalisations ($p=0.0803$) and hospitalisation days for exacerbations ($p=0.86$). The time to first exacerbation, as well as for hospitalisation for exacerbation, was significantly delayed in the tiotropium group relative to the ipratropium group ($p=0.008$ and 0.048 , respectively). Overall these data indicate that tiotropium is associated with reduced exacerbations.

Tiotropium significantly reduced the percentage of patients experiencing one or more COPD exacerbations compared with placebo in a six-month randomised, double-blind, placebo-controlled trial of 1,829 patients with COPD (27.9% vs. 32.3%, respectively, $p=0.0368$). The mean number of exacerbations per patient-year was significantly lower in the tiotropium group compared to placebo (0.85 vs. 1.05, respectively, $p=0.003$), as was the number of exacerbation days ($p<0.0001$). Time to first exacerbation was significantly increased in the tiotropium group compared to placebo (relative risk=0.834, $p=0.034$). Fewer tiotropium patients were hospitalised because of COPD exacerbation (7.0% vs. 9.5%, respectively; $p=0.056$), although this difference was not statistically significant. The number of hospitalisations for exacerbations per patient-year was significantly lower in the tiotropium group, compared to placebo ($p=0.013$). Similarly, the mean number of hospitalisations days for exacerbations was lower in the tiotropium group compared to placebo (1.43 vs 1.70 days per patient-year, $p=0.0013$). The time to first hospitalisation for an exacerbation was significantly increased in the tiotropium group compared to placebo (relative risk=0.723, $p\leq 0.05$). See Figure 1.

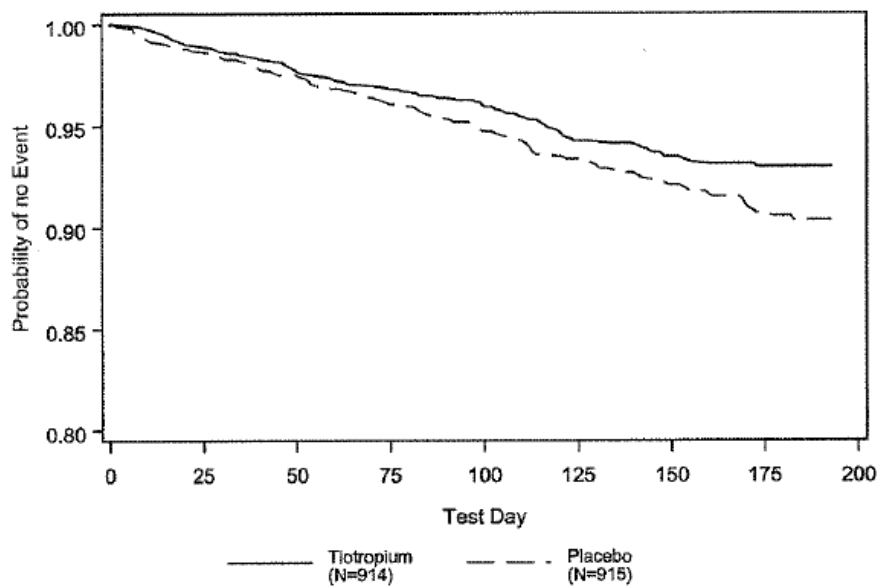


Figure 1: Kaplan-Meier estimates of the probability of no hospitalisation due to COPD exacerbation.

A one-year randomised, double-blind, double-dummy, parallel-group trial compared the effect of treatment with 18 micrograms of tiotropium once daily with that of 50 micrograms of salmeterol HFA pMDI twice daily with the primary endpoint time to first moderate or severe exacerbation in 7,376 patients with COPD and a history of exacerbations in the preceding year (74.6% of treated patients were men, 99.6% white, and 48.1% current smokers; the mean age was 62.9 years and the mean FEV₁ was 49.3% predicted). The treatment groups were balanced with respect to demographics, COPD characteristics, pulmonary medication use at baseline, and concomitant diagnoses. Patients were allowed to continue their usual medications for COPD, except for anticholinergic drugs and long-acting β 2-agonists, during the double-blind treatment phase. Short-acting β 2-agonists were also permitted, as necessary, as rescue medications for acute relief of COPD symptoms.

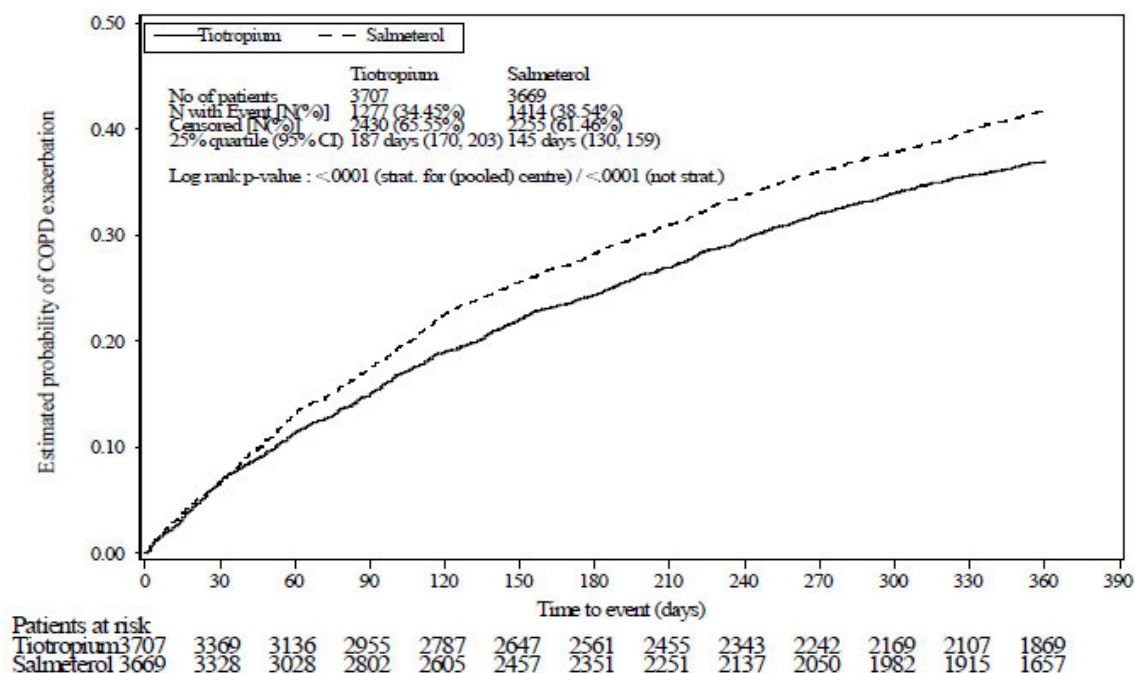


Figure 2: Kaplan-Meier estimates of the time to the first COPD exacerbation / Treated Set

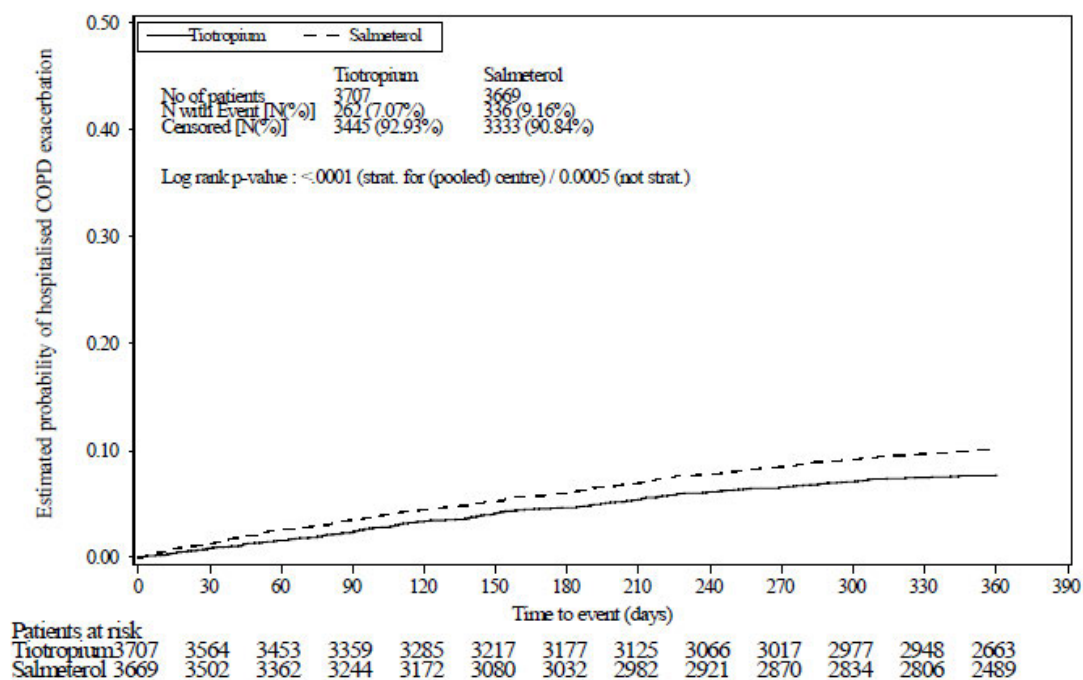


Figure 3: Kaplan-Meier estimates of the time to the first hospitalised COPD exacerbation/Treated Set

Table 2: Summary of exacerbation endpoints

Endpoint	Tiotropium 18 microgram (Dry Powder Inhaler) N = 3,707	Salmeterol 50 microgram (HFA pMDI) N = 3,669	Ratio (95% CI)	p-value
Time [days] to first exacerbation [†]	187	145	0.83 (0.77 - 0.90)	<0.001
Time to first severe (hospitalised) exacerbation [§]	-	-	0.72 (0.61 - 0.85)	<0.001
Patients with ≥ 1 exacerbation, n (%) [*]	1,277 (34.4)	1,414 (38.5)	0.90 (0.85 - 0.95)	<0.001
Patients with ≥ 1 severe (hospitalised) exacerbation, n (%) [*]	262 (7.1)	336 (9.2)	0.77 (0.66 - 0.89)	<0.001
Mean exacerbation incidence rate per patient year [#]	0.64	0.72	0.89 (0.83 - 0.96)	=0.002
Mean severe (hospitalised) exacerbation incidence rate per patient year [#]	0.09	0.13	0.73 (0.66 - 0.82)	<0.001

[†] Time to event analysis was done using Cox's proportional hazards regression model with (pooled) centre and treatment as covariate; ratio refers to hazard ratio. Number in column 2 and 3 denote the time in days to first exacerbation for the 1st quartile of patients on tiotropium experiencing an exacerbation and the 1st quartile of patients on Salmeterol experiencing an exacerbation, respectively.

[§] Time to event analysis was done using Cox's proportional hazards regression model with (pooled) centre and treatment as covariate; ratio refers to hazard ratio. Time [days] for the 1st quartile of patients cannot be calculated, because proportion of patients with severe exacerbation is too low.

^{*} Number of patients with event were analysed using Cochran-Mantel-Haenszel test stratified by pooled centre; ratio refers to risk ratio.

[#] Number of event analysis was done using Poisson regression correcting for overdispersion and adjusting for treatment exposure; ratio refers to rate ratio.

Compared with salmeterol, tiotropium increased the time to the first exacerbation (187 days vs. 145 days), with a 17% reduction in risk (hazard ratio, 0.83; 95% CI, 0.77 to 0.90; $P < 0.001$). Tiotropium also increased the time to the first severe (hospitalised) exacerbation (hazard ratio, 0.72; 95% CI, 0.61 to 0.85; $P < 0.001$), reduced the annual number of moderate or severe (hospitalised) exacerbations (0.64 vs. 0.72; rate ratio, 0.89; 95% CI, 0.83 to 0.96; $P = 0.002$), and reduced the annual number of severe (hospitalised) exacerbations (0.09 vs. 0.13; rate ratio, 0.73; 95% CI, 0.66 to 0.82; $P < 0.001$).

Long-term clinical trials (<1 up to 4 years)

In a 4-year trial of 5,993 patients, tiotropium did not alter the annualised rate of decline of FEV₁ (primary endpoint), but maintained improvements in the secondary endpoint of the difference in FEV₁ at clinic visits throughout 4 years (Figure 4).

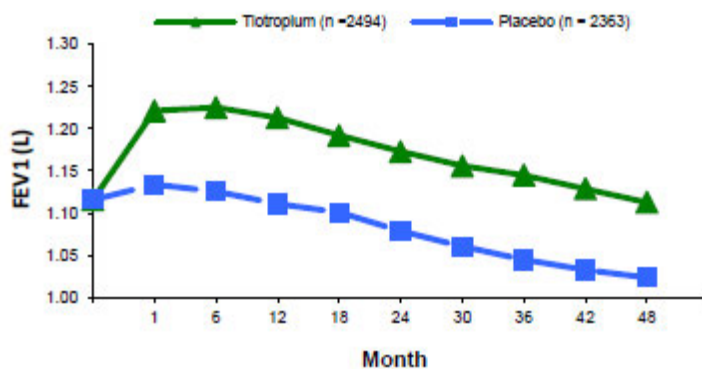


Figure 4: Morning pre-dose FEV₁ (i.e. trough) in the tiotropium and placebo groups over 4 years. $P < 0.001$ for all post-randomisation time points.

A significantly higher proportion of patients in the tiotropium group than in the placebo group had an improvement of ≥ 4 units in the secondary endpoint of SGRQ total scores (i.e. exceeded the minimal clinically important difference) from baseline at 1 year (49% vs. 41%), 2 years (48% vs. 39%), 3 years (46% vs. 37%), and 4 years (45% vs. 36%) ($p < 0.001$ for all comparisons).

In the following secondary endpoints, tiotropium significantly delayed the time to the first exacerbation and significantly delayed the time to the first hospitalisation for an exacerbation. The Hazard Ratios (95% confidence interval [CI]) for an exacerbation or exacerbation leading to hospitalisation were 0.86 (0.81, 0.91) and 0.86 (0.78, 0.95), respectively. Tiotropium was also associated with a reduction in the mean number of exacerbations of 14% ($p < 0.001$). The mean numbers of exacerbations leading to hospitalisations were infrequent and did not differ significantly between the tiotropium and placebo groups.

During treatment, there was a 16% reduction in the risk of death. The incidence rate of death was 4.79 per 100 patient years in the placebo group vs. 4.10 per 100 patient years in the tiotropium group (hazard ratio (tiotropium/placebo) = 0.84, 95% CI = 0.73, 0.97).

For the 4-year, protocol-defined study period up to day 1440, the effect of tiotropium extended

to end of treatment period. Among patients for whom vital-status information was available (95% of patients), 921 patients died: 14.4% in the tiotropium group and 16.3% in the placebo group (hazard ratio, 0.87; 95% CI, 0.76 to 0.99). During a period of 4 years plus 30 days (1470 days) included in the intention-to-treat analysis, 941 patients died: 14.9% in the tiotropium group and 16.5% in the placebo group (hazard ratio, 0.89; 95% CI, 0.79 to 1.02). Fewer vital status data were available for the day 1470 analyses (75% of patients). The effect became non-significant within the 30-day follow-up period, when according to protocol, patients were discontinued from their study medication.

Long-term tiotropium active-controlled study

A long term, large scale, randomised, double-blind, active-controlled study with an observation period up to 3 years has been performed to compare the efficacy and safety of tiotropium inhalation spray 2.5 micrograms and tiotropium powder for inhalation 18 micrograms (5,711 patients receiving tiotropium 2.5 micrograms (2 puffs comprise one medicinal dose of 5 micrograms); 5,694 patients receiving tiotropium 18 micrograms). The primary endpoints were time to first COPD exacerbation, time to all-cause mortality and in a sub-study (906 patients) trough FEV₁ (pre-dose).

The time to first COPD exacerbation was similar during the study with tiotropium inhalation spray 2.5 microgram and tiotropium powder for inhalation 18 micrograms (hazard ratio (tiotropium 2.5 micrograms/tiotropium 18 micrograms) 0.98 with a 95% CI of 0.93 to 1.03). The median number of days to the first COPD exacerbation was 756 days for tiotropium 2.5 micrograms and 719 days for tiotropium 18 microgram.

The bronchodilator effect of tiotropium 2.5 micrograms was sustained over 120 weeks, and was similar to tiotropium 18 micrograms. The mean difference in trough FEV₁ for tiotropium 2.5 micrograms versus tiotropium 18 micrograms was -0.010 L (95% CI -0.038 to 0.018 L).

All-cause mortality was similar during the study with tiotropium 2.5 micrograms and tiotropium 18 micrograms (hazard ratio (tiotropium 2.5 micrograms / tiotropium 18 micrograms) 0.96 with a 95% CI of 0.84 to 1.09).

5.2 PHARMACOKINETIC PROPERTIES

Tiotropium is a non-chiral quaternary ammonium compound and is sparingly soluble in water. Tiotropium is administered by dry powder inhalation. Generally with the inhaled route of administration, the majority of the delivered dose is swallowed and deposited in the gastrointestinal tract, and to a lesser extent is delivered to the lungs.

Absorption

Following inhalation in young healthy volunteers, the absolute bioavailability of 19.5% suggests that the proportion reaching the lung is highly bioavailable. The bioavailability is the apparent bioavailability, which is dependent upon the amount of tiotropium that is effectively inhaled. 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 2-3% for oral solutions. Food is not expected to

influence the absorption of tiotropium for the same reason. Maximum tiotropium plasma concentrations were observed 5 - 7 minutes after inhalation. 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.

Distribution

Studies in rats have shown that tiotropium does not penetrate the blood-brain barrier to any relevant extent. Tiotropium has a plasma protein binding of 72% and shows a volume of distribution of 32 L/kg.

Metabolism

Metabolism does not occur to any great extent in young healthy volunteers, as indicated by 74% renal excretion of unchanged drug after an intravenous dose. The major metabolic pathway is non-enzymatic ester cleavage to the alcohol N-methylscopine and dithienylglycolic acid that are inactive on muscarinic receptors.

In vitro metabolism: In studies in animals and in vitro experiments with human liver microsomes and hepatocytes, minor amounts of a variety of glutathione conjugates, after oxidation of the thiophene rings, were observed. In vitro studies in human liver microsomes revealed that the enzymatic pathway, relevant for only a small amount of tiotropium metabolism, can be inhibited by cytochrome P450 (CYP) 2D6 inhibitor quinidine and CYP 3A4 inhibitors ketoconazole and gestodene.

Tiotropium, even in supra-therapeutic concentrations, does not inhibit CYP 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1 or 3A in human liver microsomes.

Excretion

The effective half-life of tiotropium ranges between 27 to 45 h following inhalation by patients with COPD. Total clearance was 880 mL/min after an intravenous dose in young healthy volunteers. Urinary excretion of unchanged substance in young healthy volunteers is 74% of an intravenous dose. Following inhalation of tiotropium by patients with COPD to steady state, urinary excretion is 7% (1.3 microgram) 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.

Special populations:

Elderly Patients:

As expected for all predominantly renally excreted drugs, advancing age was associated with a decrease of tiotropium renal clearance (365 mL/min in patients with COPD < 65 years to 271 mL/min in patients with COPD > 65 years) This did not result in a corresponding increase in AUC_{0-6,ss} or C_{max,ss} values.

Renally Impaired Patients:

Following once daily inhaled administrations of tiotropium to steady-state in patients with COPD with mild renal impairment (CL_{CR} 50-80 mL/min) resulted in slightly higher $AUC_{0-6,ss}$ (between 1.8 – 30% higher) and similar $C_{max,ss}$ values compared to patients with COPD with normal renal function (CL_{CR} >80 mL/min). In patients with COPD with moderate to severe renal impairment (CL_{CR} <50 mL/min), the intravenous administration of tiotropium resulted in a doubling of the plasma concentrations (82% increase in AUC_{0-4h}) and 52% higher C_{max} compared to patients with COPD with normal renal function, which was confirmed by plasma concentrations after dry powder inhalation.

Hepatically Impaired Patients:

There are no data on the pharmacokinetics of tiotropium in hepatic impairment. Liver insufficiency is not expected to have any relevant influence on tiotropium pharmacokinetics. Tiotropium is predominantly cleared by renal elimination (74% in young healthy volunteers) and by simple non-enzymatic ester cleavage to products that do not bind to muscarinic receptors.

BRALTUS pharmacokinetic profile

In a bioequivalence study, BRALTUS (13 micrograms tiotropium) in combination with the ZONDA device was evaluated by comparing it against the innovator inhalation product, SPIRIVA (18 micrograms tiotropium) in combination with the HANDIHALER device, containing the same delivered dose of the active substance. BRALTUS (13 micrograms tiotropium) was shown to be bioequivalent to SPIRIVA (18 micrograms tiotropium) in terms of rate and extent of systemic availability.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Tiotropium (as bromide) did not exhibit any genotoxic effects in assays for gene mutation (bacteria and mammalian cells in vitro and in vivo mouse micronucleus test) or DNA damage (rat hepatocytes in vitro).

Consideration should be given to lower initial loading and maintenance doses in patients >65 years and careful monitoring for the development of hypotension when up titrating the maintenance dose (see Section 4.2 Dose and method of administration).

Carcinogenicity

Long-term carcinogenicity studies in mice and rats, with tiotropium (as bromide) administered by inhalation, showed no evidence of neoplastic responses. The highest doses studied were approximately 0.8x (male mouse), 38x (female mouse) and 16x (rat) greater than the maximum recommended human daily dose of 22.5 microgram, based on body surface area.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

BRALTUS capsules contain lactose monohydrate. The outer capsule shell is known as a Vcap - The Vegetarian Alternative empty hard capsules size 3 (Natural/Natural) (Ingredient ID 10127).

6.2 INCOMPATIBILITIES

See Section 4.5 Interactions with other medicines and other forms of interactions.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

In-use shelf life

Discard the ZONDA device after 30 uses. Do not reuse the inhaler for another bottle of capsules. There is a ZONDA inhalation device provided with each box of BRALTUS capsules.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

BRALTUS capsules for inhalation - Store below 25°C. Keep the bottle tightly closed. Store in the original package to protect from moisture. Do not refrigerate or freeze. Avoid storage in direct sunlight or heat.

6.5 NATURE AND CONTENTS OF CONTAINER

BRALTUS capsules are presented in HDPE bottles with a child resistant HDPE closure containing desiccant. The pack contains a ZONDA inhalation device. The ZONDA inhaler has a green body and a cap with a white push button.

Available in cartons containing a bottle of 30 capsules and the ZONDA device.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

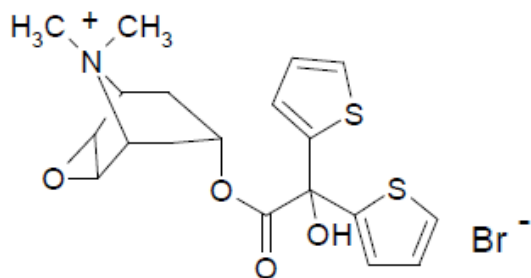
Tiotropium bromide methanol solvate is used in the manufacture of BRALTUS capsules. It is spray dried with lactose where the methanol solvate is evaporated and transformed to tiotropium bromide. Therefore tiotropium bromide is the Active Pharmaceutical Ingredient (API) in the finished product.

Tiotropium bromide is a white to yellowish-white, odourless crystalline powder. It exists as a quaternary ammonium salt, and there are no ionisable functional groups on the molecule. The active substance is not optically active.

Tiotropium bromide is freely soluble in dimethyl sulphoxide, soluble in methanol, sparingly soluble in water and practically insoluble in methylene chloride. The solubility in aqueous solutions at room temperature is approx. 2.5%, independent of pH. At pH 7.4, the apparent partition coefficient ($\log P_{app}$) is -2.25.

Chemical structure

Structural formula:



Chemical name: (1 α ,2 β ,4 β ,5 α ,7 β)-7-[(Hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo [3.3.1.0^{2,4}] nonane bromide

Molecular formula: C₁₉H₂₂NO₄S₂Br

Molecular weight: 472.412

CAS number

CAS number: 136310-93-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4).

8 SPONSOR

Teva Pharma Australia Pty Ltd

37 Epping Road

Macquarie Park NSW 2113

Email: au.teva@tevapharm.com

Phone Number: 1800 288 382

Website: www.tevapharma.com.au

9 DATE OF FIRST APPROVAL

XX XX XX

10 DATE OF REVISION

XX XX XX

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information

Label Name:	BRALTUS tiotropium (as bromide) 13 microgram powder for inhalation hard capsule	Provisional ARTG Number:	293317
Sponsor:	Teva Pharma Australia Pty Ltd	Sponsor ID:	61006
Agent:	[REDACTED]	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

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



PRODUCT DETAILS

Product Name:

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

Product ID: 591560

Product Type:

Single Medicine Product

Product Status:

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 Protect from Moisture Do not Refrigerate Keep Container Tightly Closed/Airtight

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 powder for inhalation hard capsule

Product ID: 591560

Component:

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

Component ID: 500906

Dosage Form:

Capsule, hard

Route of

Inhalation

Administration:

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			AAN	Milligram	
<div><div>Animal Origin</div><div><div>Species</div><div>Body Part</div><div>Part Text</div><div>Country</div><div>Endangered/Native</div></div><div><div>Bovine</div><div></div><div></div><div>Germany</div><div>No</div></div></div>					
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



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Attachment 3

Conditions – standard and specific

Applying to registered or listed therapeutic goods
under Section 28 of the Therapeutic Goods Act
1989

Standard – July 1995
Specific – March 1998

TGA Health Safety
Regulation



About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- 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.

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STANDARD CONDITIONS

Applying to registered or listed therapeutic goods under Section 28 of the *Therapeutic Goods Act 1989* (Effective 1 July 1995)

For the purposes of these conditions, words used in any of the paragraphs set out below shall have the same meaning as their counterparts in the *Therapeutic Goods Act 1989*. Unless otherwise specified, references to the 'Act' shall be a reference to the *Therapeutic Goods Act 1989*, as amended from time to time, and references to the 'Regulations' shall be to the Therapeutic Goods Regulations as amended from time to time. A reference to 'registered goods' or 'listed goods' shall be a reference to the goods included in the Certificate of Registration or the Certificate of Listing, as the case may be.

APPLYING TO ALL REGISTERED OR LISTED THERAPEUTIC GOODS

1 Standards

The registered/listed goods must comply with standards applicable to those goods under part 2 of the Act;

2 Changes to Goods

Changes or variations in respect of any information concerning the registered or listed therapeutic goods, being information that would have been relevant* to a decision to register/list the goods in the Register, including information on the formulation of the registered/listed goods or other aspects of their manufacture, and the labelling of the goods, shall forthwith be notified to the Secretary, or the Secretary's delegate appointed for the purposes of section 28 of the Act, and where necessary*, the change or variation shall not be implemented until approved by the Secretary. (*Reference should also be made to Appendix *Changes to Therapeutic Goods*)

3 Australian Manufacturers

The Australian manufacturer or manufacturers of the registered/listed goods, and any subcontractor or testing facilities in Australia contracted to, or otherwise engaged to, manufacture the registered/listed goods, must be appropriately licensed to carry out the manufacture, or a step in the manufacture, of the goods or the class of therapeutic goods within which the registered/listed goods are included, unless otherwise exempted under the Act from the need to comply with such a requirement.

4 Records Held

The sponsor of the registered/listed goods shall keep such records relating to the goods as are necessary:

- (a) to expedite recall if necessary of any batch of the registered/listed goods;
- (b) to identify the manufacturer(s) of each batch of the registered/listed goods.

Where any part of or step in the manufacture in Australia of the registered/listed goods is sub-contracted to a third party who is not the sponsor, copies of relevant Good Manufacturing Practice agreements relating to such manufacture shall be kept.

5

Each sponsor shall retain records of the distribution of all of the sponsor's registered/listed goods for a period of five years and upon the request of the National Manager, Therapeutic Goods Administration, shall provide the records or copies of the records to the National Manager.

6 Sampling

The sponsor of the registered/listed goods shall permit officers who have been authorised under the Regulations to do so to take samples of therapeutic goods and carry out related duties in accordance with the Regulations.

7 Overseas Regulatory Actions

Where the registered/listed goods are distributed regularly overseas as well as in Australia, product recall or any actions other similar regulatory action taken in relation to the goods outside Australia which has or may have relevance to the quality, safety or efficacy of the goods distributed in Australia must be notified to the National Manager, Therapeutic Goods Administration immediately the action or information is known to the sponsor.

8 Date of Supply

The sponsor of the registered/listed goods shall advise the National Manager, Therapeutic Goods Administration (through the Operations Manager, Australian Register of Therapeutic Goods) of the date of initial supply of those goods.

LISTED THERAPEUTIC GOODS

9 Indications

In relation to listed goods, the sponsor must have and shall retain, while the goods remain listed, evidence necessary to substantiate and support the accuracy of the indications in relation to the listed goods and, upon the request of the Director, Chemicals & Non Prescription Drug Branch, or Director, Conformity Assessment Branch, Therapeutic Goods Administration, shall produce such evidence to the Director.

CONDITIONS APPLYING TO ALL REGISTERED OR LISTED DRUGS

10 Labels (see also condition 2)

A copy¹ of the label or, if more than one label, labels to be used in respect of the registered/listed drugs shall be provided to the National Manager, Therapeutic Goods Administration (through the Operations Manager, Australian Register of Therapeutic Goods), upon:

- (a) the commencement of the supply of the registered/listed drugs; and
- (b) request by the National Manager.

- 1 Where practicable actual labels should be provided attached to a sheet of paper which identifies the product by its Registration/Listing Name and Number. Photocopies (actual size) are acceptable where the label information is printed or embossed directly onto the container.

11 Registration/Listing Number

The registration or listing number shall be placed on the label of the registered/listed drugs in accordance with the requirements of the Therapeutic Goods Act 1989 and in the manner prescribed in the Regulations.

12 Expiry dates

The sponsor shall not supply the registered/listed drugs after the expiry date of the goods.

13 Colouring

Colouring agents used in registered/listed drugs for ingestion, other agents than those listed for export only, shall be only those included in the list of "Colourings for Use in Pharmaceuticals for Ingestion" issued by the National Health and Medical Research Council in November 1988 as amended from time to time.

14 Adverse reactions

All reports of adverse reactions or similar experiences associated with the use or administration of the registered/listed drugs shall be notified to the National Manager, Therapeutic Goods Administration, as soon as practicable after the sponsor of the goods becomes aware of those reports. Sponsors of drugs must retain records of such reports for a period of not less than 18 months from the day the National Manager is notified of the report or reports. It is a condition of registration that your company must comply with Appendix 20 of Volume 1 of the Australian Guidelines for the Registration of Drugs. That appendix deals with the reporting of adverse drug reactions.

CONDITIONS APPLYING TO ALL REGISTERED DRUGS

15 Authorised Officer

It is a condition of registration that as the sponsor of this product you will comply with Regulation 24 of the Therapeutic Goods Regulations.

16 OverseasRegulatory Action

It is a condition of registration that your company must inform the TGA if an application is rejected in the USA or Canada at any time during or after registration in Australia and must submit detailed reasons for the rejection.

REGISTERED OR LISTED THERAPEUTIC DEVICES

17 Problems with Therapeutic Devices

The sponsor of registered/listed therapeutic devices shall:

- (a) keep a log of problems relating to the condition, use or application of the registered/listed therapeutic devices,
- (b) as soon as possible after the sponsor becomes aware of it, report to the Director, Conformity Assessment Branch, TGA, all deaths, serious illness and serious injuries arising from or attributable in some way to, the use or application of the registered/listed therapeutic devices.

REGISTERED THERAPEUTIC DEVICES

18 Registration Number

The registration number shall be placed on the label of the registered therapeutic devices in accordance with the requirements of the *Therapeutic Goods Act 1989* and in the manner prescribed in the Regulations.

19 Reports of Problems

The sponsor shall provide to the Director, Conformity Assessment Branch, Therapeutic Goods Administration:

- (a) a summarised report in respect of problems relating to the condition, use or application of the registered therapeutic devices between 1 July and 1 October following the date of the registration of the registered therapeutic devices,
- (b) and then submit annual summarised reports between 1 July and 1 October for the following three years.

REGISTERED AND LISTED THERAPEUTIC DEVICES SPECIFIED UNDER REGULATION 16 (SCHEDULE 6)

20 Labels (see also condition 2)

A copy¹ of the label or, if more than one label, labels to be used in respect of the registered/listed goods shall be provided to the National Manager, Therapeutic Goods Administration (through the Operations Manager, Australian Register of Therapeutic Goods), upon:

- (a) the commencement of the supply of the registered/listed goods; and
- (b) request by the National Manager.

¹ Where practicable actual labels should be provided attached to a sheet of paper which identifies the product by its Registration/Listing Name and Number. Photocopies (actual size) are acceptable where the label information is printed or embossed directly onto the container.

CONDITIONS APPLYING TO SPECIFIC CLASSES OF THERAPEUTIC GOODS

21 Conditions Applying to Drugs Which Include Bioflavonoids

Bioflavonoids shall comply with the monograph developed by the Nutritional Foods Association and the Therapeutic Goods Administration.

22 Conditions Applying to Drugs Which Contain Substances Which Are "Drugs of Dependence"

Where the registered or listed goods contain a substance which is included in the Fourth Schedule to the Customs (Prohibited Imports) Regulations or the Eighth Schedule to the Customs (Prohibited Exports) Regulations the Sponsor shall, at the time of importation or exportation of the goods, be in possession of a licence and a permission for importation or exportation of each consignment of the goods as required by those regulations.

23 Goods Manufactured Overseas

Where the registered/listed goods are imported goods which if manufactured in Australia would be required under the provisions of the Act to be manufactured in licensed premises, the sponsor of the goods shall, upon request at any time by the Secretary or the Secretary's delegate appointed for the purposes of section 31 of the Act, provide to the National Manager, Therapeutic Goods Administration, an acceptable form of evidence which establishes the standard of manufacture of the goods. If this is not available, the sponsor shall pay the costs of an inspection of the principal manufacturer of the goods by Australian inspectors where this is considered necessary by the Secretary or the Secretary's delegate referred to in this paragraph.

Specific Conditions
on Registration or Listing applying to specific groups of therapeutic devices under
Section 28 of the *Therapeutic Goods Act 1989*
EFFECTIVE 1 MARCH 1998

	Product Type	Applicable Therapeutic Goods Orders	Additional Conditions
1	Bandages, dressings and allied products supplied non-sterile		For non GMP approved manufacturers, total microbial count certificates, must be provided ³ for the subsequent five batches of product supplied following listing of the product.
1.1	Primary dressings, surgical absorbents or goods specified in Schedule 11 of the Regulations	TGO 11 - 'Standard for Sterile Therapeutic Goods'	Must be sterile and labelled "sterile"
2.	Barium hydroxide lime	TGO 47 - 'Barium Lime'	Test certificate on request ¹
3	Catheters (Urethral)	TGO 59 - 'Polymer Urethral Catheters for General Medical Use'	Test certificate on request ¹
4	Condoms	TGO 61 - 'Contraceptive Devices - Rubber Condoms'	Test certificate must be obtained for every batch prior to supply
5	Contrast media injectors (powered)		Annual problem reports to be lodged with CAB ²
6	Dental restorative materials	TGO 57 - 'Standard for Dental Materials'	Test certificate on request ¹
7	Diaphragms (Contraceptive)	TGO 28 - 'Standard for Contraceptive Devices - Diaphragms'	Test certificate must be obtained for every batch prior to supply
8.	Disinfectants & Sterilants	TGO 54 - 'Standard for Composition, Packaging, Labelling and Performance of Disinfectants and Sterilants' TGO 54A -Amendment to TGO54	Test certificate on request ¹
9	Gloves - examination	TGO 52 - 'Gloves for general medical and dental use'	Test certificate on request ¹
9.1	Gloves - surgical	TGO 53 - 'Single Use , Sterile (Surgical) Rubber Gloves'	Test certificate on request ¹
10	Implantable patient activated drug delivery systems		Annual problem reports to be lodged with CAB ²
11	In Vitro Diagnostics [IVDs] containing material of human origin	TGO 34 - 'Standard for Diagnostic Goods of Human Origin'	Test certificate on request ¹ Current catalogues and detailed records of importation and distribution of the goods must be kept by the sponsor.

	Product Type	Applicable Therapeutic Goods Orders	Additional Conditions
11.1	In Vitro Diagnostics [IVDs] approved for use as screening or as supplemental tests for the diagnosis of infection with Human Immunodeficiency Virus [HIV] (viral load assays excepted).		May be supplied to authorised laboratories only
11.2	In Vitro Diagnostics [IVDs] approved as supplemental tests for the diagnosis of infection with Hepatitis C Virus [HCV]		May be supplied to authorised laboratories only
11.3	In Vitro Diagnostics [IVDs] for home use or supplied as a Commonwealth Pharmaceutical Benefit under the <i>National Health Act 1953</i> or the <i>Veterans' Entitlement Act 1986</i>		Must be accompanied by adequate instructions and information in plain English which outlines clearly the nature, use and limitations of the test and expresses measurements in Standard International units
12	Insulin syringes	TGO 41 - 'Single-use syringes (sterile) for the injection of 100 units per millilitre of insulin (U-100)'	Test certificate on request ¹
13	Menstrual tampons	TGO 51 - 'Standard for Tampons - Menstrual'	Test certificate on request ¹
14	Penile implants - inflatable		Annual problem reports to be lodged with CAB ²
15	Pyrogen free - products presented as being such, and all devices specified in the Order	TGO 50 - 'General Standard for Pyrogen and Endotoxin Content of Therapeutic Goods'	Test certificate on request ¹
16	Silicone gel - devices containing (breast implants excepted)		Annual problem reports to be lodged with CAB ²
17	Sutures or ligatures	TGO 49 - 'General Standard for Sutures'	Test certificate on request ¹

¹ **Test certificate on request** - the sponsor of the goods must obtain a test certificate, consisting of a detailed certificate of compliance containing comments against each requirement of the Order, for each batch of goods prior to supply in Australia. These certificates must be held by the sponsor and must be available whenever the Secretary or a delegate of the Secretary appointed for the purposes of Section 28 of the Act, should request it to be produced for inspection.

² **Annual problem reports** - a report of problems relating to the condition, use or application of the devices must be submitted to the Director, Conformity Assessment Branch between 1 July and 1 October each year.

³ **Microbial count certificates** relating to non-sterile bandages, dressings and allied products must be submitted to the Senior Technical Reviewer, Conformity Assessment Branch.

For further information contact the TGA Publications Office on 1 800 020 653

Therapeutic Goods Administration

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Attachment 4

SPECIFIC CONDITIONS APPLYING TO THIS THERAPEUTIC GOOD

1. All of the manufacturing and product details as described in Attachment 2 apply to this therapeutic good.
2. The Product Information applying to this therapeutic good must meet the TGA's approval at all times. Any proposed changes to the approved text of the PI, including safety related changes, must be submitted to, and be approved by, the TGA prior to distribution.

For all injectable products the Product Information must be included with the product as a package insert.

3. Abridged Product Information must accurately reflect the approved Product Information, including safety-related statements, but may be a paraphrase or précis of the approved Product Information.
4. It is a specific condition of registration for generic medicines that the Product Information and Consumer Medicine Information documents be updated within **ONE** month of safety-related changes made by the innovator. It is your responsibility to routinely check the TGA website at www.ebs.tga.gov.au for any updates to the innovator Product Information.
5. Appropriate quantities of the reference material for the active ingredient, as well as of precursors, degradation products and other impurities for which limits are set in the finished product specifications are to be provided free of charge to the TGA, if required for testing purposes.
6. Promotional material (other than Product Information) relating to the registered good must comply with the requirements of the *Code of Conduct* of Medicines Australia.
7. You must supply a copy of any or all current labels for this product within two working days of a request from the TGA. Please note that this condition replaces Condition No. 10 of the *Standard Conditions Applying to Registered or Listed Therapeutic Goods under Section 28 of the Therapeutic Goods Act 1989* (Effective 1 July 1995).
8. 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.
9. 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 data

lock 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.

You are reminded that sections 29A and 29AA of the *Therapeutic Goods Act 1989* provide for penalties where there has been failure to inform the Secretary in writing, as soon as a person has become aware, of:

- (a) information that contradicts information already given by the person under this Act;
- (b) information that indicates that the use of the goods in accordance with the recommendations for their use may have an unintended harmful effect;
- (c) information that indicates that the goods, when used in accordance with the recommendations for their use, may not be as effective as the application for registration or listing of the goods or information already given by the person under this Act suggests;
- (d) information that indicates that the quality, safety or efficacy of the goods is unacceptable.