PUBLIC SUMMARY DOCUMENT
Product: INDACATEROL, capsule containing powder for oral inhalation, 150 micrograms and 300 micrograms (as maleate), Onbrez®
Sponsor: Novartis Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: July 2011

1. Purpose of Application

The submission sought a Restricted Benefit listing for long-term maintenance treatment of bronchospasm and dyspnoea associated with chronic obstructive pulmonary disease (COPD).

2. Background

At the November 2010 meeting, the PBAC rejected a submission to list indacaterol as a Restricted Benefit listing for the treatment of bronchospasm and dyspnoea associated with COPD because of uncertainty about the clinical place of indacaterol in the treatment of COPD, because of concerns about the long-term safety of long acting beta-agonist (LABA) without inhaled corticosteroid (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.

A copy of the Public Summary Document (PSD) from the November 2010 meeting is available at: http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-indacaterol-maleate-nov10

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 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.

NOTE:
Indacaterol is to be used only in patients with appropriately diagnosed COPD.

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 proposed that the place in therapy of indacaterol is as an alternative, long-acting bronchodilator maintenance therapy.

6. Comparator

The re-submission appropriately nominated fluticasone with salmeterol combination (FSC) as the main comparator.

In the November 2010 submission, a comparative evaluation was conducted against tiotropium as the main comparator.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

New trial data were presented in the re-submission. The previous submission presented one pivotal monotherapy trial of indacaterol versus tiotropium plus one supplementary trial whereas this submission compared indacaterol added to tiotropium versus FSC added to tiotropium. An indirect comparison was conducted using the common comparator of tiotropium 18 micrograms. Two randomised controlled trials were identified for indacaterol (Study 2341 and Study 2351). Both trials had identical protocols and were multicentre, double-blind, randomised, placebo controlled, parallel-group, 12-week treatment studies to compare the efficacy and safety of the combination of indacaterol 150 micrograms once daily with open label tiotropium 18 micrograms once daily versus blinded placebo plus open label tiotropium 18 micrograms once daily in patients with moderate-to-severe chronic obstructive pulmonary disease. The primary outcome was the area under the curve between 5 minutes and 8 hours post-dose of the forced expiratory volume in one second (FEV_1). Two trials were identified for FSC (Aaron 2007 and Cazzola 2007). Aaron 2007 compared addition of FSC to tiotropium versus tiotropium alone over 52 weeks. The primary end point was the proportion of patients who experienced an exacerbation of COPD. Cazzola 2007 was a 3 month trial comparing FSC added to tiotropium versus tiotropium alone. The primary endpoint was the mean change from baseline in predose FEV_1 after 3-months of treatment. The indirect comparison compared change in trough FEV_1 between indacaterol + tiotropium and FSC + tiotropium.

The studies published at the time of the submission are detailed in the table below.

Trial ID / First author	Protocol title / Publication title	Publication citation
Fluticasone – salmeterol plus tiotropium		
Aaron SD et al	Tiotropium in Combination with Placebo, Salmeterol, or Fluticasone–Salmeterol for Treatment of Chronic Obstructive Pulmonary Disease. A Randomized Trial	Ann Intern Med. 2007;146:545-555
Cazzola M et al	A pilot study to assess the effects of combining fluticasone propionate/salmeterol and tiotropium on the airflow obstruction of patients with severe-to-very severe COPD	Pulmonary Pharmacology & Therapeutics 2007; 20(5): 556-61

8. Results of Trials

The re-submission presented the results of the indirect comparison of mean change in trough FEV_1. The indirect mean difference was 0.02 (95% CI: -0.00, 0.04).

The re-submission claimed that the results of the indirect comparison suggest there is a strong trend towards significant improvement in lung function. The PBAC noted that according to

Cazzola et al (2008), a minimum clinically important difference (MCID) for FEV_1 of 100-140mL could be considered an appropriate range of values. The indirect comparison showed a difference between the two medications of 0.02 (20 mL), which is below any clinically relevant change, and the upper 95% CI was also below the MCID of 100 mL.

For PBAC's comments on these results, see Recommendation and Reasons.

The re-submission presented new toxicity data from the trials included in the indirect comparison. Adverse events were similar to those in the monotherapy trials and were mostly mild and transient in nature. The most common serious adverse events in Studies 2341 and 2351 were COPD exacerbations and pneumonia.

The re-submission provided additional data on potential safety concerns beyond those identified in the clinical trials, particularly in response to the concerns raised in the November 2010 PBAC minutes about serious adverse events occurring with LABA monotherapy use in asthma. The re-submission presented a new Periodic Safety Update Report (PSUR) and provided comparisons of LABA/ICS and LABA monotherapy in COPD and asthma using published reviews.

The key results are summarised in the table below:

Issue addressed	Summary of findings
Overall safety	No significant safety issues and no changes to the PI as a result of the report
Cardio-vascular safety	Safety profile compares favourably with other LABAs. Indacaterol not associated with any statistically significant risk compared with placebo for CCV AEs and SAEs.
LABA versus LABA/ICS in COPD	Compared with monotherapy; LABA/ICS benefits did not reach that of pre-defined clinically important effects and was associated with more serious adverse events.
LABA versus LABA/ICS in COPD Mortality outcome	No significant differences in mortality have been observed in meta-analyses (Rodrigo et al., 2009).
LABA versus LABA/ICS in asthma	A statistically significant increased risk of events in asthma patients treated with LABA compared to treatment with non-LABA, RD = 0.4 per 1000 subjects (95% CI, 0.11 to 0.69). Data disaggregated for age showed a trend among the age groups for the asthma composite endpoint, with substantially higher risk difference estimates among the younger age groups. The risk difference estimates for all the age groups except for the ≥65 age group were positive and statistically significant.

PI = product information; LABA = long-acting β_2-adrenoceptor agonist; ICS = inhaled corticosteroids; CCV = cardio-cerebro vascular; AE = adverse event; SAE = serious adverse event; RD = risk difference.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The submission described indacaterol in combination with tiotropium as non-inferior in terms of comparative effectiveness and similar or superior in terms of comparative safety over FCS with tiotropium.

The PBAC accepted the submission's claim.

10. Economic Analysis

The submission presented a cost minimisation analysis. The equi-effective doses were considered to be indacaterol 150 micrograms daily , fluticasone with salmeterol 250/25 micrograms, 2 puffs twice daily and tiotropium 18 micrograms.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated in the submission to be between 10,000 and 50,000 in Year 5 at a net cost per year to the PBS of less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC recommended the listing of indacaterol on the PBS as a Restricted Benefit for the treatment of chronic obstructive pulmonary disease on a cost-minimisation basis compared with fluticasone in combination with salmeterol. The equi-effective doses were considered to be indacaterol 150 micrograms daily, fluticasone with salmeterol 250/25 micrograms, 2 puffs twice daily and tiotropium 18 micrograms daily.

The appropriate main comparator is fluticasone with salmeterol as previously agreed by the PBAC in November 2010.

The PBAC noted that none of the four trials included in the indirect comparison showed a clinically important difference of either indacaterol in addition to tiotropium (trials 2341 and 2351) or fluticasone/salmeterol in addition to tiotropium (Cazzola, Aaron). The indirect comparison showed a difference in trough $FEV_{1,}$ between the addition of indacaterol to tiotropium compared to the addition of fluticasone/salmeterol to tiotropium, of 0.02 (or FEV_1 of 20mL) which is below the generally accepted minimum clinically important difference of FEV_1 of 100-140 mL (Cazzola et al 2008) and is not statistically significant. For the sub-group of patients with severe COPD, the difference in trough FEV_1 was 70 mL in Trial 2341 and 60 mL in Trial 2351. Although there was some uncertainty regarding the comparability of the trials used in the indirect comparison, the PBAC considered that this was a valid comparison and that indacaterol was no worse when added to tiotropium compared with fluticasone/salmeterol added to tiotropium.

The PBAC considered that the additional safety data provided to address concerns raised in November 2010 about serious adverse events occurring with LABA monotherapy use in asthma, was supportive of monotherapy LABA use in COPD only. The PBAC noted that safety concerns arise when monotherapy LABAs are used for asthma and this is particularly evident in younger age groups. The PBAC considered that there are safety concerns if there is substantial use of indacaterol outside the requested listing for COPD. Therefore, the PBAC recommended the addition of a NOTE to the restriction stating that indacaterol is not PBS-subsidised in asthma to minimise use for this indication.

The PBAC accepted the submission's claim that indacaterol in combination with tiotropium is non-inferior in terms of comparative effectiveness and similar safety to fluticasone/salmeterol in combination with tiotropium.

The PBAC requested that the National Prescribing Service (NPS) provide an educational strategy for the clinical algorithm for COPD, including a guide to improved diagnosis of COPD, as the addition of indacaterol is likely to change the current treatment algorithm.

PBAC recommended that indacaterol be included in the PBS medicines for prescribing by nurse practitioners.

Recommendation:
INDACATEROL, capsule containing powder for oral inhalation, 150 microgram and 300 microgram (as maleate)

Restriction:	Restricted benefit Chronic obstructive pulmonary disease. NOTE: Indacaterol is not PBS-subsidised for the treatment of asthma.
Maximum quantity:	30
Repeats:	5

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 believes indacaterol provides an important additional treatment option for Australian patients with COPD and looks forward to the finalisation of listing and the product being made available on the PBS.