Public Assessment Report

Decentralised Procedure

BRALTUS 10 MICROGRAM PER DELIVERED DOSE INHALATION POWDER, HARD CAPSULE

GREGAL 10 MICROGRAM PER DELIVERED DOSE INHALATION POWDER, HARD CAPSULE (tiotropium bromide)

Procedure No: UK/H/5648/001/DC & UK/H/5875/001/DC

UK Licence No: PL 00289/1870 & PL 00289/1957

Teva UK Limited
LAY SUMMARY

Braltus 10 microgram per delivered dose inhalation powder, hard capsule
Gregal 10 microgram per delivered dose inhalation powder, hard capsule
(tiotropium bromide)

This is a summary of the Public Assessment Report (PAR) for Braltus 10 microgram per delivered dose inhalation powder, hard capsule (PL 00289/1870; UK/H/5648/001/DC) and Gregal 10 microgram per delivered dose inhalation powder, hard capsule (PL 00289/1957; UK/H/5875/001/DC). It explains how the applications for these products were assessed and their authorisation recommended as well as their conditions of use. It is not intended to provide practical advice on how to use Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule.

For practical information about using Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule, patients should read the package leaflets or contact their doctor or pharmacist.

What are Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule and what are they used for?
The applications for Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule were submitted as hybrid applications. This means that Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule are similar to a ‘reference medicine’ already authorised in the European Union (EU) called Spiriva 18 microgram, inhalation powder, hard capsule.

Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule, are labelled according to their delivered dose of tiotropium (10 micrograms), whereas the reference medicine, Spiriva 18 microgram, inhalation powder, hard capsule, is labelled according to its pre-metered dose of tiotropium (18 micrograms). It is important to note that Spiriva 18 microgram, inhalation powder, hard capsule and Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule, provide the same ‘delivered dose’ of tiotropium to the patient (10 micrograms) and the dosing regimen of one capsule, once daily, is the same for both products.

These medicines are used to help people who have chronic obstructive pulmonary disease (COPD) to breathe more easily. COPD is a chronic lung disease that causes shortness of breath and coughing. The term COPD is associated with the conditions chronic bronchitis and emphysema.

How do Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule work?
These medicines contain the active substance tiotropium bromide. Tiotropium is a long-acting bronchodilator that helps to open the airways and makes it easier to get air in and out of the lungs.

How are Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule used?
These medicines can only be obtained with a prescription.

The recommended dose is one capsule per day, inhaled with the Zonda inhaler. One capsule provides the required daily dose of tiotropium (a delivered dose of 10 micrograms of tiotropium); patients should not take more than the recommended dose.

Patients should try to take the capsule at the same time every day. This is important because these medicines are effective over 24 hours. The capsules are only for inhalation, should only be used with the Zonda inhaler and should not be swallowed.

The Zonda inhaler, which the Braltus/Gregal capsule is placed into, makes holes in the capsule and allows the patient to breathe in the powder. The capsules must only be inhaled using the Zonda inhaler.
Patients should make sure they know how to use the Zonda inhaler properly. If patients have any problems using the Zonda inhaler, they should ask their doctor, pharmacist or nurse to show them how it works.

If necessary, patients may wiping the mouthpiece of the Zonda inhaler after use with a dry cloth or tissue. Patients should not blow into the Zonda inhaler and should take care not to let any of the powder enter their eyes. If any powder does get into the eyes, patients may get blurred vision, eye pain and/or red eyes; eyes should be washed in warm water immediately. Patients should then talk to their doctor immediately for further advice.

If a patient feels that their breathing is worsening, they should tell their doctor as soon as possible.

These medicines should not be used by children and adolescents under the age of 18 years.

**What benefits of Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule have been shown in studies?**
The Marketing Authorisation Holder has provided comparative quality data to demonstrate that Braltus/Gregal delivers the same dose of tiotropium (10 micrograms) as the reference product. Studies in patients have been limited to tests to determine that Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule are bioequivalent to the reference medicine, Spiriva 18 microgram, inhalation powder, hard capsule. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

Since the applications for Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule were submitted as hybrid applications and the products are considered to be equivalent to the reference product, Spiriva 18 microgram, inhalation powder, hard capsule, their benefits and risks are taken as being the same as those of the reference medicine.

**What are the possible side effects of Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule?**
Like all medicines, Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

**Why were Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule approved?**
It was concluded that, in accordance with EU requirements, Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule have been shown to be equivalent to Spiriva 18 microgram, inhalation powder, hard capsule. Therefore, the MHRA decided that the benefits outweigh the identified risks and recommended that Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule can be approved for use.

**What measures are being taken to ensure the safe and effective use of Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule?**
A risk management plan (RMP) has been developed to ensure that Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics (SmPCs) and the package leaflets for Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule, including
the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

**Other information about Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule**

Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Iceland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the UK agreed to grant Marketing Authorisations for Braltus 10 microgram per delivered dose inhalation powder, hard capsule on 25 May 2016.

Italy, Portugal, Spain and the UK agreed to grant Marketing Authorisations for Gregal 10 microgram per delivered dose inhalation powder, hard capsule on 25 May 2016.

Marketing Authorisations were granted in the UK on 24 June 2016.

The full public assessment report (PAR) for Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule follows this summary. For more information about treatment with Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule read the package leaflets, or contact your doctor or pharmacist.

This summary was last updated in August 2016.
SCIENTIFIC DISCUSSION

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Braltus 10 microgram per delivered dose inhalation powder, hard capsule (PL 00289/1870; UK/H/5648/001/DC) and Gregal 10 microgram per delivered dose inhalation powder, hard capsule (PL 00289/1957; UK/H/5875/001/DC) could be approved. The applications were submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS), and the following Concerned Member State (CMS):

For UK/H/5648/001/DC - Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Iceland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain and Sweden.

For UK/H/5875/001/DC – Italy, Portugal and Spain

These products are prescription-only medicines (legal classification POM).

The applications were submitted according to Article 10(3) of Directive 2001/83/EC, as amended, as hybrid applications. The originator product is Spiriva 18 microgram, inhalatiepoeder in harde capsules, which was granted a Marketing Authorisation to Boehringer Ingelheim International GmbH, in the Netherlands, on 09 October 2001. The reference product for these applications in the UK is Spiriva 18 microgram, inhalation powder, hard capsule (PL 14598/0062), which was granted a Marketing Authorisation to Boehringer Ingelheim International GmbH, in the UK, on 14 May 2002.

Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule are indicated for use in adults as a maintenance bronchodilator treatment to relieve symptoms in patients with chronic obstructive pulmonary disease (COPD).

Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsules must only be inhaled with the Zonda inhaler.

These products contain the active substance tiotropium bromide. Tiotropium is a long-acting, specific, muscarinic receptor antagonist, in clinical medicine often called an anticholinergic. By binding to the muscarinic receptors in the bronchial smooth musculature, tiotropium inhibits the cholinergic (bronchoconstrictive) effects of acetylcholine, released from parasympathetic nerve endings. It has similar affinity to the subtypes of muscarinic receptors, M1 to M5. In the airways, tiotropium competitively and reversibly antagonises the M3 receptors, resulting in relaxation. The effect was dose dependent and lasted longer than 24 hours. The long duration is probably due to the very slow dissociation from the M3 receptor, exhibiting a significantly longer dissociation half-life than ipratropium. As an N-quaternary anticholinergic, tiotropium is topically (broncho-) selective when administered by inhalation, demonstrating an acceptable therapeutic range before systemic anticholinergic effects may occur.

With the exception of the bioequivalence and inhalation parameter studies, no new clinical or non-clinical studies were conducted, which is acceptable given that this is a hybrid application cross-referring to a reference product that has been licensed for over 10 years.

The applicant has submitted three pharmacokinetic studies in support of these applications, one pilot study and two pivotal studies to compare the bioavailability of Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule, with that of the reference product, Spiriva 18 microgram, inhalation powder, hard capsule (Boehringer Ingelheim International GmbH).
Two further studies were submitted to compare the inhalation characteristics in patients with COPD or in healthy volunteers, when inhaling from a Zonda inhalation device and a HandiHaler device (used for the reference product).

The RMS considers that the pharmacovigilance system, as described by the Marketing Authorisation Holder, fulfils the requirements and provides adequate evidence that the Marketing Authorisation Holder has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. The Marketing Authorisation Holder has provided a Risk Management Plan (RMP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved at the end of the procedure on 25 May 2016. After a subsequent National phase, authorisations were granted in the UK on 24 June 2016.
II QUALITY ASPECTS

II.1 Introduction

Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsules are colourless and transparent, size 3 capsules, containing white powder. Each capsule contains 16 micrograms of tiotropium bromide, equivalent to 13 micrograms of tiotropium. The delivered dose (the dose that leaves the mouthpiece of the Zonda inhaler) is 10 micrograms of tiotropium per capsule.

Other ingredients consist of the pharmaceutical excipients, namely lactose monohydrate (which contains milk protein) and a capsule composed of hydroxypropylmethylcellulose (HPMC), commonly known as hypromellose.

The finished products are packaged in high density polyethylene bottles closed with polypropylene screw-caps with polyethylene safety rings and low density polyethylene desiccant capsules containing silica gel. Each bottle contains 15 or 30 capsules, supplied in a carton with a Zonda inhaler.

The Zonda inhaler is a single dose inhalation device with a green body and cap and a white push button, made from acrylonitrile butadiene styrene plastic and stainless steel.

Braltus 10 microgram per delivered dose inhalation powder, hard capsules is also available in multipacks containing either 60 capsules (2 packs of 30), and 2 Zonda inhalers or 90 capsules (3 packs of 30), and 3 Zonda inhalers.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug substance

rINN: Tiotropium bromide
Chemical name(s): 6β,7β-epoxy-3β-hydroxyl-8-methyl-1αH,5αH-tropanium bromide,di-2-thienylglycolate
(1R,2r,4S,5S,7SO-7-{(2-Hydroxy-2,2-dithiophen-2-ylacetyl)oxy}-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.02,4]nonane bromide

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

3-Oxa-9-azoniatricyclo[3.3.1.0^{2,4}]nonane, 7-[(2-hydroxy-2,2-di-2-thienylacetyl)oxy]-9,9-dimethyl-, bromide, (1α,2β,4β,5α,7β)-compd.

Structure:
Molecular formula: \( \text{C}_{19}\text{H}_{22}\text{NO}_4\text{S}_2 \cdot \text{Br} \)
Molecular weight: 488.3
Appearance: White to yellowish-white mixture of powder and isolated crystals
Solubility: Sparingly soluble in water, freely soluble in methanol, freely soluble in dimethylformamide, slightly soluble in acetone.

An Active Substance Master File (ASMF) has been provided by the active substance manufacturer, covering the manufacture and control of the active substance tiotropium bromide.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

Appropriate specifications are provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specifications.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

II.3 Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate stable products that could be considered equivalent in delivered dose and performance to the currently licensed product, Spiriva 18 microgram, inhalation powder, hard capsule (PL 14598/0062; Boehringer Ingelheim International GmbH).

A satisfactory account of the pharmaceutical development has been provided.

In accordance with the CHMP Guideline for Orally Inhaled Products (CPMP/EWP/4151/00 Rev. 1), the applicant has submitted comparative quality data and in vitro aerodynamic particle size distribution (APSD) profile studies between the test and reference products, to demonstrate pharmaceutical equivalence. Resistances to airflow between the Zonda inhaler and the reference product (Handihaler) devices were studied and were found to be comparable.

All excipients comply with their respective European Pharmacopoeia monographs. With the exception of lactose monohydrate, none of the excipients are sourced from animal or human origin. The milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. No genetically modified organisms (GMO) have been used in the preparation of these products.
PAR Braltus/Gregal 10 microgram per delivered dose
inhalation powder, hard capsule

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate description of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished products. Process validation has been carried out on three production scale batches of finished product. The results are satisfactory.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the product
Stability studies were performed, in accordance with current guidelines, on batches of finished product in the packaging proposed for marketing. The results from these studies support a shelf-life of 24 months, with the special storage conditions of “Keep the bottle tightly closed”, “Store in the original package to protect from moisture”, and “Do not refrigerate or freeze”. After first opening the shelf life is 30 days (15 capsule bottle) or 60 days (30 capsule bottle).

II.4 Discussion on chemical, pharmaceutical and biological aspects
The dose delivered by the products is equal to that of the reference medicine Spiriva 18 microgram, inhalation powder, hard capsule (PL 14598/0062). It is recommended that Marketing Authorisations are granted for Braltus 10 microgram per delivered dose inhalation powder, hard capsule and Gregal 10 microgram per delivered dose inhalation powder, hard capsule.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPCs, PILs and labels are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current versions of the SmPCs and PILs are available on the MHRA website.

The approved labelling for Braltus 10 microgram per delivered dose inhalation powder, hard capsule is shown below:
Each capsule contains 13 micrograms of tiotropium bromide.
The delivered dose is 10 micrograms of tiotropium per capsule.
Contains lactose monohydrate.
Inhale the contents of one capsule once daily with the Zonda inhaler.
Read the package leaflet and the separate instructions for the use of the Zonda inhaler carefully before use.
Keep out of the sight and reach of children.
Use as directed by the doctor.
Discard the Zonda device after 30 uses.
Keep the bottle tightly closed.
Store in the original package to protect from moisture.
Do not refrigerate or freeze.
Use the product within 60 days of opening the bottle.

MA Holder: TEVA UK Limited, Eastbourne, BN22 9AG
PL D0289/1870
20401-B

Do not swallow. Inhale the contents of one capsule once daily with the Zonda Inhaler. Keep out of the sight and reach of children. Contains lactose monohydrate. Read the package leaflet carefully before use. Use within 60 days of opening.

MA Holder: TEVA UK Limited, Eastbourne, BN22 9AG
PL 00289/1870
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON - MULTIPACK

1. NAME OF THE MEDICINAL PRODUCT

Bralitus 10 microgram per delivered dose inhalation powder, hard capsule
tiotropium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 13 micrograms of tiotropium (as bromide).
The delivered dose is 10 micrograms of tiotropium per capsule.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, hard capsule

Combo pack
30 capsules and 1 Zonda inhaler

Component of a multipack, can’t be sold separately

Contains 60 capsules (2 x 30) and 2 Zonda inhalers
Contains 90 capsules (3 x 30) and 3 Zonda inhalers

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use.
Inhale the contents of one capsule once daily with the Zonda inhaler.
Read the package leaflet and the separate instructions for the use of the Zonda inhaler carefully before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow.
Capsules must be inhaled with Zonda inhaler only.
Discard the Zonda device after 30 uses.
8. EXPIRY DATE

EXP
Use the product within 60 days of opening the bottle.

9. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed.
Store in the original package to protect from moisture.
Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPLICABLE

11. NAME AND ADDRESS OF THE MARKETING AUTHORIZATION HOLDER

MA Holder: TEVA UK Limited, Eastbourne, BN22 9AG

12. MARKETING AUTHORIZATION NUMBER(S)

PL 00289/1870

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by the doctor.

16. INFORMATION IN BRAILLE

Braltus 10 microgram

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:
PAR Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule

UK/H/5648/001/DC
UK/H/5875/001/DC

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON – SAMPLE PACK

1. NAME OF THE MEDICINAL PRODUCT

Bral tus 10 microgram per delivered dose inhalation powder, hard capsule
tiotropium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 13 micrograms of tiotropium (as bromide).
The delivered dose is 10 micrograms of tiotropium per capsule.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, hard capsule

Combo pack
15 capsules and 1 Zonda inhaler

Free medical sample – not for resale

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use.
Inhale the contents of one capsule once daily with the Zonda inhaler.
Read the package leaflet and the separate instructions for the use of the Zonda inhaler carefully before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow.
Capsules must be inhaled with Zonda inhaler only.
Discard the Zonda device after 15 uses.

8. EXPIRY DATE
EXP
Use the product within 30 days of opening the bottle.

9. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed.
Store in the original package to protect from moisture.
Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MA Holder: TEVA UK Limited, Eastbourne, BN22 9AG

12. MARKETING AUTHORISATION NUMBER(S)

PL 00289/1870

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by the doctor.

16. INFORMATION IN BRAILLE

Braltus 10 microgram

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:
The following text is the currently approved label text for Gregal 10 microgram per delivered dose inhalation powder, hard capsule. No label mock-ups have been provided for this product. In accordance with medicines legislation, this product shall not be marketed in the UK until approval of the label mock-ups has been obtained.

### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**CARTON – COMBO PACK**

<table>
<thead>
<tr>
<th><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></th>
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<tbody>
<tr>
<td>Gregal 10 microgram per delivered dose inhalation powder, hard capsule</td>
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<tr>
<td>tiotropium</td>
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<tr>
<th><strong>2. STATEMENT OF ACTIVE SUBSTANCE(S)</strong></th>
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<tbody>
<tr>
<td>Each capsule contains 13 micrograms of tiotropium (as bromide). The delivered dose is 10 micrograms of tiotropium per capsule.</td>
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<tr>
<th><strong>3. LIST OF EXCIPIENTS</strong></th>
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<tbody>
<tr>
<td>Contains lactose monohydrate.</td>
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<tr>
<th><strong>4. PHARMACEUTICAL FORM AND CONTENTS</strong></th>
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<tbody>
<tr>
<td>Inhalation powder, hard capsule</td>
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<tr>
<td><strong>Combo pack</strong></td>
</tr>
<tr>
<td>15 capsules and 1 Zonda inhaler</td>
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<tr>
<th><strong>5. METHOD AND ROUTE(S) OF ADMINISTRATION</strong></th>
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<tr>
<td>Inhalation use</td>
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<tr>
<td>Inhale the contents of one capsule once daily with the Zonda inhaler</td>
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<td>Read the package leaflet and the separate instructions for the use of the Zonda inhaler carefully before use.</td>
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<th><strong>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</strong></th>
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<tbody>
<tr>
<td>KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.</td>
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<tr>
<th><strong>7. OTHER SPECIAL WARNING(S), IF NECESSARY</strong></th>
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<tr>
<td>Do not swallow.</td>
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<td>Capsules must be inhaled with Zonda inhaler only.</td>
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<td>Discard the Zonda device after 15 uses</td>
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<tr>
<td>Discard the Zonda device after 30 uses</td>
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</table>

| **8. EXPIRY DATE** |
Use the product within 30 days of opening the bottle.
Use the product within 60 days of opening the bottle.

9. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed.
Store in the original package to protect from moisture.
Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MA Holder: TEVA UK Limited, Eastbourne, BN22 9AG

12. MARKETING AUTHORISATION NUMBER(S)

PL 00289/1957

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by the doctor

16. INFORMATION IN BRAILLE

Gregal 10 microgram

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON – SAMPLE PACK

1. NAME OF THE MEDICINAL PRODUCT

Gregal 10 microgram per delivered dose inhalation powder, hard capsule tiotropium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 13 micrograms of tiotropium (as bromide). The delivered dose is 10 micrograms of tiotropium per capsule.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, hard capsule

Combo pack
15 capsules and 1 Zonda inhaler

Free medical sample – not for resale

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use
Inhale the contents of one capsule once daily with the Zonda inhaler
Read the package leaflet and the separate instructions for the use of the Zonda inhaler carefully before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow.
Capsules must be inhaled with Zonda inhaler only.
Discard the Zonda device after 15 uses.
8. EXPIRY DATE

EXP
Use the product within 30 days of opening the bottle.

9. SPECIAL STORAGE CONDITIONS

Keep the bottle tightly closed.
Store in the original package to protect from moisture.
Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MA Holder: TEVA UK Limited, Eastbourne, BN22 9AG

12. MARKETING AUTHORISATION NUMBER(S)

PL 00289/1957

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by the doctor.

16. INFORMATION IN BRAILLE

Gregal 10 microgram

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Gregal 10 microgram per delivered dose inhalation powder, hard capsule
tiotropium

2. METHOD OF ADMINISTRATION

For inhalation use
Do not swallow.
Inhale the contents of one capsule once daily with the Zonda inhaler

3. EXPIRY DATE

EXP
Use within 30 days of opening.
Use within 60 days of opening

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

15 capsules
30 capsules

6. OTHER

MA Holder: TEVA UK Limited, Eastbourne, BN22 9AG
PL 00289/1957

Keep out of the sight and reach of children
Contains lactose monohydrate.
Read the package leaflet carefully before use.
III NON-CLINICAL ASPECTS

III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of tiotropium bromide are well known. No new non-clinical data have been submitted for these applications and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

III.2 Pharmacology
No new pharmacology data are required for these applications and none have been submitted.

III.3 Pharmacokinetics
No new pharmacokinetic data are required for these applications and none have been submitted.

III.4 Toxicology
No new toxicology data are required for these applications and none have been submitted.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)
No Environmental Risk Assessment has been conducted and an acceptable justification for its absence has been provided. It is anticipated that use of the proposed products will replace the use of similar products already available and so no increase in environmental exposure to tiotropium bromide is anticipated. Thus the absence of an ERA is accepted.

III.6 Discussion of the non-clinical aspects
It is recommended that Marketing Authorisations are granted for Braltus 10 microgram per delivered dose inhalation powder, hard capsule and Gregal 10 microgram per delivered dose inhalation powder, hard capsule.

IV. CLINICAL ASPECTS

IV.1 Introduction
No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of tiotropium bromide. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
The applicant has submitted three pharmacokinetic studies in support of these applications, one pilot study and two pivotal studies, to compare the bioavailability of Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule, with that of the reference product, Spiriva 18 microgram, inhalation powder, hard capsule (Boehringer Ingelheim International GmbH).

Two further studies were submitted to assess the inhalation characteristics in patients with COPD or in healthy volunteers when inhaling from a Zonda inhalation device and a HandiHaler (device used for the reference product).

Study 1. Pilot study
An open, randomised, three-way crossover study to compare the bioavailability of two formulations of test product, Tiotropium 12 μg inhalation powder (Test 1) and Tiotropium 18 μg inhalation powder (Test 2), to that of the reference product, Spiriva 18 microgram inhalation powder, hard capsule (Boehringer Ingelheim International GmbH) in healthy human subjects.
This study was conducted using a dry powder inhalation device that was not the final device used in the pivotal studies and proposed for the market. The metered dose detailed above (i.e. 12 μg for test 1 and 18 μg for Test 2 and reference) is the amount of tiotropium contained in the capsule. The delivered dose (the dose leaving the mouthpiece of the device) for both the Test 1 product and the reference product was 10 μg tiotropium; the delivered dose for the Test 2 product was 16 μg tiotropium.

The applicant’s conclusions were as follows:

- Based on AUC(0-t) and Cmax of tiotropium, the extent and rate of absorption of the Test 1 and Test 2 products are not comparable with those of the reference product whereby Test 1 performed somewhat better as compared with Test 2.

- The tolerability of the two test products and the reference product was comparable. Both test formulations and the reference product were similarly well tolerated.

Twelve non-serious adverse events (AEs) were recorded in 7 subjects in the course of the trial:

- four AEs were observed in 4 subjects after administration of the Test 1 product,
- three AEs were observed in 3 subjects after administration of the Test 2 product,
- five AEs were observed in 3 subjects after administration of the reference drug.

All adverse events were assessed as not serious. Nine AEs were assessed by the investigator as possibly related to the administration of study medication, one AE as probably related and two AEs were assessed as unlikely to be related. All AEs resolved completely. The results of laboratory screening gave no indication of any adverse events or adverse drug reactions.

The findings in this study led to the further development of the Test 1 Product with a delivered dose of tiotropium of 10 μg.

**Study 2. 1st Pivotal Study**

A randomised, double-blind, double-dummy, three-way, semi-replicate, crossover pharmacokinetic study in a two-stage design for evaluation of the systemic safety of Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule (Test) compared to Spiriva 18 microgram, inhalation powder, hard capsule (10μg delivered dose) (Reference), administered as a single dose in healthy human subjects, under fasting conditions.

Volunteers were given each treatment under fasting conditions. There were three treatment periods, one in which a single dose of test product was administered and two in which a single dose of reference product was administered (semi-replicate design). Each treatment period was separated by a washout period of 10 days. Blood samples were collected for the measurement of pharmacokinetic parameters pre-dose and up to 48 hours post dose.

A summary of the main pharmacokinetic results is presented below:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Method</th>
<th>Point estimator</th>
<th>Confid. intervals</th>
<th>CV (%) (T/R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(0-t) (ratio T/R)</td>
<td>ANOVA</td>
<td>193.26%</td>
<td>92.11% -405.47%</td>
<td>undef. / 103.20%</td>
</tr>
<tr>
<td>Cmax (ratio T/R)</td>
<td>ANOVA</td>
<td>99.57%</td>
<td>66.53% -149.03%</td>
<td>undef. / 41.50%</td>
</tr>
</tbody>
</table>

The safety findings are as follows:
The Test and the Reference products were similarly well tolerated. No serious AEs were recorded. One non-serious AE was recorded by one subject during the study:

- no AEs were observed in any subject after administration of the Test product,
- one AE was observed in one subject after administration of the Reference product.

The single AE of moderate severity (a case of dizziness) was assessed as possibly related to the study treatment. The AE/dizziness resolved completely within three minutes.

The results of clinical examination and laboratory screening gave no indication of adverse events or adverse drug reactions.

Conclusion:
The 90 % confidence intervals for tiotropium for the ratio of test/reference are not within 80.00-125.00 % for Cmax and AUC. Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule, therefore, cannot be considered bioequivalent to Spiriva 18 microgram, inhalation powder, hard capsule (Boehringer Ingelheim International GmbH).

The applicant explained that the failure to show bioequivalence could be due to very low plasma concentrations of tiotropium such that the plasma concentration time curve could not be adequately evaluated from the data generated in this study. This explanation is accepted and therefore explains why 20 µg delivered dose of tiotropium (2 capsules) was administered in the second pivotal bioequivalence study, detailed below.

Study 3. 2nd Pivotal Study
A randomised, open, three-way, semi-replicate, crossover pharmacokinetic study in a two-stage design for evaluation of the systemic safety of Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule (Test) compared to Spiriva 18 microgram, inhalation powder, hard capsule (10µg delivered dose) (Reference), each one administered as a single dose of 20 µg delivered dose of tiotropium (2 capsules) in healthy human subjects, under fasting conditions.

Volunteers were given each treatment under fasting conditions. There were three treatment periods, one in which a single dose of 20 µg test product was administered and two in which a single dose of 20 µg reference product was administered (semi-replicate design). Each treatment period was separated by a washout period of 14 days. Blood samples were collected for the measurement of pharmacokinetic parameters pre-dose and up to 48 hours post dose.

A summary of the main pharmacokinetic results is presented below:

<table>
<thead>
<tr>
<th>Variable</th>
<th>method</th>
<th>point estimator (%)</th>
<th>confidence intervals (%)</th>
<th>Within subject CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{0-∞} (ratio test/reference)</td>
<td>ANOVA-log</td>
<td>106.36</td>
<td>101.33-111.64</td>
<td>11.92% (R)</td>
</tr>
<tr>
<td>C\text{max} (ratio test/reference)</td>
<td>ANOVA-log</td>
<td>96.45</td>
<td>87.26-106.60</td>
<td>22.40% (R)</td>
</tr>
</tbody>
</table>

The safety findings are as follows:

The Test and the Reference products were similarly well tolerated. No serious AEs were recorded.
Four non-serious AEs were recorded by four subjects during the study. One AE (pyrexia) was reported prior to receiving any study treatments on Day 0 in the first study period, the subject was withdrawn from the study and was reported as a screened-only subject. Two AEs (asthenia and dizziness), both described as being of moderate severity, followed inhalation of the Test product and were judged unlikely to be due to the study drug and one AE (asthenia), also described as being of moderate severity, followed the Reference product and again was judged unlikely to be due to the study drug.

All four AEs resolved completely.

The results of clinical examination and laboratory screening gave no indication of adverse events or adverse drug reactions.

Conclusion:
The 90% confidence intervals for tiotropium for the ratio of test/reference are within 80.00-125.00 % for Cmax and AUC. Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule, can, therefore, be considered bioequivalent to Spiriva 18 microgram, inhalation powder, hard capsule (Boehringer Ingelheim International GmbH). Both the Test and the Reference product also appear to be safe.

The pharmacokinetic programme of studies submitted saw the recruitment of normal healthy volunteers, which is acceptable in such a pharmacokinetic development, but no recruitment of the patient population in whom these new formulations of tiotropium bromide will be used. Therefore comparative in vitro data was also provided to demonstrate that the Test and Reference products produce comparable particle size distribution through the flow rate and pressure drop range which are clinically applicable to all patients in whom the Test product will be used.

**Study 4. Study of inhalation characteristics in patients with COPD**

A two-way, open label, randomised study to compare the inhalation characteristics in patients with COPD when inhaling from a Zonda inhalation device and a HandiHaler (device used for the reference product) after training in the use of each device according to the respective Patient Information Leaflet.

The study used empty capsule placebo Zonda and HandiHaler devices. The aims of the study were as follows:

- To use the Patient Information Leaflet (PIL) of each device to train patients with COPD to use each type of device
- To measure the inhalation profiles through each device, post PIL training
- To compare the inhalation characteristics of the patients when using each device

Results:
Although some of the parameters were shown to be slightly different when using the Zonda inhalation device compared with the HandiHaler, the majority of peak inhalation flows for both inhalers were similar between 30 to 60 L/min which would be ideal for dose emission from these dry powder inhalers, which have comparable resistance. Only two patients inhaled <30L/min with the Zonda device and the HandiHaler, however this type of inhaler ensures a high pressure change so de-aggregation with these lower flows is not expected to be a problem.

Dose emission from a capsule based dry powder inhaler is also affected by the inhalation volume because the capsule needs to be emptied. Only three patients when using the Zonda inhalation device and the HandiHaler had an inhalation volume of less than one litre. However the duration of the inhalations suggests that there will not be a problem especially if patients are encouraged to make two
separate inhalations with each dose.

The inhaled volumes were similar between Zonda inhalation device and HandiHaler. However, the analysis of the 90% confidence interval based on the mean and standard deviation results did not achieve similarity within ±15%.

Conclusion:
The above study characterised the inhalation parameters, such as the patient flow rate range, of the Zonda and HandiHaler devices in the intended patient population. The inhalation parameters were compared with healthy volunteers (Study 5). Please see detailed conclusion on Study 4 & 5 in the section below.

**Study 5. Study of inhalation characteristics in healthy volunteers**

A two-way, open label, randomised study to compare the inhalation characteristics in healthy volunteers when inhaling from a Zonda inhalation device and a HandiHaler (device used for the reference product) after training in the use of each device according to the respective Patient Information Leaflet.

The study used empty capsule placebo Zonda and HandiHaler devices. The aims of the study were as follows:

- To compare the inhalation characteristics of volunteers when using a HandiHaler and a Zonda dry powder inhaler, operated following standard training using the patient information leaflet for each inhaler
- To compare the inhalation characteristics of healthy volunteers to those of patients with COPD (from study 4) when inhaling through a HandiHaler and a Zonda device

Results:
As expected, due to better inspiratory effort and greater lung volumes, inhalation parameters measured in the healthy volunteers were better than those of the patients with COPD in the earlier study. Healthy volunteers achieved higher peak inspiratory flows (PIF in L/min) and greater inhalation volumes than were achieved by patients with COPD.

To evaluate the impact of the differences in the inhalation parameters achieved by the two populations (patients with COPD and Healthy Volunteers) *in vitro* studies have been carried out, at the relevant flow rates for both devices.

Conclusion on Study 4 & 5:
The applicant has compared the *in vitro* APSD profile, delivered dose and fine particle dose at flow rate ranges of 20-90L/min for the two devices (Zonda and HandiHaler), to justify extrapolating data from healthy volunteers to the intended population. The PIF rates are generally lower in patients with COPD although the PIF relationships in the two populations are similar for the two inhaler devices. The APSD in all groups of stages and the delivered dose are equivalent for both inhalers at different flow rates and follow similar trends.

The fine particle dose is also comparable for both inhalers at different flow rates and follows a similar trend; however it is noted that the fine particle dose falls at the lowest flow rate of 20L/min in Group 4 of the grouped stages, but this fall is seen for both inhaler devices (Zonda and HandiHaler) with a slightly greater fall seen with the HandiHaler, the reference product device. This finding is not deemed to be clinically significant.

**IV.3 Pharmacodynamics**
No new pharmacodynamic data were submitted and none were required (see Section IV.2).
IV.4 Clinical efficacy
No new data on efficacy have been submitted and none were required (see Section IV.2).

IV.5 Clinical Safety
With the exception of the data submitted during the bioequivalence studies, no new safety data were submitted and none were required (see Section IV.2). No new or unexpected safety issues were raised by the bioequivalence studies.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has submitted a RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Braltus/Gregal 10 microgram per delivered dose inhalation powder, hard capsule.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IMPORTANT POTENTIAL RISKS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac mortality</td>
<td>Prescription only medicine.</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Prescription only medicine.</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>Blood glucose increased</td>
<td>Prescription only medicine.</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Prescription only medicine.</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>Syncope</td>
<td>Prescription only medicine.</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>Cardiac disorders (Ischaemic heart disease, myocardial infarction, cardiac arrhythmia, cardiac failure)</td>
<td>Warnings in sections 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use, 4.5 Interaction with other medicinal products and other forms of interaction, 4.8 Undesirable effects and 4.9 Overdose. Reactions described in section 4.8 Undesirable effects.</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>Vascular disorders (aneurysm, hypertension)</td>
<td>Prescription only medicine.</td>
<td>Not applicable.</td>
</tr>
</tbody>
</table>
### IV.7 Discussion of the clinical aspects

It is recommended that Marketing Authorisations are granted for Braltus 10 microgram per delivered dose inhalation powder, hard capsule and Gregal 10 microgram per delivered dose inhalation powder, hard capsule.

### V. USER CONSULTATION

The package leaflet has been evaluated in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that patients/users are able to act upon the information that it contains.

### VI OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data supplied support the claim that the applicant’s products and the reference products are interchangeable. Extensive clinical experience with tiotropium bromide is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is therefore considered to be positive.
Annex 1  Table of content of the PAR update for MRP and DCP
Steps taken after the initial procedure with an influence on the Public Assessment Report

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
</table>

Y/N (version)