PUBLIC SUMMARY DOCUMENT
Product: Indacaterol maleate, capsules containing powder for oral inhalation, 150 microgram (base) and 300 microgram (base), Onbrez® Breezhaler®
Sponsor: Novartis Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: November 2010

1. Purpose of Application
The submission sought a Restricted Benefit listing for the treatment of bronchospasm and dyspnoea associated with chronic obstructive pulmonary disease (COPD).

2. Background
This drug had not previously been considered by the PBAC.

3. Registration Status
Indacaterol maleate was TGA registered on 3 August 2010 for long-term, once-daily, maintenance bronchodilator treatment of airflow limitation in patients with chronic obstructive pulmonary disease (COPD).

4. Listing Requested and PBAC's View
Restricted Benefit
For the long-term maintenance treatment of bronchospasm and dyspnoea associated with chronic obstructive pulmonary disease.

For PBAC's view, see Recommendation and Reasons

5. Clinical Place for the Proposed Therapy
COPD is characterised by airway obstruction that is not fully reversible. The airway obstruction is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases, most commonly cigarette smoke.

In the long-term treatment of COPD, long-acting bronchodilators (e.g. tiotropium, eformoterol, salmeterol) are indicated in patients who remain symptomatic despite treatment with short-acting bronchodilators at adequate doses and optimal use of inhalers. They are usually used in conjunction with short-acting 'rescue' bronchodilators.

The submission claimed that indacaterol would provide an alternative, maintenance therapy to tiotropium.

6. Comparator
The submission nominated tiotropium as the main comparator.

For PBAC's view, see Recommendation and Reasons

7. Clinical Trials
The submission presented Study 2335, a multicenter, double-blind, randomised, placebo and active controlled study consisting of:

- Stage 1: a dose finding study comprising of a double-blind study of indacaterol (75 microgram, 150 microgram, 300 microgram or 600 microgram once daily),

formoterol 12 microgram twice-daily, tiotropium 18 microgram once daily open-label or placebo; and

- Stage 2: a study of 2 out of 4 indacaterol doses selected following interim analysis to continue into a second stage for comparisons of efficacy, safety and tolerability for up to 26 weeks total treatment.

The stage 2 selected doses for indacaterol of 150 microgram and 300 microgram were based on efficacy criteria for trough (24 hours post-dose) and early (1-4 hours post-dose) bronchodilator effect after 14 days. Indacaterol 150 microgram was the lowest dose exceeding both criteria. Indacaterol 300 microgram was the next highest dose to 150 microgram. Patients were randomised to four arms: indacaterol 150 microgram, indacaterol 300 microgram, tiotropium and placebo.

As supporting evidence, the submission also presented Study 2331, a Phase III, multicenter, randomised, double blind placebo-controlled trial which compared groups administered indacaterol 150 microgram, indacaterol 300 microgram, tiotropium 18 microgram, and placebo in patients with COPD. Study 2331 employed a crossover method with each treatment period lasting 14 days and with a 14 day washout period in between treatments.

No data were presented for the addition of indacaterol to tiotropium, which was a treatment option recommended in both international (GOLD) and Australian guidelines (COPD-X) for COPD.

The studies published at the time of the submission are as follows:

Trial ID / First author	Protocol title / Publication title	Publication citation
indacaterol vs placebo		
Study 2335 Barnes et al	Integrating indacaterol dose selection in a clinical study in COPD using an adaptive seamless design	Pulm Pharmacol Ther, 2010 Jun;23(3):165-71;
Donohue et al	Once-daily Bronchodilators for Chronic Obstructive Pulmonary Disease: Indacaterol versus Tiotropium	Am J Respir Crit Care Med, 2010; 182(2): 155-62.

8. Results of Trials

Trial 2335 assessed a primary outcome of the superiority of indacaterol to placebo in trough forced expiratory volume in the first second of breath (FEV_1) at 12 weeks; and a secondary outcome of non-inferiority of indacaterol to tiotropium in trough FEV_1 at 12 weeks.

Trial 2331 assessed a primary outcome of superiority of indacaterol to placebo in trough FEV_1 after 14 days and a secondary outcome of non-inferiority of indacaterol to tiotropium in trough FEV_1 after 14 days.

In the two trials, both indacaterol dose groups showed a significant and clinically relevant improvement over placebo. Subtracting the least squares (LS) mean for the placebo group from either LS mean in the indacaterol groups gave a statistically significant improvement in

trough FEV_1 of 0.18 L (180 mL), with confidence intervals that did not cross zero. Relative to tiotropium, both indacaterol doses met the trial requirements for non-inferiority in both trials, which was a secondary outcome of the trials. Both doses of indacaterol were found in Study 2335 to be superior to tiotropium at the 95% confidence level in trough FEV_1 score with a 40-50 mL improvement.

There did not appear to be any major safety concerns for patients treated with indacaterol compared with tiotropium or placebo from the clinical trials. The proportions of patients with any adverse event (AE) or with a serious AE were approximately the same in all groups in Study 2335 and individual AEs occurred at levels too small for differences between treatment groups to be observed.

Limited additional data were provided as part of the extended assessment of safety of indacaterol owing to the fact that the drug is not widely available around the world. A potential risk highlighted in the submission was that of serious asthma-related events (intubation, hospitalisation and death) when long acting beta agonist (LABA) monotherapy is used in asthma,

9. Clinical Claim

The submission claimed that indacaterol is non-inferior in terms of efficacy and comparable in terms of safety with the main comparator tiotropium.

For PBAC's view, see Recommendation and Reasons

10. Economic Analysis

The submission presented a cost-minimisation analysis. The equi-effective doses were estimated as indacaterol 150 microgram once daily equal to tiotropium 18 microgram once daily, and indacaterol 300 microgram once daily equal to tiotropium 18 microgram once daily. These doses were used in the main and supporting clinical trials.

The PBAC noted that the submission did not provide data on add-on use where indacaterol would be added to regimens of tiotropium monotherapy rather than replacing tiotropium outright. The submission did not investigate the incremental benefit of the tiotropium plus indacaterol regimen over the use of tiotropium only.

11. Estimated PBS Usage and Financial Implications

The financial cost per year to the PBS was estimated in the submission to be less than $10 million in Year 5.

The submission's estimates were uncertain. A sensitivity analysis performed during the evaluation for a higher uptake of indacaterol use as add-on therapy in patients who would otherwise receive tiotropium only, increased the financial cost per year to the PBS to in the range of $10 – 30 million in Year 5. There was also an identified risk for usage off-label in patients with asthma.

12. Recommendation and Reasons

The PBAC considered that, if listed, the restriction initially proposed for indacaterol by the sponsor would be appropriate, noting that it was the same as the current restriction for

tiotropium and this was consistent with the TGA indication and the GOLD and the COPD-X guidelines. Furthermore, not all General Practitioners have easy access to spirometry.
The Committee agreed with its Economics Sub-Committee (ESC) that the choice of comparator was a central issue for this submission, noting that compared to fluticasone propionate plus salmeterol xinafoate (Seretide®), the only other PBS listing for COPD, tiotropium was the most prescribed drug, as shown in the BEACH data for 2008-09. However, the PBAC considered that in clinical practice, indacaterol would replace tiotropium as the initial treatment in some newly diagnosed patients, but would be added to tiotropium in many other patients in place of a long acting beta agonist – inhaled corticosteroid combinations (LABA/ICS). This was consistent with the sponsor's own usage estimates which suggested that less than half of use would be as a replacement to tiotropium. On the other hand, PBAC did not consider that LABA alone was an appropriate comparator in the Australian context.

Although the cost to Government of adding indacaterol on to tiotropium in place of a LABA/ICS will be the same as adding a LABA/ICS (as LABA/ICS therapy for COPD was cost-minimised with tiotropium), no data were provided by the submission to establish that the efficacy and safety of indacaterol was non-inferior to a LABA/ICS.

The Committee was satisfied that the clinical evidence presented in the submission was adequate to support the claim that indacaterol was non-inferior to tiotropium in terms of efficacy. However, the PBAC considered the safety of indacaterol in COPD to be particularly important as the use of single agent LABA treatment in asthma had been associated with hospitalisation, intubation and sudden death. Around 15% of COPD patients have concomitant asthma so serious asthma related events are a potential risk if indacaterol was used in this patient group. The relative paucity of long-term safety data for indacaterol also made it hard for PBAC to assess the magnitude of these risks.

The PBAC therefore rejected the submission because of uncertainty about the clinical place of indacaterol in the treatment of COPD, because of concerns about the long-term safety of LABA without ICS therapy in COPD, and because the submission did not provide any data on the comparative efficacy and safety of indacaterol and LABA/ICS combinations, which the PBAC considered indacaterol would also replace in clinical practice.

Recommendation:
Reject

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor's submission provided long term safety data **(**All-cause mortality) of LABA monotherapy as part of 6000-patient, 3 year Towards a Revolution in COPD Health (TORCH) study. The sponsor believes that such data supports the long-term safety of

indacaterol and the LABA class in COPD. The sponsor will be making another submission to address the issues raised by the PBAC