

**7.11 INDACATEROL WITH GLYCOPYRRONIUM (FDC),
indacaterol 110 microgram + glycopyrronium 50 microgram,
inhalation: powder for, 30 capsules,
Ultibro[®] Breezhaler[®] 110/50,
Novartis Pharmaceuticals Australia Pty Ltd**

1 Purpose of Application

- 1.1 To request a Restricted Benefit listing for once daily maintenance bronchodilation in patients with chronic obstructive pulmonary disease (COPD) currently on a long-acting beta₂-agonist (LABA) or a long acting muscarinic antagonist (LAMA) monotherapy and requiring additional relief from symptoms and in patients who have been stabilised on a combination of a LAMA and LABA in separate devices.

2 Requested listing

- 2.1 The submission requested the following restriction:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary and Manufacturer	Name
INDACATEROL/GLYCOPYRRONIUM Inhalation: powder for, 30 capsules, indacaterol maleate 110 microgram + glycopyrronium bromide 50 microgram	1	5	Ultibro [®] Breezhaler [®] 110/50	Novartis

<p>Restricted benefit Chronic obstructive pulmonary disease</p> <p>Patient must have symptoms that persist despite regular bronchodilator treatment with a long acting muscarinic antagonist and/or long acting beta2-agonist; OR Patient must have been stabilised on a combination of a long acting muscarinic agonist and long acting beta2-agonist.</p>
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- 2.2 Listing was sought on a cost-minimisation basis compared to the components given concomitantly.
- 2.3 The requested listing is the same as was proposed in the March 2014 submission with the addition of an administrative note specifying that indacaterol/glycopyrronium is not PBS-subsidised for the treatment of asthma, and not indicated for the initiation of bronchodilator therapy.

For more detail on PBAC's view, see section 7 "PBAC outcome"

3 Background

- 3.1 Indacaterol/glycopyrronium was TGA registered in March 2014 for once-daily bronchodilator treatment to relieve symptoms in patients with chronic obstructive pulmonary disease (COPD).

- 3.2 Indacaterol/glycopyrronium was considered by the PBAC in March 2014. The PBAC rejected the submission. In its recommendations the committee concluded that the evidence presented in the SHINE study (that the incremental gain in FEV₁ of adding glycopyrronium to indacaterol (70 mL (95% CI: 50-100 mL)) was not twice the incremental gain of indacaterol over placebo (130 mL (95% CI: 100-160 mL) and the evidence did not support the usual PBAC approach for combination products i.e. that the FDC would be priced as the sum of the component parts.
- 3.3 In addition, the PBAC considered that the incremental gain in FEV₁ of indacaterol/glycopyrronium FDC was not able to be translated into more clinically relevant measures of effect (e.g. frequency of exacerbations, hospitalisations). Therefore the PBAC considered it was unable to determine and value the incremental benefit associated with use of the FDC compared with use of components given concurrently. Thus the Committee was unable to determine an appropriate price for the FDC.
- 3.4 The PBAC also noted that the treatment algorithm for COPD is changing given the potential safety risks associated with inhaled corticosteroid (ICS) use, therefore there is potential for greater switching from ICS/LABA than what was considered in the original submission.

4 Clinical place for the proposed therapy

- 4.1 The listing of indacaterol/glycopyrronium FDC would provide an alternative in one inhaler for a LABA/LAMA combination, rather than LABA + LAMA in two inhaler devices.

For more detail on PBAC's view, see section 7 "PBAC outcome"

5 Comparator

- 5.1 The submission nominated four comparators:
- Indacaterol 150 µg and glycopyrronium 50 µg given concurrently
 - Indacaterol + tiotropium
 - LABA/ICS plus tiotropium
 - Indacaterol 150 µg and glycopyrronium 50 µg mono-components.
- 5.2 In consideration of the initial submission in March 2014, the PBAC considered the nominated comparators to be generally appropriate.
- 5.3 The PBAC noted that a second LAMA/LABA combination FDC, umeclidinium with vilanterol is also being considered by PBAC on this agenda, and considered this also an appropriate comparator.

For more detail on PBAC's view, see section 7 "PBAC outcome"

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted the input from one healthcare professional on the PBS website expressing that LABA/LAMA in one device would improve the management of COPD patients requiring two classes of bronchodilator.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Clinical trials

- 6.3 The resubmission does not present any new clinical data. There is a new utilisation study (using General Practice data collected through the Sydney University Family Medicines Research Centre (BEACH-SAND) data collection). This study provides the basis for a new pricing proposal.

- 6.4 The submission proposes that patients would use indacaterol/glycopyrronium to add a second agent despite the BEACH Report indicating that some patients commenced on combination therapy.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Clinical claim

- 6.5 As for the March 2014 submission, this submission claimed that indacaterol/glycopyrronium is superior in terms of comparative effectiveness and equivalent in terms of safety over either of the components given as monotherapy.

- 6.6 The PBAC considered that the claim of superiority for the FDC, in terms of additional change in FEV₁ was supported by the data, but that the change was not clinically significant based on the previous definition of minimum clinically important difference used by the Committee.

- 6.7 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

- 6.8 The PBAC noted that while improvement in FEV₁ has previously been accepted as a surrogate outcome in the treatment of COPD, they were concerned that this may not translate into clinically meaningful benefits to the patient. The PBAC noted that reduction in exacerbations and hospitalisations are outcomes that could potentially be used to measure effectiveness of COPD therapies

- 6.9 The PBAC recalled that in March 2014, aclidinium (a LAMA), was recommended for listing on the PBS at the lower price requested by the sponsor. The PBAC noted that the Department's advice at the meeting that the Minister (through his Delegate) intends to declare aclidinium as a pharmaceutical benefit under section 85(2) of the *National Health Act 1953* and that the PBS listing will proceed with the lower price. As the main comparators in this submission, indacaterol and tiotropium are cost-minimised to aclidinium (the former via tiotropium), the PBAC considered it is appropriate for the new lower aclidinium price to be used in calculating the price for indacaterol/glycopyrronium.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Economic analysis

- 6.10 Switching from ICS/LABA to indacaterol/glycopyrronium is now appropriately included in the pricing and estimates used in the current submission, however, the switching rates applied for these patients are still uncertain.
- 6.11 The sponsor originally proposed a DPMQ of [REDACTED], which is equivalent to the sum of the component products. This was modified to extend the population to include patients currently on ICS/LABA alone (rather than only in combination with LAMA as for the previous submission), and by recalculating the price based on the weighted average of the medications currently used to treat COPD based on BEACH data. This has resulted in a proposed DPMQ of [REDACTED]. It was noted that there is considerable uncertainty in the derived weighted price of [REDACTED] due to concerns that the small sample size used in the BEACH data (medicine use in 61 patients recorded by 41 GPs) could potentially have high bias and poor applicability.
- 6.12 The evaluation also noted that the recalculated proposed DPMQ has not considered the following:
- The published price for ICS/LABA is a weighted price allowing for use in asthma and COPD for the highest strength formulation; and
 - Patients who are inappropriately prescribed more than 1 LABA should have been excluded from weighting. This is because if a patient was on more than 1 LABA (such as an ICS/LABA and LABA monotherapy), the overall price of their treatment regimen would be high and would disproportionately contribute to the final weighted price resulting in an inappropriately high DPMQ.
- 6.13 The PBAC also noted that the sponsor for the second LAMA/LABA that is being considered on this agenda had used a different approach to address the concerns previously raised by PBAC, and that the alternative approach resulted in a lower price. The PBAC further considered that, in the absence of any evidence to the contrary, it would be reasonable to assume the two combination LAMA/LABAs would deliver similar outcomes.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Estimated PBS usage & financial implications

- 6.14 The submission recalculated market size to incorporate switching from ICS/LABA but this is still a source of uncertainty. It is likely that the introduction of a fixed dose combination could grow the overall market and that patients could be initiated on the FDC earlier than clinically appropriate without the adequate titration of individual components. DUSC has noted emerging trends with some FDC products, such as a higher proportion of patients commencing de novo, and FDCs increasing the market rather than substituting within current markets (DUSC Outcome Statement February 2013).
- 6.15 In March 2014, the PBAC considered that a risk sharing arrangement would be required to manage the risk associated with higher than estimated usage and cost however no details have been proposed by the sponsor.

For more detail on PBAC's view, see section 7 "PBAC outcome"

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of indacaterol/glycopyrronium as an Authority required (STREAMLINED) listing for the treatment of chronic obstructive pulmonary disease for patients already stabilised on concomitant LAMA and LABA therapy.
- 7.2 The PBAC considered, amongst other matters, that the cost-effectiveness of indacaterol/glycopyrronium would be acceptable if it were cost-minimised against the umeclidinium/vilanterol FDC when used for COPD. The equi-effective doses are considered to be indacaterol 110 microgram with glycopyrronium 50 microgram to umeclidinium (as bromide) 62.5 microgram with vilanterol (as trifenate) 25 microgram.
- 7.3 While other treatments for COPD are currently Restricted Benefits, the PBAC considered it would be appropriate for indacaterol/glycopyrronium to be listed as a Streamlined Authority in an attempt to address inappropriate prescribing of the product, particularly in the first-line setting. The PBAC noted clinical input that confirmed initial treatment will be as monotherapy, with patients likely to be transitioned to FDC treatment only when clinically necessary.
- 7.4 The PBAC noted that the primary concerns raised in the March 2014 submission were not adequately addressed in the resubmission as the incremental benefit of the combination product could not be translated into clinically relevant measures of effect. However, the Committee accepted that there are both benefits and cost savings for patients who are already using individual LAMA and LABA in separate devices.
- 7.5 The PBAC accepted that indacaterol/glycopyrronium has a place in therapy for patients already stabilised on individual components, noting one consumer comment which stated that a combination product would improve management for COPD patients.
- 7.6 The PBAC noted that there is significant confusion among prescribers regarding medicines used in COPD and as such, names of individual LAMAs and LABAs should be noted in the restriction.
- 7.7 Advice to the Minister under Subsection 101 3BA of the *National Health Act*
In accordance with subsection 101(3BA) of the *National Health Act* 1953, the PBAC advised that it is of the opinion that indacaterol/glycopyrronium should be treated as interchangeable on an individual patient basis with umeclidinium/vilanterol.
- 7.8 The PBAC advised that indacaterol/glycopyrronium is suitable for prescribing by nurse practitioners.
- 7.9 The PBAC recommended that the Safety Net 20 Day Rule should apply.

Outcome:

Recommended.

8 Recommended listing

- 8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary and Manufacturer	Name
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Condition:	Chronic Obstructive Pulmonary Disease
Restriction:	Authority required (STREAMLINED)
Clinical criteria:	Patient must have been stabilised on a combination of a long acting muscarinic antagonist and long acting beta-2 agonist.
Administrative Advice	<p>The treatment must not be used in combination with an ICS/LABA, or LAMA or LABA monotherapy.</p> <p>A LAMA includes tiotropium, glycopyrronium, aclidinium or umeclidinium.</p> <p>A LABA includes indacaterol, salmeterol or eformoterol.</p> <p>This product is not PBS-subsidised for the treatment of asthma.</p> <p>This product is not indicated for the initiation of bronchodilator therapy in COPD.</p>

9 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.

10 Sponsor's Comment

Novartis is pleased that the positive recommendation of Ultibro will allow COPD patients access to both component products, already available on the PBS.